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The Influence Of Sodium And Potassium On Blood Pressure Genetics In The Population Architecture Using Genomics And Epidemiology Study

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THE INFLUENCE OF SODIUM AND POTASSIUM ON BLOOD PRESSURE GENETICS IN THE POPULATION ARCHITECTURE USING GENOMICS AND EPIDEMIOLOGY STUDY

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Multiple polymorphisms have shown associations with blood pressure (BP) levels and hypertension status, but the overall genetic effect on BP has been small and accounts for only a small fraction of the variation in population-wide BP characteristics. These weak associations of BP with genotype may not be attributable to the examining the "wrong" single nucleotide polymorphism (SNP) but may instead be the result of noisy BP phenotypes based on mmHg alone. Adding information from the underlying mechanisms of nutritional intake, reuptake, and excretion on BP may produce more informative BP phenotypes to study.

To explore this complex relationship between diet, genes, and BP we chose 186 BP-related SNPs from previous genome-wide association studies (GWAS) to test if sodium and potassium intake modify the existing BP-SNP relationship. Next, we tested if these BP-related SNPs are associated with sodium and potassium intake. Lastly, we tested if the

effects of sodium and potassium intake on BP are heterogeneous across race/ethnic groups. We combined data across four cohorts representing 3 racial ancestry groups (Black, White, and Hispanic participants) from the Population Architecture using Genomics and Epidemiology (PAGE) consortium to test our hypotheses. All analyses used participant-level data stratified by cohort and racial ancestry. Model coefficients were combined by meta-analysis and assessed for effect heterogeneity across strata.

We were unable to demonstrate experiment-wide significant interaction effect of dietary intake on the BP-SNP relationship but the closest nominally significant result indicated that the CASZ1 gene may play a part in the modulation of BP by both sodium and potassium among Hispanics. All nominally significant interactions between diet, gene, and BP showed heterogeneity of effects across racial ancestry groups. As for dietary associations with BP, we found a higher association between nutritional intake and BP among non-White participants which support current guideline recommendations of sodium sparing diets particularly in Black and Hispanic hypertensive patients.

This study has provided more evidence of the heterogeneity of BP phenotypes among ancestry groups, particularly as they relate to nutritional intake and genetics. While dietary intake is likely an intermediate phenotype mediating gene-BP relationships, the effects are small and difficult to detect with highly variable intake measures. We suggest future studies focus on an alternate subset of SNPs from trans-ancestry BP association

studies and employ a larger sample size in order to demonstrate significant interactions with dietary intake measures.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

BACKGROUND

Literature Review

Worldwide more than 1 billion adults have hypertension, making it the most common modifiable risk factor for cardiovascular disease and cardiovascular-related death, accounting for more than 9 million deaths annually (WHO, 2013). Hypertension occurs more frequently in populations of African ancestry and is associated with more severe clinical sequelae and twice the mortality risk compared to populations of European ancestry (Benjamin et al., 2017). These disparities underscore the fact that hypertension is etiologically and genetically heterogeneous. The pathophysiologic nature of hypertension is multifactorial, but primarily driven by renal regulation of urinary excretion of water and soluble ions (specifically sodium and potassium) to maintain a constant extracellular environment for proper cell function (Rose & Post, 2001). Multiple genetic loci associated with blood pressure (BP) levels by genome-wide association studies (GWAS) in populations of European (Ehret et al., 2011; Levy et al., 2009; Newton-Cheh et al., 2009) and African ancestry (Fox et al., 2011; Franceschini et al., 2013) are functionally related to the maintenance of vascular tone and renal regulation of soluble ions (Franceschini et al., 2013) but causal pathways have yet to be determined for the majority of the GWAS-discovered BP-related loci.

Treatments to reduce BP currently consist of a low-sodium diet and/or trial and error of anti-volume or anti-renin medications. Recently, the evidence of benefit from a low sodium diet has weakened. In response, the Institute of Medicine (IOM) raised the recommended sodium intake to <2.3 grams/day for most individuals but kept intake recommendations at <1.5 grams/day for African-Americans and other higher risk subgroups (Strom, Anderson, & Ix, 2013). These new racially stratified recommendations are informed by randomized control trials showing “salt sensitivity”, a precursor of hypertension, to be more frequent in those of African ancestry. However, the IOM recommendations failed to discuss that this salt-sensitive hypertension is only present when dietary potassium is deficient (Adrogué & Madias, 2014; Morris, Sebastian, Forman, Tanaka, & Schmidlin, 1999; Rodrigues et al., 2014). Further results from a multi-racial, international cohort recently confirmed the association of high sodium and low potassium intake with higher BP at baseline but found both low and high sodium intake increased the risk of mortality upon follow up (Mente et al., 2014; O'Donnell et al., 2014). These recent findings indicate a paradigm shift in the field of BP that highlight the uncertainty of low sodium diet recommendations, the importance of potassium as an often-ignored co-factor in BP regulation, and the racial heterogeneity of environment-influenced BP traits.

Public Health Significance

While multiple polymorphisms have shown associations with BP levels and hypertension status, the overall genetic influence on BP has been small and accounts for only a small fraction of the variation in population-wide BP characteristics. These weak associations of BP with genotype may not be attributable to the field examining the "wrong" single nucleotide polymorphism (SNP) but instead be the result of non-specific BP phenotypes based on mmHg alone. By adding information from the underlying mechanisms of nutritional intake, reuptake, and excretion on BP, we may be able to create more informative BP phenotypes. In addition, we know the genetic effect of BP varies by racial and ethnic ancestry. Only through a large consortium of multiethnic genotypic and epidemiologic studies like the Population Architecture using Genomics and Epidemiology (PAGE) consortium can these specific BP phenotypes be studied in large enough numbers to provide powerful links to established BP genetic markers. Once genetic markers are related to these precise BP phenotypes, biological pathways of BP dysfunction will be better elucidated giving practitioners superior tools to control one of the largest contributing factors to cardiovascular morbidity and mortality worldwide.

Specific Aims

To explore the complex relationship between diet, genes, and BP we first tested if BP-related SNPs are also associated with sodium and potassium intake. Next, we tested if

the effects of sodium and potassium intake on BP are heterogeneous across race/ethnic groups. Lastly, we tested if sodium and potassium intake modify the existing BP-gene relationship. We selected SNPs identified as associated with BP or hypertension in the GWAS catalog (*Buniello* et al., 2019) before 2017 in European (Bis et al., 2015; Ehret et al., 2011; Franceschini et al., 2013; Germain et al., 2013; Levy et al., 2009; Newton-Cheh et al., 2009; Org et al., 2009; Padmanabhan et al., 2010; Salvi et al., 2017; Schneider et al., 2014; Simino et al., 2014; Turner et al., 2013; Wain et al., 2011), African (Adeyemo et al., 2009; Bis et al., 2015; Fox et al., 2011; Franceschini et al., 2013; Lettre et al., 2011; Salvi et al., 2017; Taylor et al., 2016), and Asian (Ehret et al., 2011; Franceschini, Reiner, & Heiss, 2011; He et al., 2013; Kato et al., 2015; Kato et al., 2011; Kelly et al., 2013; Kim et al., 2014; Leu et al., 2014; Lu et al., 2015; Newton-Cheh et al., 2009; Simino et al., 2014; Yang et al., 2009) ancestry studies and stratified all analyses by self-reported ancestry group, testing all available SNPs in each ancestry group. Findings from this study may elucidate mediation pathways of BP-related SNPs across race/ethnic groups, define a more specific hypertension phenotype, and guide effective treatment and prevention of cardiovascular disease.

Specific Aims 1: Test dietary phenotype-gene associations between GWAS-established BP-related SNPs and sodium and potassium in each race/ethnic group.

i. Determine if BP-related SNPs are related to sodium and potassium intake from dietary questionnaires.

ii. Confirm findings of association between BP-related SNPs and sodium and potassium excretion from a subsample of PAGE studies with 24-hour urine collections.

Specific Aim 2: Estimate the heterogeneity of the effects of sodium and potassium intake on BP across race/ethnic groups.

i. Test the extent of effect modification of potassium intake on the relationship between sodium and BP levels; specifically, if high potassium intake counteracts the effects of high sodium intake on BP similarly in all race/ethnic groups.

ii. Determine if the effect of the sodium/potassium ratio on BP is consistent across low and high sodium intake groups in all race/ethnic groups.

Specific Aim 3: Test the gene-environment interaction of BP-related SNPs with sodium and potassium intake phenotypes on BP in each race/ethnic group within PAGE.

i. Test phenotype effect modification of sodium and potassium intake on the association between established SNPs and BP outcomes in each race/ethnic group.

METHODS

Study Setting

The PAGE study was initiated by the National Human Genome Research Institute in 2008 to investigate the current epidemiologic knowledge base of well-replicated genetic variants associated with complex diseases in large, ethnically diverse population-based studies. PAGE is currently in its third phase of funding from the National Institute of Health and combines DNA samples and hundreds of phenotypes from the following studies: Atherosclerosis Risk In Communities (ARIC), Coronary Artery Risk In Young Adults (CARDIA), Cardiovascular Heart Study (CHS), Hispanic Community Health Study/Study of Latinos (SOL), The Strong Heart Cohort Study (SHS), The Strong Heart Family Study (SHFS), The Multiethnic Cohort (MEC), Mount Sinai Medical Center Institute for Personalized Medicine BioMe Biobank (MSMC), and The Women's Health Initiative (WHI). This study incorporates biomarker and genetic data from 4 large studies which includes participants of varying ethnicity: ARIC (European American and African Americans)("The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators," 1989), WHI (Hispanic Americans and African Americans)(Anderson et al., 2003), CARDIA (European American and African Americans)(Hughes et al., 1987), and SOL (Hispanic Americans)(Matise et al., 2011; Sorlie et al., 2010).

Study Subjects

Study participants were included in the analysis if they were genotyped on the Illumina Metabochip platform or had previously genotyped GWAS data available and imputed to 1000 Genomes Phase 3. Participants were required to have non-missing systolic blood pressure (SBP), diastolic blood pressure (DBP), sodium intake, potassium intake, age, sex, BMI, total protein intake, total caloric intake, serum creatinine, use of anti-hypertensive medications, and principal component ancestry estimates. Participants were excluded if dietary caloric intake was outside described thresholds (see Data Analysis section). Subgroup racial ancestry category was also required for inclusion of participants from the SOL study.

Data Analysis

The primary phenotypes of interest in this study was BP (systolic and diastolic) and prevalent hypertension. BP was measured at Visit 1 in ARIC and SOL, Visit 2 in CARDIA, and observational study Visit 1 in WHI. BP was manually measured in a resting state by a sphygmomanometer twice in WHI and 3 times in CARDIA and ARIC. Resting BP in SOL was measured 3 times by automated BP device (OMRON HEM -907XL). The average of the second and third BP measurements in mmHg were used for CARDIA and ARIC. The average of all BP measurements in mmHg were used for SOL and WHI. For all studies, SBP was truncated to a minimum of 30 mmHg and a maximum of 300 mmHg and DBP was truncated to a minimum of 10 mmHg and a maximum of 150 mmHg. For patients concurrently treated

with anti-hypertensive medication, 15 mmHg was added to SBP and 10 mmHg was added to DBP (Tobin et al., 2005). Hypertension was defined as (unadjusted) BP greater than 140/90 or concurrently taking anti-hypertensive medications.

Dietary intake of sodium, potassium, total calories, and total protein were estimated by food-frequency questionnaires (ARIC, CARDIA, WHI) and by 24-hour recall (SOL). ARIC employed an interviewer-administered validated 61-question food-frequency questionnaire modified from the Willett questionnaire (Willett et al., 1985) to determine dietary intake patterns over the previous year. CARDIA employed a validated interviewer-administered food-frequency questionnaire by Burke which was modified from the food-frequency questionnaire used in the Western Electric Study (McDonald et al., 1991) to determine dietary intake patterns over the previous month. The SOL study conducted in-person 24-hour food recall with random telephone follow-up 24-hour recalls within 6 weeks after in-person interview. Results from a later food propensity questionnaire were used to enhance the predictive power of the 24-hour recall data. The food propensity questionnaire is similar to a food-frequency questionnaire but without portion sizes. In the WHI observational study, the food-frequency questionnaire was designed based on previous WHI studies in order to assess dietary intake patterns over the previous 3 months and validated using 24 hour recall surveys (Patterson et al., 1999). Dietary intake estimates from WHI and SOL were determined using the nutrient database from the University of Minnesota Nutrition

Coding Center nutrient database (Nutrition Coordinating Center, Minneapolis, MN)(Patterson et al., 1999; Sorlie et al., 2010). All studies were first analyzed separately in order to account for differential dietary assessment methods then estimates were meta-analyzed and tested for homogeneity of effects.

Multiple procedures were undertaken in order to standardize dietary intake measurements. Observations with calories <600 or > 6000 for women and <800 or >8000 for men were removed within CARDIA, WHI, and SOL as this level of caloric intake indicates inaccurate dietary measurement (Chatterjee et al., 2012; Patterson et al., 1999; Sorensen et al., 2014). Observations within ARIC were removed if caloric intake was <500 or >3600 for women and <600 or >4200 for men before being sent to PAGE, thus cutoffs were not modifiable. While it is known food-frequency questionnaires are prone to underestimation of sodium intake (Harnack et al., 2017), there is concern that ARIC nutritional data may even further underestimate true dietary consumption as evidenced in the lower cutoffs employed for this study. Thus, to control for any bias due to this underestimation in ARIC dietary data, we conducted a sensitivity analysis excluding ARIC data to confirm any results. Daily potassium intake (g), sodium intake (g), and protein intake (g) were winsorized at 6 standard deviations to reduce the effect of extreme outliers. BP across quartiles of sodium and potassium were first examined to assess linearity of effect. Binary categories based on the median value of sodium intake within study were used to define high vs low sodium and

potassium exposure groups. In addition, relationship between BP and sodium:potassium ratio was examined on a continuous scale.

A total of 186 SNPs that reached genome-wide significance for association with SBP, DBP, or hypertension in European, African, South Asian, or East Asian populations before 2017 were selected for inclusion from the GWAS catalog (*Buniello* et al., 2019)– accessed 7/10/2017. All 186 GWAS-established SNPs were required to have shown validated associations through replication studies. These 186 variants are located in or nearby 162 different gene or gene regions (with 19 of the gene regions represented by 2 or more SNPs). Of the 186 variants, 9 are non-coding transcript exon variants, 4 are missense, 2 are synonymous, with the remainder located in introns, flanking, or intergenic regions. Locations and previous associations of the included variants are in Appendix A. Study participants were previously genotyped using commercially available genotyping arrays (Affymetrix 6.0 for ARIC and CARDIA cohorts, MEGAchip for SOL as well as Black and Hispanic WHI cohorts, and Illumina HumanOmniExpress for White WHI cohort). Genotyped data was imputed to 1000 Genomes Phase 3 for all studies. Subject level data for replicated SNPs based on GRCh37 chromosome:position was extracted. A total of 183 replicated SNPs available from at least one or more PAGE studies were examined in this analysis.

All analyses were run with individual level data within each study stratified by study and self-reported ancestry group. Regression models were fit using SUGEN v8.7 which accounts for family related dependencies (relevant for SOL study only) (Lin et al., 2014). Baseline SBP and DBP models were fit by linear regression and prevalent hypertension models were fit by logistic regression (Table 1). Consistent with the original GWAS studies, additive genetic effects were assumed for all models. Tests of interactions by sodium and potassium categories with SNPs were made to determine effect modification. To confirm the adequacy of the linear regression fit we used scatter plots to confirm linearity assumptions of the model, histograms and QQ plots of residuals to assess normality assumptions, and scatter plots of predicted values by residuals to determine if any heteroscedasticity is present. Logistic regression fit was assessed by comparing predicted versus observed outcomes, and scatter plots of log odds by the continuous covariates were examined to ensure linearity assumptions of the model are met. Model adequacy was assessed in models containing all covariates.

Model coefficients were combined by meta-analysis across studies, stratified by self-reported ancestry group. Meta-analysis testing the interaction of genetic by diet effects across studies were combined using METAL (Willer, Li, & Abecasis, 2010) and a joint 2df test (Manning et al., 2011; Wu & Becker, 2013). R package “metafor” was used to combine effects by inverse variance weighted meta-analysis, allowing for random effects by study

(Viechtbauer, 2010). After meta-analyzing across studies, heterogeneity of effects across racial group was tested by inverse variance weighted meta-analysis. Heterogeneity between study or self-reported ancestry groups were considered significant if I^2>75% or Cochran's Q p-value<0.05.

Sample Size Calculation

Based on the 183 SNPs available to be tested for significant effect (as outlined in the specific aims) across 3 ancestry groups (6339 tests), we controlled for Type 1 error with a Bonferroni corrected significance level of $<7.89 \times 10^{-6}$. Meta-analyzed coefficients with a p<0.05 were considered nominally significant. To ensure that we had the power to detect a gene-environment additive effect of at 3-5 mmHg, we completed an *a priori* power analysis for Aim 3 based on an additive genetic model, SBP standard deviation of 20, allele frequency range 0.2-0.4, desired power of 0.8, and high sodium or low potassium prevalence of 0.5 using Quanto software (Thomas, 2010). The original power analysis assumed an experiment-wide Type I Error rate of 7.3×10^{-5}, sample size requirements range from n=3,188 with 0.5 allele frequency and 5 mmHg gene-environment effect, n=9,462 with 0.4 allele frequency and 3 mmHg gene-environment effect, or at most n=14,323 under the most constrained condition with 0.2 allele frequency and 3 mmHg gene-environment effect.

Human Subjects, Animal Subjects, or Safety Considerations

This research study has obtained IRB approval from the UTH CPHS # HSC-SPH-08-0549 to ensure protections of human subjects. All sites that are part of this consortium have completed comparable IRB approvals from their respective CPHS committees.

RESULTS

The PAGE study is made up of multiple diverse studies and participants (Table 2). Participant data from the earliest study visit where both BP and dietary intake data are available were included in this dissertation study analysis. Individuals were only included once to ensure independence of observations. The data collection era varied by study with ARIC and CARDIA data collected before 1990, WHI between 1994 and 1998 as part of the observational study component, and SOL most recently from 2009 to 2012. Another dissimilarity between studies is the age range: ARIC and WHI representing mostly older participants >40 years, SOL comprising adults ages 18-76 years, and CARDIA representing only younger adults less than 36 years of age. All studies employed different types of food frequency questionnaires with the exception of SOL which used a 24-hour food recall to determine dietary intake. Variability in dietary intake measurements likely results from differences in methodology as well as from era of the study and age of study participants. The highest sodium, potassium, and caloric intake were seen in the youngest CARDIA cohort, and the lowest intakes were seen in the older ARIC cohort. BP also followed a similar trend with much lower BP and hypertension prevalence (14%) in younger cohorts and higher BP and hypertension prevalence (30-60%) seen in the older cohorts of ARIC, SOL, and WHI. Due to the possibility of sodium underestimation in the ARIC cohort, a sensitivity analysis excluding ARIC participants was completed in additional to the main analysis.

In evaluating the phenotype-phenotype associations of sodium and potassium intake on BP, we found no evidence of significant interaction effects between sodium and potassium on BP outcomes within race/ethnic groups. Moreover, interactions between sodium:potassium ratio and sodium category did not show significant effects. The closest nominally significant interaction was observed between sodium:potassium ratio and high sodium category on DBP in Blacks ($\beta = 1.2$, $p = 0.049$). Specifically, while DBP increased slightly with sodium:potassium ratio among those with low sodium intake, a markedly stronger positive association between sodium:potassium ratio and DBP was observed in participants with the high sodium intake (Figure 1). No other interactions between dietary intake factors showed significant effect on BP outcomes.

In terms of main effects of dietary intake on BP outcomes, sodium:potassium ratio did show highly significant positive associations with SBP, DBP, and hypertension among non-Whites (all $p<7.89x10\text{-}06$, see Table 3). Specifically, for each 1 unit increase in the sodium:potassium ratio, Blacks showed a 2.1 mmHg rise in SBP and Hispanics showed a 1.4 mmHg increase in SBP, 1.0 mmHg increase in DBP, and a 3% increase in the odds of being hypertensive. For each of these associations, there was a consistently positive (and nominally significant effect for SBP and hypertension) across all self-reported ancestry groups. Of the 14 nominally significant associations, 8 were associated with sodium:potassium ratio (all higher DBP mmHg, SBP mmHg or hypertension odds with more

intake), 5 with potassium (all lower DBP mmHg or hypertension odds with more intake), and only 1 with sodium intake (higher SBP mmHg with more intake).

In evaluating gene-environment interaction of BP-related SNPs with sodium and potassium intake on BP, we found no experiment-wide significant interactions between SNPs and dietary measures (Table 4). All nominally significant interactions are shown in figures stratified by ancestry group (Figure 2, Figure 3). The most significant SNP-diet interaction was for the interaction of rs12046278-T (CASZ1) on Chr 1 with both sodium (p =1.7 x 10-04) and potassium (p =1.3 x 10-04) intake on DBP in Hispanics (Figure 4). Both interactions similarly affected DBP such that higher sodium intake or higher potassium intake lessened the SNP-associated increase in DBP seen in participants with low intake. Another CASZ1 variant rs880315-T showed a similar interaction effect in the same direction on DBP in Hispanics but with slightly higher p-values (sodium p = 5.4 x 10-04, potassium p = 4.6 x 10-04). Nominally significant interactions were also observed for SBP in Hispanics between rs12046278-T and sodium (p=1.1 x 10-03) and potassium (p=9.3 x 10-04). However, while more sodium intake further increased SBP among participants with one or more T alleles at rs12046278, higher potassium intake lessened the SBP-SNP effect. Similarly, rs12046278-T also showed a significant interaction with sodium:potassium ratio on DBP (p=4.6x10-04), indicating increased intake of sodium:potassium increases the harmful effect of the SNP seen in participants with low sodium intake. CASZ1 variant rs880315-T showed similar significant interactions between sodium:potassium ratio with

DBP in Hispanics (p = 4.6x10-04). No other self-reported ancestry groups saw consistently significant results at the rs12046278 or rs880315 loci.

There was a potential interaction effect of SV2C associated variant rs6453204-A on Chr 5 in Whites for DBP with sodium (p = 8.6 x 10-03), potassium (p = 2.7 x 10-03), and the sodium:potassium ratio (p = 4.2 x 10-03). While the SNP effect from additional A alleles imparted lower DBP among those with low sodium intake, high sodium intake switched the direction of the SNP effect to increase DBP. As for the potassium interaction, the more potassium intake the larger the decrease in DBP associated with the allele. Furthermore, increases in intake of sodium:potassium ratio attenuated the protective effect from having one or more A alleles at the rs6453204 locus. Whites also saw similar effects on the odds of hypertensive in dietary interactions with rs12195230-C (KLHL32) on Chr 6 such that high sodium intake imparted larger odds of hypertension among participants with the allele (p = 3.9 x 10-03) while high potassium intake reduced the SNP-associated odds of hypertension compared to participants with low potassium diet (p = 2.5 x 10-03).

In Blacks, 2 loci showed potential interaction effects on DBP between SNPs and all dietary variables: rs6782531-C (FHIT) on Chr 3 and rs11222084-A (LOC646383) on Chr 11. In participants with low sodium or low potassium intake, rs6782531-C (Chr 3 FHIT) was associated with lower DBP. However, high sodium intake attenuated this lower DBP-SNP

effect (p = 5.3 x 10-03), high potassium magnified this lower DBP-SNP effect (p = 2.7 x 10-03), and thus participants with high sodium:potassium ratio showed an attenuated lowering DBP-SNP effect (p = 3.4 x 10-04). Dietary intake had a consistent effect on rs11222084 such that increases in sodium (p = 1.5 x 10-03) or potassium (p = 3.4 x 10-03) both lessened the overall decrease in DBP associated with additional A alleles at the rs11222084 locus. However, when considering sodium and potassium together the lower DBP-SNP effect was magnified in those with increased intake of sodium:potassium ratio (p = 5.6 x 10-04).

Two SNPs were found to be highly associated with dietary intake interactions for SBP and hypertension in Blacks. Interactions with rs13178964-A (RAB9BP1) on Chr 5 showed varied association with SBP in Blacks for both sodium (p = 4.2 x 10-03) and potassium (p = 5.3 x 10=03) intake. While the underlying SNP effect imparted decreases in SBP in participants with low sodium or potassium intake and one or more A alleles, the impact of increased sodium and potassium intake in this context are opposite from what may be expected. Specifically, high sodium intake amplified the SNP associated SBP decrease while high potassium intake attenuated the SNP associated SBP decrease. Similar impact was seen on the odds of hypertension with dietary interactions with rs6495122 (CPLX3 - ULK3) on Chr 15. High sodium intake increased the odds of hypertension among participants with the allele and, while the SNP was associated with lower odds of hypertension in participants with low potassium intake, participants with high potassium showed evidence for an

increased odds of hypertension associated with the SNP. Similarly, dietary interactions with rs16982520 (ZNF831) on Chr 20 also showed this unintuitive effect on the odds of hypertension in Hispanics: the lower odds of hypertension associated with the SNP was enhanced in participants with high sodium intake ($p = 9.1 \times 10\text{-}03$) but diminished in participants with high potassium intake ($p = 7.7 \times 10\text{-}03$).

Lastly, we investigated possible BP-related SNP associations with dietary intake measures in hopes of elucidating mechanistic pathways for the established SNP-BP relationships. No experiment-wide significant findings were found, but nominally significant associations were found with 63 SNPs (Table 4). The most significant association demonstrated lower sodium:potassium ratio in Whites with the T allele at rs2014912 (ARHGA24) on Chr 4 ($\beta = -0.01$, $p = 1.4 \times 10\text{-}04$) (Figure 5). This effect was heterogeneous across ancestry groups with Blacks having a similar negative T allele effect but Hispanics with a positive effect (Cochran's $Q = 9.4$, $p = 8.9 \times 10\text{-}03$).

There were SNPs highly associated with variation in dietary intake. The variant rs1530440-T (C10orf107) on Chr 10 was associated with lower potassium ($\beta = -57.8$, $p = 1.1 \times 10\text{-}03$) and higher sodium:potassium ratio ($\beta = 0.03$, $p = 3.3 \times 10\text{-}03$) in Blacks. Moreover, two SNPs were associated with lower sodium intake in Blacks: s11891401-A (PRPS1P1) on Chr 2 ($\beta = -20$, $p = 1.5 \times 10\text{-}03$) and rs2782980-T (LOC10537) on Chr 10 ($\beta = -17$, $p = 3.5 \times 10\text{-}03$). This same SNP, rs2782980-T, also showed nominally significant interactions with

dietary intake on BP levels and hypertension status in all race groups, although with differing effect directions (Table 4). There were 2 different SNPs among Hispanics that showed association to lower sodium: rs10931896-T (LOC10537) on Chr 2 (β = -29.6, p = 3.7 x 10-03) and rs6015450-A (ZNF831) on Chr 20 (β = -49.9, p = 4.6 x 10-03). Among Whites one additional SNP, -rs2014912-T (ARHGAP2) on Chr 4, showed high association with decreased sodium intake (β = -18, p = 2.4 x 10-03). All of these SNPs showed significant heterogeneity of effects across self-reported ancestry group (Cochrane's Q $p<0.05$ for all except rs2014912 and rs2782980 $p<0.1$). In addition, no apparent associations were seen between the first 5 ancestry principal components and dietary intake variables (Figures 6-8).

Allele frequencies at each locus often varied between self-reported ancestry groups potentially impacting the power to detect associations between SNPs and outcomes (Figure 2, Figure 3). Specifically, effects related to rs12046278 and rs880315 (both markers of CASZ1) were only seen in Hispanics who had coded allele frequency (CAF) near 50% while the CAF in other ancestry groups ranged from 15-35%. Conversely, associations with rs6453204 on Chr 5 only in Whites were seen despite high CAF (>80%) in all ancestry groups. Similarly, associations with rs11222084 (LOC646383) were found only among Blacks while no associations were found in Hispanic or Whites despite common CAF of 20-40% in all ancestry groups. rs2782980 CAF was common in all ancestry groups and showed significant dietary interactions with all outcomes in all ancestry groups. In this situation,

both the power from the CAF and true SNP x diet interaction effect size may both assist in the detection of a statistically significant association.

DISCUSSION

In this dissertation, we have shown that dietary intake of sodium and potassium are highly associated with SBP, DBP, and hypertension particularly in non-Whites across four separate cohort studies. Moreover, the association between BP and some SNPs have marginal evidence for potential modulation by sodium and potassium intake. These interaction effects between diet, gene, and BP were not consistent across racial ancestry groups, indicating the need for more stratified or advanced analysis techniques that takes into account ancestral admixture.

The most nominally significant interaction between dietary intake and SNPs affected DBP in Hispanics. Specifically, this interaction was seen with the T allele of SNP rs12046278, a marker for gene CASZ1 on chromosome 1. While high intake of both sodium and potassium decreased the SNP associated rise in DBP, high sodium increased and high potassium decreased the SNP associated rise in SBP. This SBP relationship with diet is more what would be expected to occur knowing the general impact shown by potassium lowering and sodium intake increasing BP. CASZ1 has shown previous association with an increase in SBP in Europeans with replication among Europeans with additional minor alleles at rs12046278 (Levy et al., 2009). Recent replication in two female-only European cohorts observed association with SBP but not with DBP or hypertension (Ho et al., 2011; Won, Ehret, Chakravarti, & Olshen, 2011). However, no experiment-wide significance with any BP

phenotypes was found in a recent validation study with an African ancestry cohort (Fox et al., 2011). No other studies to date have examined this SNP in a Hispanic population. CASZ1 encodes a zinc finger transcription factor potentially related to blood vessel assembly and morphogenesis (Liu et al., 2014). Liu et al recently developed a knockout mouse model and determined that CASZ1 is critical to mammalian heart development, specifically relating CASZ1 to congenital heart disease through decreased cardiomyocyte proliferation.

As for any genetic associations with dietary intake, the closest nominally significant SNP was rs2014912-T showing increased sodium:potassium ratio in Whites. This SNP is located in an intron of ARHGAP24 on Chr 4 that has shown previous association with SBP increase in Euro/Asians by Kato et al (Kato et al., 2015). Mechanistic studies have shown this intron variant to be related to podocyte formation in the kidney and to the development of proteinuric kidney diseases in humans as well (Akilesh et al., 2011). Through the creation of mouse knockdown podocyte cell lines, Akilesh et al showed ARHGAP24 was highly expressed in podocytes and upregulated as the cells differentiate in vivo. Earlier work by Ohta et al also confirmed that the highest level of ARHGAP24 transcript was expressed in the kidney and this GTPase-activating protein for Rac1 specifically suppresses lamellipodia formation and cell spreading downstream of RhoA signaling which plays a role in the vasoconstriction characteristic of hypertension (Lee, Webb, & Jin, 2004; Ohta, Hartwig, & Stossel, 2006). Moreover, Rac1 has been shown to mediate

mineralocorticoid receptor activation in several animal models of salt-sensitive hypertension and kidney disease(Nagase & Fujita, 2013).

There was substantial variability of results across ancestry groups with most significant results detected only in one ancestry group. Despite lack of experiment-wide significance for the main hypotheses of this study, we have shown important racial heterogeneity in allele frequency, dietary intake, and BP that should be accounted for in future studies. While it is known that there are important effects of diet (Benjamin et al., 2017; Sacks et al., 2001; Strom et al., 2013) and genetic admixture on BP (Franceschini et al., 2011; Wojcik et al., 2019), a deeper understanding of these effects can only be obtain when examined in a large sample stratified by race/ancestry group.

In this study, we chose to focus on SNPs previously shown in the literature to be associated with BP in GWAS studies assuming these SNPs were most likely to show a significant interaction effect with diet; and such a strategy would improve power by controlling the number of tests. However, most of these chosen SNPs were only studied and validated in European and Asian populations. Only 47 SNPs of the 186 chosen were tested or validated in African ancestry population. Moreover, none of the SNPs had been studied in Hispanic populations. More recently discovered SNPs in large trans-ancestry analysis may provide more signal to detect these diet-genetic interaction effects on BP (Giri et al., 2019).

A recent study by Li et al examined a similar question of urinary sodium excretion interactions with SNPs affecting BP outcomes(Li et al., 2017). Li et al's study differed from the current study primarily due to the subset of chosen SNPs examined as well as population ancestry (only GENSalt and MESA Asian cohorts) and use of urinary excretion instead of intake. However, the authors did examine the *ARHGAP42* variant rs633185 on Chr11 showing a significant sodium intake x SNP interaction on pulse pressure. While we did not examine pulse pressure as an outcome, we did show nominally significant sodium intake x SNP interaction in Blacks on DBP and hypertension for this variant as well. Specifically, high sodium intake increased the protective effect of the SNP seen in participants with low sodium intake.

Urinary sodium and potassium excretion are often more accurate measures of renal load but were not available for the majority of this study sample. Originally, we had planned to confirm any significant findings using sodium and potassium excretion in a subset of patients who underwent 24-hour urine collection analysis. Unfortunately, excretion data was only available for 485 whites and 558 Blacks from CARDIA, while our most significant findings were among Hispanics. Moreover, we failed to find any experiment-wide significant results to confirm. The recent study by Li et al reported significant sodium and SNP interactions on BP using sodium excretion measures instead of dietary intake measures(Li et

al., 2017). However, the findings in Li et al are not directly comparable to this study since our chosen SNPs to investigate did not considerably overlap.

While we failed to find experiment-wide significant results we were able to confirm the utility of dietary intake data to correlate with BP across multiple large, observational cohorts, specifically in Black and Hispanic populations using the sodium:potassium ratio (Table 3). While there are many criticisms of retrospective dietary intake assessment, we have employed multiple recommended strategies to mitigate the most commonly discussed issues (Subar et al., 2015). To address systematic underestimation of dietary intake by nutritional data surveys, we used total energy intake as a covariate in models to improve the risk estimation of other dietary intake variables. To account for variation between studies in measurement technique, we employed meta-analysis techniques to first estimate within study effects and combine effects only if homogenous results. Moreover, to ensure that underestimation of sodium intake from the ARIC study did not skew results, we conducted a sensitivity analysis excluding ARIC estimates from the meta-analysis and noted findings that remained significant. Additional strategies used to ameliorate these issues included excluding participants with extreme caloric based on each study's guidelines, winzorizing continuous dietary intake variables, and dichotomized sodium and potassium by medians within each study. While the variability of dietary measures may be a major hurdle

in achieving powerful results in the interaction analysis, they are still useful measures when carefully employed.

Lastly, in the *a priori* power analyses we assumed a 3-5mmHg effect from the interaction between dietary intake and a SNP. However, the actual observed effect size from the interaction was much smaller; closer to ~1mmHg change in BP due to low or high intake adjustment to allele effect. This smaller effect size is likely the primary reason for the lack of experiment-wide significance found in this study. In addition, only a subsample of SNPs was chosen, many of them not validated in trans-ancestry studies. In the future, an alternate choice of SNPs with previously demonstrated trans-ancestry effects on BP analyzed in a larger sample would likely demonstrate significant interactions with dietary intake measures.

CONCLUSION

While dietary intake is likely an intermediate phenotype mediating gene-BP relationships, the effects are small and difficult to detect with highly variable intake measures. Sodium and potassium excretion measures may provide more precise estimates but reflect similarly small modulating effects on BP. As of now, no studies have demonstrated that adding information from the underlying mechanisms of nutritional intake or excretion on BP actually produces significantly more precise BP phenotypes to associate with genetic markers. This study does provide more evidence of the heterogeneity of BP phenotypes among ancestry groups, particularly as they relate to nutritional intake and genetics. The findings of higher association between nutritional intake and BP among non-White participants support current guideline recommendations of sodium sparing diets particularly in Black and Hispanic hypertensive patients. Among Hispanics, the CASZ1 gene may play a part in the modulation of BP by both sodium and potassium. In order to build on this work towards elucidating the physiologic pathways between diet, genetics, and BP future studies should focus on a broader set of SNPs identified through trans-ethnic studies with large sample sizes that may be able to detect small population level dietary effects on BP.

TABLES

Table 1. Model equations

Specific Aim 1	
Is sodium or potassium intake associated with SNP?	$sodium = B_0 + B_1SNP + covariates$ $potassium = B_0 + B_1SNP + covariates$ $soidum:potassium = B_0 + B_1SNP + covariates$
Specific Aim 2	
Is BP associated with sodium, potassium, or sodium:potassium ratio? Is the effect of sodium:potassium ratio on BP consistent across sodium intake?	$systolic\ BP = B_0 + B_1sodium + B_2potassium + B_3sodium * potassium + covariates$ $systolic\ BP = B_0 + B_1sodium + B_2sodium:potassium + B_3sodium:potassium * sodium + covariates$ $diastolic\ BP = B_0 + B_1sodium + B_2potassium + B_3sodium * potassium + covariates$ $diastolic\ BP = B_0 + B_1sodium + B_2sodium:potassium + B_3sodium:potassium * sodium + covariates$ $logit(HTN) = B_0 + B_1sodium + B_2potassium + B_3sodium * potassium + covariates$ $logit(HTN) = B_0 + B_1sodium + B_2sodium:potassium + B_3sodium:potassium * sodium + covariates$
Specific Aim 3	
Is BP-SNP association modified by sodium, potassium, or sodium:potassium ratio?	$systolic\ BP = B_0 + B_1SNP + B_2sodium + B_3potassium + B_4SNP * sodium + B_5SNP * potassium + covariates$ $diastolic\ BP = B_0 + B_1SNP + B_2sodium + B_3potassium + B_4SNP * sodium + B_5SNP * potassium + covariates$ $logit(HTN) = B_0 + B_1SNP + B_2sodium + B_3potassium + B_4SNP * sodium + B_5SNP * potassium + covariates$ $systolic\ BP = B_0 + B_1SNP + B_2sodium:potassium + B_3SNP * sodium:potassium + covariates$ $diastolic\ BP = B_0 + B_1SNP + B_2sodium:potassium + B_3SNP * sodium:potassium + covariates$ $logit(HTN) = B_0 + B_1SNP + B_2sodium:potassium + B_3SNP * sodium:potassium + covariates$

SNP: single nucleotide polymorphism, BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, HTN: hypertension, SA: specific aim

Covariates in all models were sex, age, BMI category, total protein intake, total calorie intake, serum creatinine, and the first 5 ancestry principal components.

All dietary intake measures were analyzed as continuous variables in SA1. Sodium and potassium intake were analyzed as binary variables and sodium:potassium ratio was analyzed as a continuous variable in SA2 and SA3.

Table 2. Participant characteristics by study cohorts

	ARIC	CARDIA	SOL	WHI
Study type	Cohort	Cohort	Cohort	Cohort
Number with phenotype	15,121	4,144	11,516	46,188
Number with phenotype and genotype	11,747	2,322	11,449	14,107
Black	2,661	744		5,228*
Hispanic			11,449*	3,378*
White	9,086	1,578		5,501
SNPs available	183	183	180	184
Era (Study Visit)	1989 (V1)	1987 (V2)	2009-2012 (V1)	1994-1998 (OS V1)
Median age	54	26	47	65
Age range	44-66	17-36	18-76	49-81
Percent female	55%	54%	59%	100%
Median SBP	123	108	122	134
SBP range	61-259	74-166	74-246	80-235
Median DBP	75	68	74	80
DBP range	10-143	15-111	40-134	40-125
Percent HTN	37%	14%	30%	60%
Median sodium	1390.91	3153.7	2946.0145	2472.295
Sodium range	210-5214	506-14291	47-21761	343-11638
Median potassium	2506.62	3010.7	2351.056	2346.974
Potassium range	382-9097	512-19202	155-14472	325-9384
Median sodium:potassium ratio	0.56	1.06	1.29	1.08
Sodium:potassium ratio range	0-2	0-4	0-9	0-3

*All genotypes imputed to 1000 Genomes Phase 3 from GWAS files except SOL and Black and Hispanic WHI genotypes imputed to 1000 Genomes Phase 3 from Illumina Metabochip.
Note: race, age, sex, SBP, DBP, hypertension, sodium, potassium, and sodium:potassium ratio statistics are within the sample of participants with all phenotype and genotype data available.

Table 3. Blood pressure phenotype associations to dietary intake measures in each racial ancestry group (Specific Aim 2)

Outcome	Race	NObs	NStudies	Factor	Beta	SE	p-value	I^2	Q Hetero Statisitc	Q Hetero p-value	which studies
SBP*	Black	13829	3	POT	-0.975	0.402	1.541E-02	0.000	0.469	7.909E-01	WHI ARIC CARDIA
SBP*	Hispanic	14919	2	POT	-1.271	0.348	2.634E-04	0.000	0.013	9.082E-01	WHI SOL
SBP	White	24832	3	POT	-0.212	0.278	4.440E-01	0.000	0.343	8.425E-01	WHI ARIC CARDIA
SBP	Black	13829	3	SOD	-0.053	0.438	9.032E-01	0.000	0.519	7.716E-01	WHI ARIC CARDIA
SBP	Hispanic	14919	2	SOD	0.446	0.353	2.067E-01	0.000	2.051	1.521E-01	WHI SOL
SBP	White	24832	3	SOD	0.044	0.335	8.957E-01	0.000	0.188	9.105E-01	WHI ARIC CARDIA
SBP*	**Black**	**13829**	**3**	**SODPOTRATIO**	**2.090**	**0.434**	**1.488E-06**	**0.000**	**2.021**	**3.640E-01**	**WHI ARIC CARDIA**
SBP*	**Hispanic**	**14919**	**2**	**SODPOTRATIO**	**1.395**	**0.212**	**4.669E-11**	**0.000**	**0.833**	**3.614E-01**	**WHI SOL**
SBP*	White	24833	3	SODPOTRATIO	1.118	0.446	1.219E-02	0.001	2.182	3.359E-01	WHI ARIC CARDIA
DBP	Black	13829	3	POT	-0.395	0.326	2.248E-01	27.401	4.022	1.339E-01	WHI ARIC CARDIA
DBP*	Hispanic	14919	2	POT	-0.556	0.222	1.214E-02	0.000	0.430	5.119E-01	WHI SOL
DBP	White	24832	3	POT	-0.239	0.172	1.663E-01	0.004	2.619	2.699E-01	WHI ARIC CARDIA
DBP	Black	13829	3	SOD	-0.378	0.284	1.827E-01	0.000	1.380	5.017E-01	WHI ARIC CARDIA
DBP*	Hispanic	14919	2	SOD	0.496	0.225	2.748E-02	0.001	1.270	2.597E-01	WHI SOL
DBP	White	24832	3	SOD	-0.357	0.308	2.471E-01	44.318	5.419	6.658E-02	WHI ARIC CARDIA
DBP	Black	13829	3	SODPOTRATIO	1.284	0.901	1.541E-01	83.008	14.443	7.308E-04	WHI ARIC CARDIA
DBP*	**Hispanic**	**14919**	**2**	**SODPOTRATIO**	**0.950**	**0.137**	**4.274E-12**	**0.000**	**0.297**	**5.856E-01**	**WHI SOL**
DBP*	White	24833	3	SODPOTRATIO	0.815	0.284	4.097E-03	0.001	2.532	2.820E-01	WHI ARIC CARDIA
HTN*	Black	13829	3	POT	-0.023	0.010	2.195E-02	0.067	2.460	2.923E-01	WHI ARIC CARDIA
HTN*	Hispanic	14919	2	POT	-0.017	0.009	4.671E-02	0.000	0.490	4.841E-01	WHI SOL
HTN	White	24832	3	POT	-0.012	0.007	1.016E-01	0.000	0.395	8.208E-01	WHI ARIC CARDIA
HTN	Black	13829	3	SOD	0.021	0.015	1.587E-01	26.288	4.159	1.250E-01	WHI ARIC CARDIA
HTN	Hispanic	14919	2	SOD	0.012	0.013	3.676E-01	31.052	3.730	5.346E-02	WHI SOL
HTN	White	24832	3	SOD	-0.002	0.009	8.325E-01	0.000	1.643	4.397E-01	WHI ARIC CARDIA
HTN*	Black	13829	3	SODPOTRATIO	0.041	0.011	2.495E-04	0.000	1.696	4.282E-01	WHI ARIC CARDIA
HTN*	**Hispanic**	**14919**	**2**	**SODPOTRATIO**	**0.025**	**0.005**	**1.904E-06**	**0.028**	**2.248**	**1.338E-01**	**WHI SOL**
HTN*	White	24833	3	SODPOTRATIO	0.036	0.014	9.014E-03	16.331	3.355	1.868E-01	WHI ARIC CARDIA

* nominal significance, p<0.05

*** experiment-wide significance, p<7.89x10-06**

SBP: systolic blood pressure, DBP: diastolic blood pressure, HTN: hypertension, SOD: sodium, POT: potassium, SODPOTRATIO: sodium-to-potassium ratio

Table 4. Summary of nominal SNP associations with dietary intake (Specific Aim 1) and nominal BP associations with dietary intake and SNP interaction (Specific Aim 3)

SNP	Chr	Mapped Gene	Nominal Dietary Intake Association*	Nominal BP Association with Dietary Intake x SNP Interaction	Previous SNP Effect in GWAS†
rs10745332	1	CAPZA1		HTN~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs17030613	1	CAPZA1	SOD(Black-)	SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake)	harmful/ protective
rs12046278	1	CASZ1		SBP~SODxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) HTN~SODxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake)	protective
rs880315	1	CASZ1	POT(Black-)	SBP~SODxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake)	harmful

				DBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake)	
rs4077408	1	HHAT		SBP~SODxSNP (White, Quantitative: High intake more protective SNP effect than low intake) SBP~POTxSNP (White, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	harmful
rs1330225	1	LOC126987 - LOC105378887		HTN~SODPOTRATIOxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake)	protective
rs309064	1	LPPR5		HTN~SODPOTRATIOxSNP (White, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs17367504	1	MTHFR	POT(Black+)		protective
rs3768939	2	AGAP1		SBP~SODxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake)	protective
rs4665630	2	KLHL29		SBP~SODxSNP (White, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (White, Quantitative: High intake less protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (White, Quantitative: High intake more protective SNP effect than low intake) HTN~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake)	
rs825937	2	LINC01249 - RNU6-	POT(Black-)		harmful

		649P			
rs7604423	2	LOC100506047	POT(Black-) SODPOTRATIO(Black+)		protective
rs7565329	2	LOC101927701 - LOC402076		SBP~SODxSNP (Hispanic, Qualitative: High intake switches to harmful SNP effect from protective in low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) DBP~SODxSNP (Hispanic, Qualitative: High intake switches to harmful SNP effect from protective in low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake)	protective
rs897876	2	LOC105369166	POT(White-)	SBP~SODPOTRATIOxSNP (White, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	harmful
rs10931896	2	LOC105373833 - SPATS2L	SOD(Hispanic-) SODPOTRATIO(Hispanic-)	SBP~SODxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake) SBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs7577262	2	MSL3P1 - TRPM8	POT(Black+) SODPOTRATIO(Black-)		protective
rs11891401	2	PRPS1P1 - CYP2C56P	SOD(Black-)	DBP~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) DBP~POTxSNP (Black, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs4638749	2	SULT1C3 - WASF1P1	SODPOTRATIO(Black+)	SBP~SODxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) DBP~SODxSNP (Hispanic, Qualitative: High intake switches to protective SNP effect from harmful in low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake),	protective
rs13067306	3	ARMC10P1 - LOC105373992		SBP~POTxSNP (Hispanic, Qualitative: High intake switches to protective SNP effect from harmful in low intake) SBP~SODPOTRATIOxSNP (Hispanic,	harmful

				Qualitative: High intake switches to harmful SNP effect from protective in low intake)	
rs9810888	3	CACNA1D		SBP~SODxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake)	harmful
rs6782531	3	FHIT		SBP~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) DBP~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) DBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less protective SNP effect than low intake)	protective
rs319690	3	MAP4		DBP~SODxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake) DBP~POTxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake), NA,	harmful
rs419076	3	MECOM	POT(Black+)	SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) DBP~SODxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) DBP~POTxSNP (Black, Quantitative: High intake less harmful SNP effect than low intake) HTN~SODPOTRATIOxSNP (White, Quantitative: High intake less protective SNP effect than low intake)	harmful

rs448378	3	MECOM	POT(Black-)	SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) DBP~SODxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) DBP~POTxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) HTN~SODPOTRATIOxSNP (White, Quantitative: High intake less harmful SNP effect than low intake)	protective
rs1918974	3	MECOM, LOC105374205	SOD(Black-)	SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) HTN~POTxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake)	protective
rs13082711	3	UBA52P4 - LOC105377005	SOD(Hispanic+)		protective
rs820430	3	UBA52P4 - LOC105377005	SODPOTRATIO(Black+)	SBP~POTxSNP (White, Quantitative: High intake less protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (White, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs3774372	3	ULK4		SBP~SODPOTRATIOxSNP (Black, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs9815354	3	ULK4		SBP~SODPOTRATIOxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake)	harmful
rs2014912	4	ARHGAP24	SOD(White-) SODPOTRATIO(White-)	SBP~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs13143871	4	GUCY1A3		DBP~SODxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake),	harmful
rs13139571	4	GUCY1A3,		DBP~SODxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low	harmful

		LOC107984032		intake) HTN~SODxSNP (White, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	
rs871606	4	LOC100129728 - RPL21P44	SOD(Black+)	HTN~SODxSNP (White, Quantitative: High intake less protective SNP effect than low intake) HTN~POTxSNP (White, Quantitative: High intake less protective SNP effect than low intake) HTN~SODPOTRATIOxSNP (White, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	harmful
rs991316	4	LOC102723576		HTN~SODPOTRATIOxSNP (White, Quantitative: High intake less harmful SNP effect than low intake)	
rs12642634	4	LOC105377468 - LOC105377469	POT(Black+ hispanic+) SODPOTRATIO(Black-)	HTN~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) HTN~POTxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) HTN~SODPOTRATIOxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake)	harmful
rs11099098	4	PRDM8 - FGF5		DBP~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) DBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) HTN~SODPOTRATIOxSNP (White, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	harmful
rs1458038	4	PRDM8 - FGF5		DBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) HTN~SODPOTRATIOxSNP (White, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	harmful
rs16998073	4	PRDM8 - FGF5		HTN~SODPOTRATIOxSNP (White, Qualitative: High intake switches to	harmful

				protective SNP effect from harmful in low intake)	
rs1902859	4	PRDM8 - FGF5		DBP~POTxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less harmful SNP effect than low intake) HTN~SODPOTRATIOxSNP (White, Qualitative: High intake switches to protective SNP effect from harmful in low intake)	harmful
rs13107325	4	SLC39A8	SOD(Hispanic-)	HTN~SODxSNP (Hispanic, Qualitative: High intake switches to harmful SNP effect from protective in low intake) HTN~POTxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake)	protective
rs6825911	4	ZNF969P - ENPEP		SBP~SODPOTRATIOxSNP (Hispanic, Qualitative: High intake switches to protective SNP effect from harmful in low intake) DBP~SODxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (Hispanic, Qualitative: High intake switches to protective SNP effect from harmful in low intake)	harmful
rs9313772	5	LOC101927697		DBP~SODxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake) DBP~POTxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less harmful SNP effect than low intake)	protective
rs13178964	5	LOC105379111 - RAB9BP1	POT(Black-) SODPOTRATIO(Black+)	SBP~SODxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) SBP~POTxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake)	protective
rs1421811	5	NPR3	SOD(Black-)		protective

rs822127	5	PLCXD3 - TCP1P2		HTN~SODPOTRATIOxSNP (White, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	protective
rs9687065	5	SH3TC2	SOD(White-)		harmful
rs6453204	5	SV2C	POT(Black+)	DBP~SODxSNP (White, Qualitative: High intake switches to harmful SNP effect from protective in low intake) DBP~POTxSNP (White, Quantitative: High intake more protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (White, Quantitative: High intake less protective SNP effect than low intake)	
rs9370524	6	COL21A1		DBP~SODxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs1799945	6	HFE	SOD(Hispanic+)		harmful
rs198846	6	HIST1H4C - HIST1H1T	SOD(Hispanic-)		protective
rs12195230	6	KLHL32		DBP~SODxSNP (Hispanic, Qualitative: High intake switches to protective SNP effect from harmful in low intake) HTN~SODxSNP (White, Quantitative: High intake more harmful SNP effect than low intake) HTN~POTxSNP (White, Qualitative: High intake switches to protective SNP effect from harmful in low intake)	harmful
rs6924906	6	LOC105377871		SBP~SODxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake) SBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake)	protective
rs13209747	6	LOC105377992 - LOC105377989		DBP~SODxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs12195036	6	LOC105378117		SBP~SODPOTRATIOxSNP (White, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	protective

				HTN~SODPOTRATIOxSNP (White, Quantitative: High intake more harmful SNP effect than low intake)	
rs675026	6	OPRM1		HTN~SODxSNP (Black, Quantitative: High intake less harmful SNP effect than low intake) HTN~POTxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) HTN~SODPOTRATIOxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake)	
rs17080102	6	PLEKHG1	SOD(White-)		protective
rs11750990	6	RNU2-8P - SLC25A5 P7	SOD(Black+)	DBP~SODxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake) DBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs2021783	6	TNXB		SBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs17477177	7	LOC1027 24339 - RNA5SP2 36	POT(White-)		protective
rs17428471	7	RPL35P4 - LOC1079 86733	SOD(White+) SODPOTRATIO(White+)	HTN~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) HTN~SODPOTRATIOxSNP (Black, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs7801190	7	SLC12A9		HTN~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake)	
rs12541063	8	LOC1019 27845		HTN~SODPOTRATIOxSNP (Hispanic, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	protective
rs10504249	8	LOC1053 75856		SBP~POTxSNP (White, Quantitative: High intake more protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (White, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs2627282	8	LOC1053 77787, LOC1053 77786		HTN~SODxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	protective

rs11775334	8	MSRA		HTN~SODxSNP (Black, Quantitative: High intake less harmful SNP effect than low intake) HTN~POTxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) HTN~SODPOTRATIOxSNP (Black, Quantitative: High intake less harmful SNP effect than low intake)	harmful
rs2198596	8	SGCZ	POT(Black-) SOD(Hispanic-) SODPOTRATIO(Hispanic-)		protective
rs3118867	9	DAPK1		SBP~POTxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) SBP~SODPOTRATIOxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (White, Quantitative: High intake more protective SNP effect than low intake)	protective
rs17755650	9	LOC107987026 - MTAP	SOD(White-)	HTN~SODxSNP (White, Quantitative: High intake less protective SNP effect than low intake) HTN~POTxSNP (White, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs1530440	10	C10orf107	POT(Black-) SODPOTRATIO(Black+)	DBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (White, Quantitative: High intake less harmful SNP effect than low intake) HTN~SODPOTRATIOxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake)	protective
rs4590817	10	C10orf107	SOD(White+)		harmful
rs12416687	10	C10orf32-ASMT		HTN~SODPOTRATIOxSNP (White, Quantitative: High intake less harmful SNP effect than low intake)	protective
rs4409766	10	C10orf32-ASMT, C10orf32	SODPOTRATIO(Hispanic+)	SBP~POTxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (Hispanic,	harmful

				Quantitative: High intake more protective SNP effect than low intake)	
rs11014166	10	CACNB2	SODPOTRATIO(Black-)		harmful
rs11191548	10	CNNM2	SODPOTRATIO(Hispanic+)	SBP~POTxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake)	harmful
rs1004467	10	CYP17A1	SODPOTRATIO(Hispanic+)	SBP~SODxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) SBP~POTxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs3824755	10	CYP17A1	SODPOTRATIO(Hispanic-)	SBP~POTxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake)	protective
rs7088591	10	LOC105378314 - MRPS35P3		DBP~SODxSNP (White, Quantitative: High intake less harmful SNP effect than low intake) DBP~POTxSNP (White, Quantitative: High intake less harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (White, Quantitative: High intake less harmful SNP effect than low intake) HTN~SODPOTRATIOxSNP (White, Qualitative: High intake switches to protective SNP effect from harmful in low intake)	protective

rs2782980	10	LOC105378492	SOD(Black-)	SBP~POTxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake) SBP~SODxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) HTN~SODxSNP (White, Qualitative: High intake switches to protective SNP effect from harmful in low intake) HTN~POTxSNP (White, Quantitative: High intake more harmful SNP effect than low intake)	protective
rs11191593	10	NT5C2	SODPOTRATIO(Hispanic+)	SBP~SODxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) SBP~POTxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake) HTN~POTxSNP (Black, Quantitative: High intake less harmful SNP effect than low intake)	harmful
rs932764	10	PLCE1	POT(White+)	HTN~SODxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) HTN~POTxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake)	harmful
rs9663362	10	PLCE1	POT(White-)		protective

rs4373814	10	SLC39A12 - CACNB2		SBP~SODxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) DBP~SODxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake)	protective
rs633185	11	ARHGAP42		DBP~SODxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) HTN~SODxSNP (Black, Quantitative: High intake more protective SNP effect than low intake)	harmful/protective
rs7129220	11	CAND1.11	POT(Black-)		protective
rs1943466	11	GRAMD1B		SBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) SBP~SODxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) DBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) HTN~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) HTN~SODPOTRATIOxSNP (Black, Quantitative: High intake less protective SNP effect than low intake)	
rs10832417	11	KCNQ1OT1, KCNQ1	SOD(White-)		protective

rs11222084	11	LOC646383		SBP~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake) DBP~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) DBP~POTxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (Black, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs2196122	11	OR51H1 - OR51H2P		HTN~SODxSNP (Hispanic, Qualitative: High intake switches to protective SNP effect from harmful in low intake) HTN~POTxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) HTN~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake)	harmful
rs11024074	11	PLEKHA7	SODPOTRATIO(Hispanic-)		protective
rs4757391	11	SOX6		SBP~SODxSNP (Hispanic, Qualitative: High intake switches to protective SNP effect from harmful in low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake)	harmful
rs17249754	12	ATP2B1		DBP~SODxSNP (Hispanic, Qualitative: High intake switches to harmful SNP effect from protective in low intake) HTN~SODPOTRATIOxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	harmful/protective
rs2681492	12	ATP2B1		HTN~POTxSNP (White, Quantitative: High intake more protective SNP effect than low	harmful

				intake)	
rs11066280	12	HECTD4	SODPOTRATIO(Hispanic-)		harmful/protective
rs12579720	12	LOC100506393		DBP~POTxSNP (White, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (White, Quantitative: High intake less harmful SNP effect than low intake)	protective
rs35444	12	LOC102723639 - LOC105370003		SBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs11067763	12	LOC105370003	SOD(White+)	DBP~SODxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake) DBP~POTxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake) DBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs7960884	12	OVOS2 - LOC107987168		SBP~SODxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs4842666	12	POC1B - ATP2B1		HTN~POTxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake) HTN~POTxSNP (White, Quantitative: High intake more protective SNP effect than low intake)	harmful
rs2315885	13	MIR5007 - HNF4GP1	SODPOTRATIO(Black+)	SBP~SODxSNP (White, Quantitative: High intake less protective SNP effect than low intake)	harmful
rs8002688	13	PIBF1	SOD(White+)	DBP~SODxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake)	harmful
rs11158609	14	NEDD8, NEDD8-MDP1	POT(White+) SOD(Hispanic+)		
rs10143078	14	SYNJ2BP		DBP~SODPOTRATIOxSNP (Hispanic,	protective

		SYNJ2BP-COX16		Qualitative: High intake switches to protective SNP effect from harmful in low intake)	
rs177848	14	TTC6	SOD(White-)	SBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (Black, Quantitative: High intake less protective SNP effect than low intake)	protective
rs6495122	15	CPLX3 - ULK3		DBP~SODxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) HTN~SODxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) HTN~POTxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	harmful
rs1378942	15	CSK		HTN~SODxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake)	harmful/protective
rs1550576	15	LOC107984724 - ALDH1A2		SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) HTN~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake)	
rs16962897	16	DNAAF1		HTN~SODxSNP (White, Quantitative: High intake less harmful SNP effect than low intake)	protective
rs1862746	16	LOC101927605		DBP~SODPOTRATIOxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake)	
rs2030114	16	LOC102723323 - LOC107984892		HTN~SODxSNP (Hispanic, Quantitative: High intake less harmful SNP effect than low intake) HTN~POTxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) HTN~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake)	protective
rs4150161	16	TAF1C		HTN~SODxSNP (Black, Quantitative: High intake more harmful SNP effect than low intake)	harmful

rs17608766	17	GOSR2		SBP~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) DBP~SODxSNP (Black, Quantitative: High intake less protective SNP effect than low intake) DBP~POTxSNP (Black, Quantitative: High intake less protective SNP effect than low intake)	protective
rs16948048	17	LOC102724596		SBP~SODxSNP (Hispanic, Qualitative: High intake switches to harmful SNP effect from protective in low intake)	harmful
rs747685	17	NXN	SODPOTRATIO(White+)		harmful
rs747687	17	NXN	SODPOTRATIO(White+)		harmful
rs12946454	17	PLCD3		SBP~SODxSNP (Black, Qualitative: High intake switches to harmful SNP effect from protective in low intake) SBP~POTxSNP (Black, Quantitative: High intake more protective SNP effect than low intake) SBP~SODxSNP (White, Quantitative: High intake less harmful SNP effect than low intake) SBP~POTxSNP (White, Quantitative: High intake less harmful SNP effect than low intake)	harmful
rs8065772	17	PRKCA - CACNG5	SODPOTRATIO(White+)	, NASBP~SODxSNP (White, Quantitative: High intake more harmful SNP effect than low intake) SBP~POTxSNP (White, Quantitative: High intake less harmful SNP effect than low intake)	
rs8078051	17	TTYH2	POT(Black-) SODPOTRATIO(Black+)		
rs2217560	18	LOC105372189 - CBLN2	SOD(White+)	HTN~SODPOTRATIOxSNP (White, Quantitative: High intake more harmful SNP effect than low intake)	
rs7233332	18	RAB31	POT(White-)		harmful

rs16964543	19	ZNF536		SBP~SODxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) HTN~SODxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) HTN~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) HTN~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake)	protective
rs2273359	20	NELFCD	SOD(White+)		harmful
rs16982520	20	ZNF831	SOD(Hispanic-)	SBP~SODxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (White, Quantitative: High intake less protective SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) HTN~SODxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) HTN~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake)	protective
rs6015450	20	ZNF831	SOD(Hispanic-) SODPOTRATIO(Hispanic-)	SBP~SODxSNP (White, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (White, Quantitative: High intake less protective SNP effect than low intake) DBP~SODxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake) DBP~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low	harmful

				intake) HTN~SODxSNP (Hispanic, Quantitative: High intake more protective SNP effect than low intake) HTN~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake)	
rs1735151	21	IGSF5	POT(Black+) SODPOTRATIO(Hispanic+)	SBP~SODxSNP (White, Quantitative: High intake less protective SNP effect than low intake) SBP~POTxSNP (White, Quantitative: High intake less protective SNP effect than low intake) SBP~SODPOTRATIOxSNP (White, Quantitative: High intake more protective SNP effect than low intake) DBP~SODxSNP (White, Quantitative: High intake less protective SNP effect than low intake) DBP~POTxSNP (White, Quantitative: High intake more protective SNP effect than low intake) DBP~SODPOTRATIOxSNP (White, Quantitative: High intake more protective SNP effect than low intake)	
rs1475591	21	UBE3AP2 - TIAM1	SOD(Black-) SODPOTRATIO(Black-)	DBP~SODPOTRATIOxSNP (Hispanic, Quantitative: High intake more harmful SNP effect than low intake) HTN~POTxSNP (Black, Qualitative: High intake switches to protective SNP effect from harmful in low intake)	
rs7286472	22	LARGE - LOC105373010	SOD(Black+)	HTN~POTxSNP (Hispanic, Quantitative: High intake less protective SNP effect than low intake),	protective
rs130318	22	PARVB	SODPOTRATIO(Hispanic+)		

SNP: single nucleotide polymorphism identifier based on Human Genome Assembly GRCh37, Chr: chromosome, BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, HTN: hypertension, SOD: sodium, POT: potassium, SODPOTRATIO: sodium-to-potassium ratio

*Association between dietary intake and SNP only listed when nominally significant with ancestry group and direction of effect, increased (+) or decreased (+) intake with each additional coded allele, noted in parentheses.

†Harmful effect defined as increase in SBP, DBP, or odds of hypertension with each additional coded allele; protective effect defined as decrease in SBP, DBP, or odds of hypertension with each additional coded allele.

FIGURES

Figure 1. DBP association with sodium:potassium ratio at low and high sodium intake levels in Blacks (Specific Aim 2)

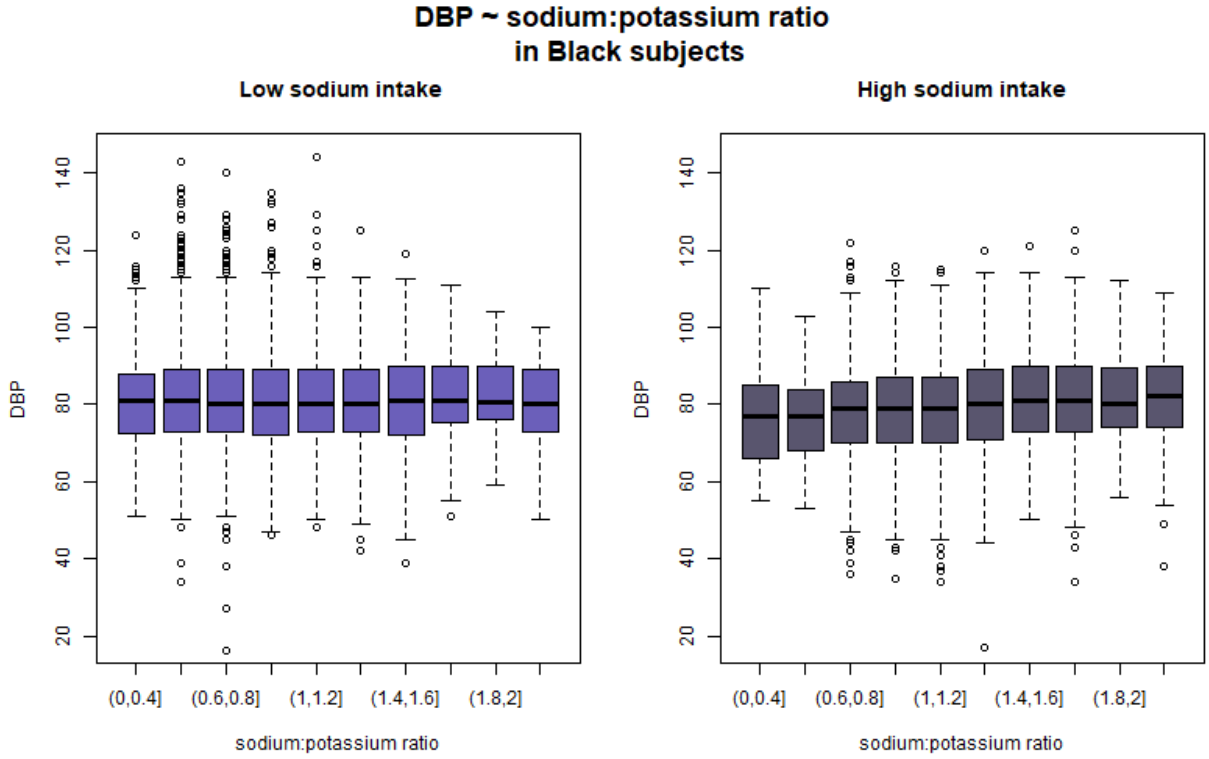


Figure 2. Interaction effects between SNPs and sodium or potassium intake on BP phenotypes (Specific Aim 3)

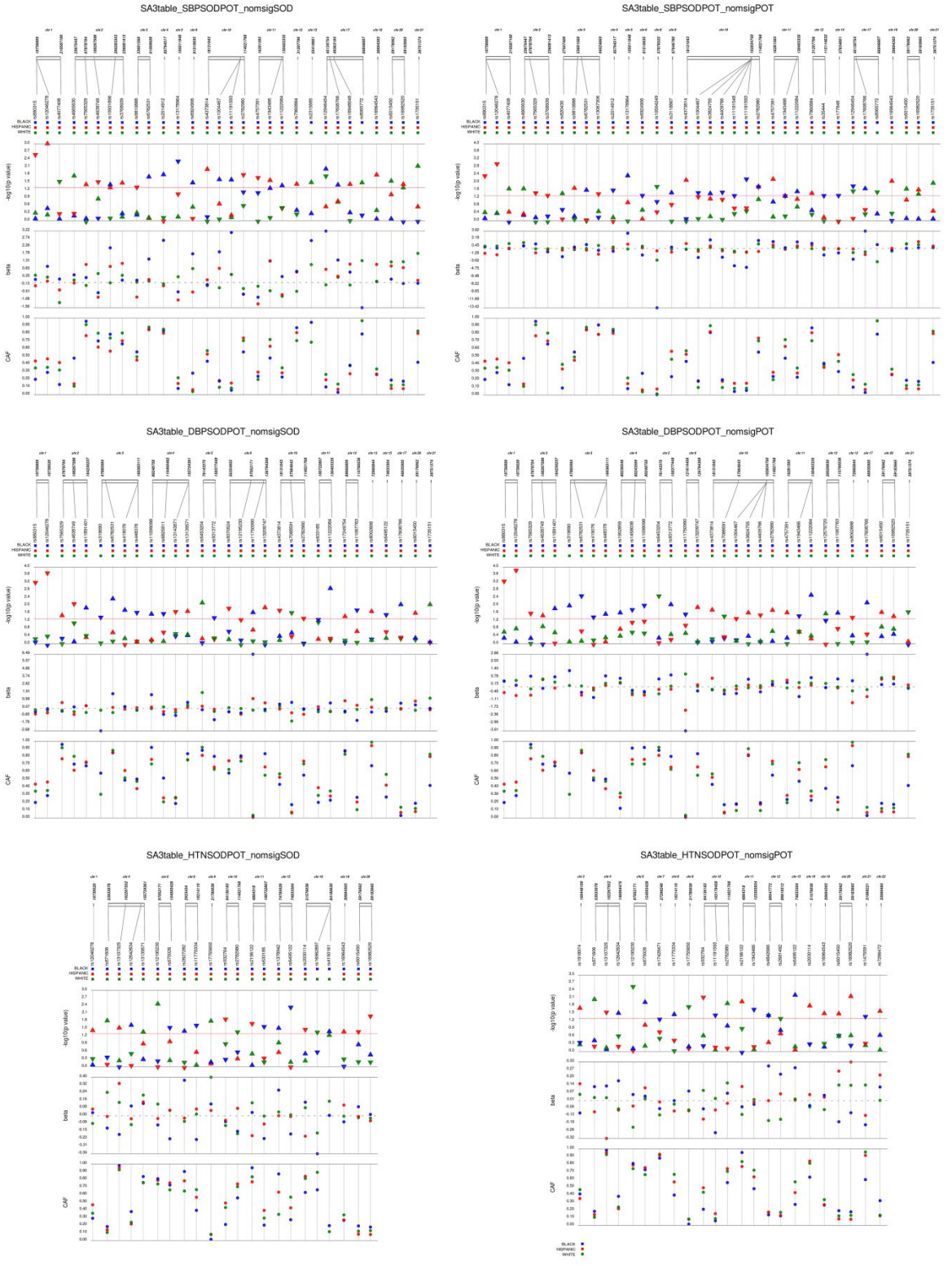


Figure 3. Interaction effects between SNPs and sodium:potassium ratio on BP phenotypes (Specific Aim 3)

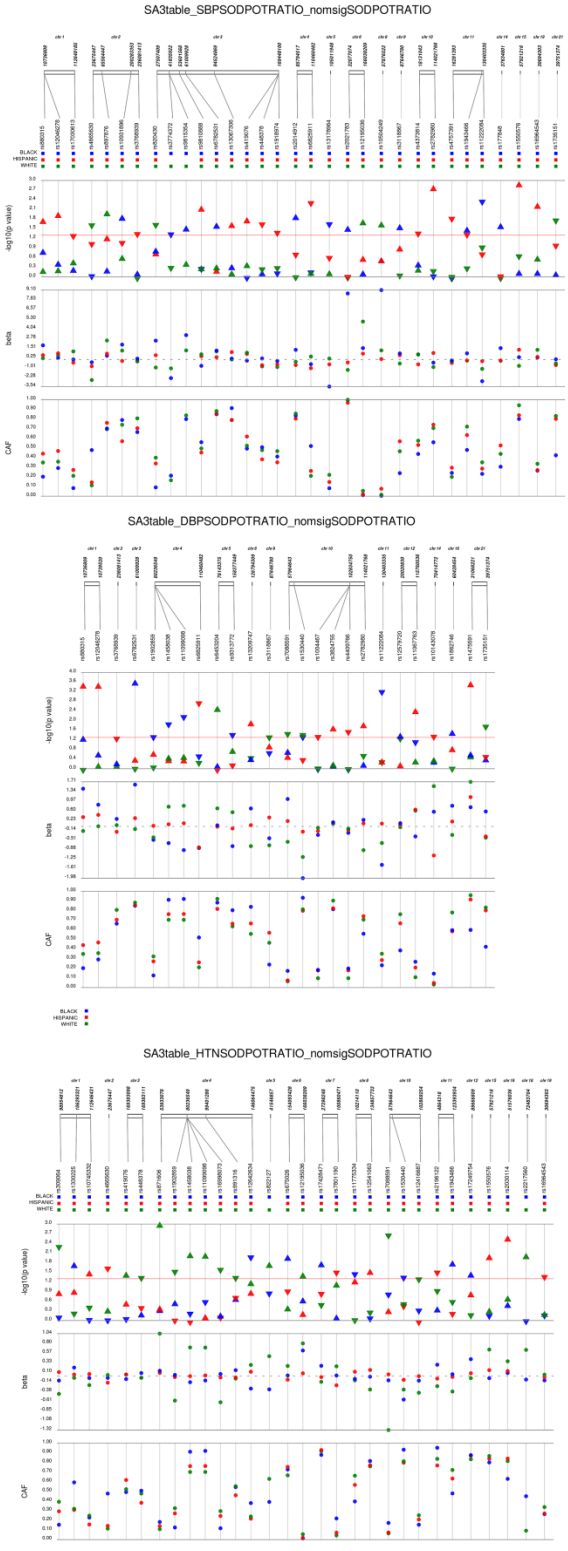


Figure 4. Manhattan plots of interaction effects between SNPs and dietary intake on DBP (Specific Aim 3)

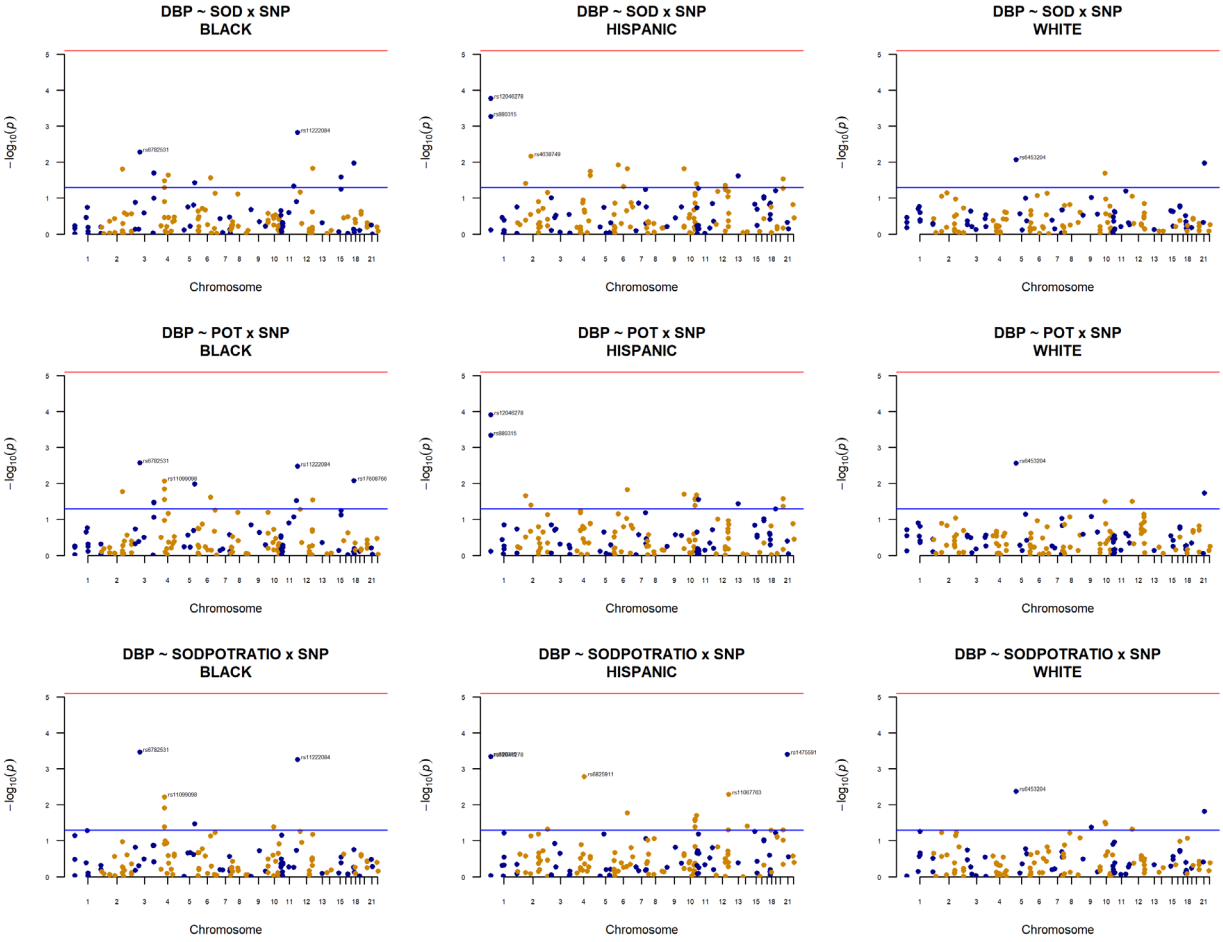


Figure 5. Manhattan plots of SNPs effects on dietary intake (Specific Aim 1)

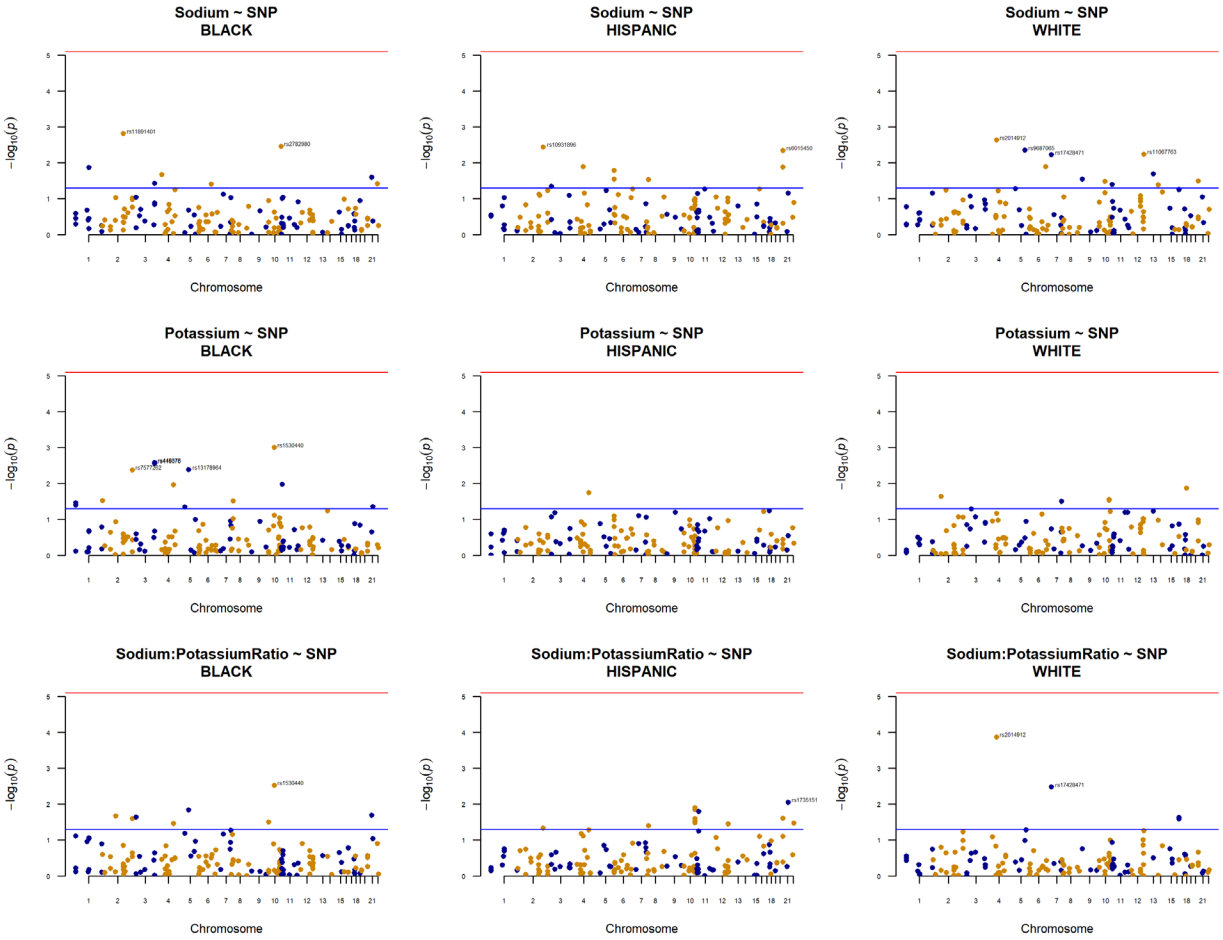


Figure 6. Evaluation of principal component association with sodium intake

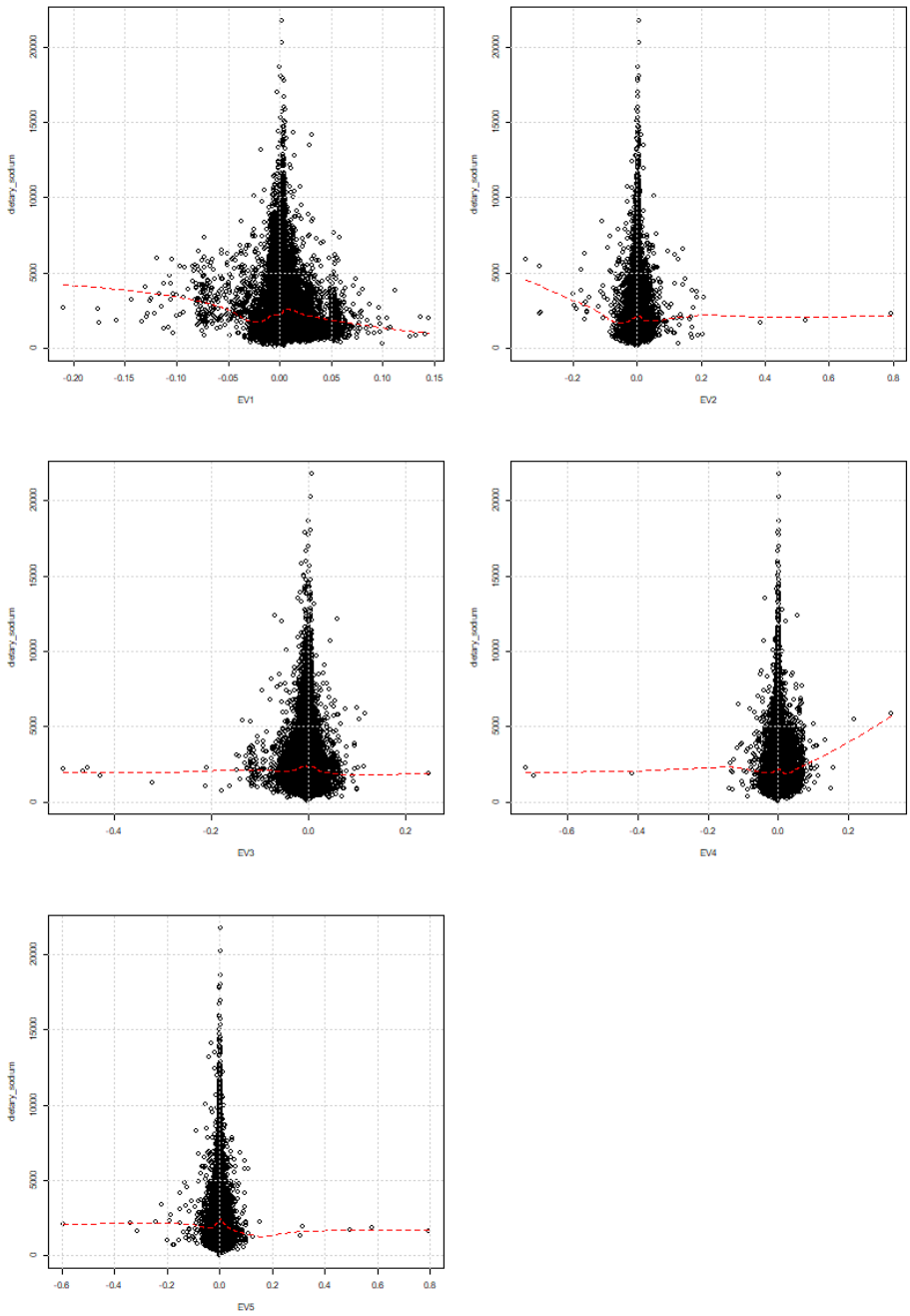


Figure 7. Evaluation of principal component association with potassium intake

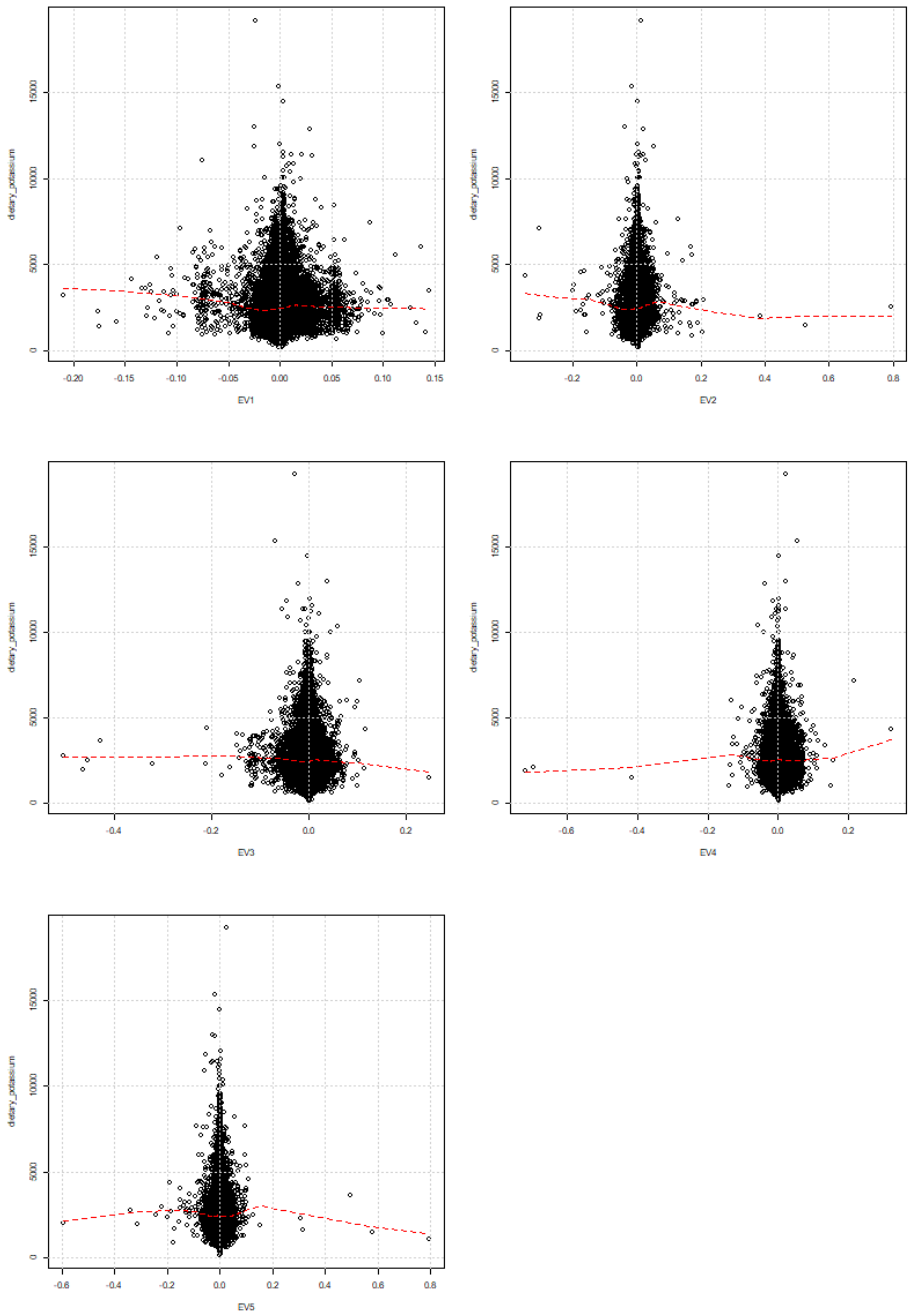
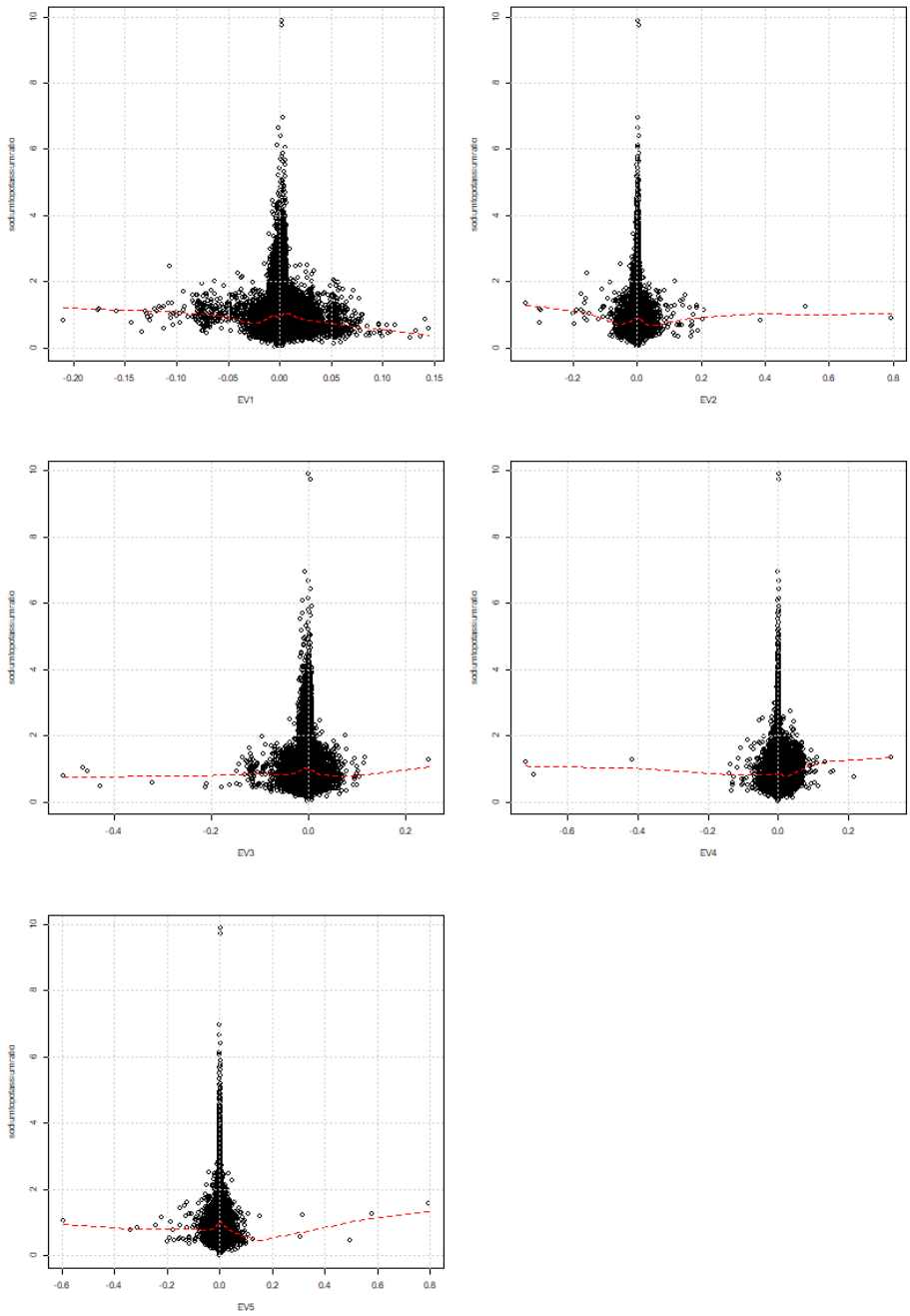


Figure 8. Evaluation of principal component association with sodium:potassium ratio intake



APPENDICES

Appendix A: Location and previous association of 186 chosen SNPs related to SBP, DBP, or hypertension identified from previous GWAS

SNP	Chr	Mapped Gene	Disease Trait	Effect	Interpretation	Publication
rs10745332	1	CAPZA1	SBP, DBP, HTN	[0.61-1.31] unit increase	harmful	Lu X, 2015
rs17030613	1	CAPZA1	BP	[0.27-0.71] mm Hg increase	harmful; protective	Kato N, 2011; Kato N, 2015
rs2932538	1	CAPZA1 - MOV10	HTN, SBP	[0.14-0.36] mmHg increase	harmful	Wain LV, 2011; Ehret GB, 2011
rs12046278	1	CASZ1	SBP	[0.29-0.77] mm Hg decrease	protective	Levy D, 2009
rs880315	1	CASZ1	SBP, DBP	[0.38-0.74] mm Hg increase	harmful	Kato N, 2011, Lu X, 2015
rs4077408	1	HHAT	HTN	0.25 unit increase	harmful	Bis JC, 2015
rs1330225	1	LOC126987 - LOC105378887	SBP, DBP	[3.60-7.36] mmHg decrease	protective	He J, 2013
rs309064	1	LPPR5	BP	[0.11-0.27] unit increase	harmful	Kim YK, 2014
rs17367504	1	MTHFR	DBP, HTN	[0.63-1.07] mm Hg decrease	protective	Newton-Cheh C, 2009; Wain LV, 2011
rs7526425	1	RD3 - LOC107985261	HTN	[1.09-1.24]	NA	Lettre G, 2011
rs3768939	2	AGAP1	HTN	0.35 unit decrease	protective	Bis JC, 2015
rs11693319	2	CCDC141	BP	[2.94-6.50] mmHg decrease	protective	He J, 2013
rs13002573	2	FIGN - PRPS1P1	BP	[0.20-0.42] mmHg decrease	protective	Wain LV, 2011
rs1446468	2	FIGN - PRPS1P1	BP	[0.24-0.44] mmHg decrease	protective	Wain LV, 2011
rs16849225	2	FIGN -	BP	[0.53-0.97]	harmful;	Kato N, 2011; Kato N,

		PRPS1P1		mm Hg increase	protective	2015
rs4665630	2	KLHL29	HTN	[1.13-1.3]	NA	Lettre G, 2011
rs825937	2	LINC01249 - RNU6-649P	BP	[0.52-1.14] mmHg increase	harmful	Simino J, 2014
rs7604423	2	LOC100506047	DBP	[0.14-0.28] mmHg decrease	protective	Kato N, 2015
rs7565329	2	LOC101927701 - LOC402076	SBP	1.7 mm Hg decrease	protective	Salvi E, 2017
rs897876	2	LOC105369166	BP	[0.45-1.62] unit increase	harmful	Leu HB, 2014
rs13390641	2	LOC105373519 - LOC728815	BP	[0.37-0.81] unit increase	harmful	Kim YK, 2014
rs10930597	2	LOC105373744 - LOC100131562	DBP, HTN	[2.06-4.34] mmHg decrease	protective	He J, 2013
rs10931896	2	LOC105373833 - SPATS2L	SBP	[0.16-0.37] mmHg increase	harmful	Kato N, 2015
rs7577262	2	MSL3P1 - TRPM8	BP	[0.61-1.39] mmHg decrease	protective	He J, 2013
rs11891401	2	PRPS1P1 - CYP2C56P	BP	[0.4-0.94] mmHg increase	harmful	Simino J, 2014
rs11887188	2	RPS20P12 - LOC105373934	BP	[2.14-4.42] mmHg decrease	protective	He J, 2013
rs6749447	2	STK39	BP	[1.2-2.6] mm Hg increase in DBP	harmful	Wang Y, 2008
rs4638749	2	SULT1C3 - WASF1P1	BP	[0.5-1.12] mmHg decrease	protective	Simino J, 2014
rs13067306	3	ARMC10P1 - LOC105373992	BP	[2.98-6.74] mmHg increase	harmful	He J, 2013
rs9810888	3	CACNA1D	SBP, DBP, HTN	[0.33-0.73] unit increase	harmful	Lu X, 2015
rs6782531	3	FHIT	BP	[0.58-1.36] mmHg decrease	protective	Simino J, 2014

rs16833934	3	LOC730129 - LOC102724419	BP	[1.06-2.2] mmHg decrease	protective	Simino J, 2014
rs319690	3	MAP4	BP	[0.20-0.40] mmHg increase	harmful	Wain LV, 2011
rs419076	3	MECOM	BP, SBP, DBP	[0.25-0.43] mmHg increase	harmful	Wain LV, 2011; Ehret GB, 2011
rs448378	3	MECOM	SBP	[0.31-0.71] mm Hg decrease	protective	Levy D, 2009
rs1918974	3	MECOM, LOC105374205	DBP	[0.17-0.37] mm Hg decrease	protective	Newton-Cheh C, 2009
rs13082711	3	UBA52P4 - LOC105377005	BP, SBP, DBP	[0.22-0.45] mmHg decrease	protective	Wain LV, 2011; Ehret GB, 2011
rs820430	3	UBA52P4 - LOC105377005	SBP, DBP, HTN	[0.54-0.98] unit increase	harmful	Lu X, 2015
rs1717027	3	ULK4	BP	[0.29-0.69] unit increase	harmful	Franceschini N, 2013
rs3774372	3	ULK4	BP	[0.18-0.42] mmHg increase	harmful	Wain LV, 2011
rs9815354	3	ULK4	DBP	[0.33-0.65] mm Hg increase	harmful	Levy D, 2009
rs2014912	4	ARHGAP24	SBP	[0.48-0.76] mmHg increase	harmful	Kato N, 2015
rs13143871	4	GUCY1A3	SBP,DBP,HTN	[0.61-1.88] unit increase	harmful	Lu X, 2015
rs13139571	4	GUCY1A3, LOC107984032	BP, SBP, DBP, HTN	[0.18-0.40] mmHg increase	harmful	Wain LV, 2011; Ehret GB, 2011, Lu X 2015
rs871606	4	LOC100129728 - RPL21P44	BP	[0.28-0.58] mmHg increase	harmful	Wain LV, 2011
rs991316	4	LOC102723576	HTN	1.62	NA	Adeyemo A, 2009
rs17589290	4	LOC105377369 - CCDC34P1	HTN	[1.22-1.67]	NA	Lettre G, 2011
rs10026364	4	LOC105377436	HTN	[1.15-1.42]	NA	Lettre G, 2011

rs12642634	4	LOC105377468 - LOC105377469	SBP	1.1 mm Hg increase	harmful	Salvi E, 2017
rs1596724	4	LOC107986223	SBP	NA	NA	Taylor JY, 2016
rs11726022	4	LOC107986335	SBP	NA	NA	Taylor JY, 2016
rs11099098	4	PRDM8 - FGF5	BP	[0.32-0.72] mmHg increase	harmful	Simino J, 2014
rs1458038	4	PRDM8 - FGF5	BP, SBP, DBP, HTN	[0.30-0.51] mmHg increase	harmful	Wain LV, 2011; Ehret GB, 2011; Kato N, 2015
rs16998073	4	PRDM8 - FGF5	DBP	[0.40-0.60] mm Hg increase	harmful	Newton-Cheh C, 2009
rs1902859	4	PRDM8 - FGF5	SBP, DBP, HTN	[1.07-1.61] unit increase	harmful	Lu X, 2015
rs13107325	4	SLC39A8	BP, SBP, DBP, HTN	[0.44-0.82] mmHg decrease	protective	Wain LV, 2011; Ehret GB, 2011
rs6825911	4	ZNF969P - ENPEP	BP	[0.38-0.82] mm Hg increase	harmful	Kato N, 2011
rs9313772	5	LOC101927697	BP	[0.24-0.44] mmHg decrease	protective	Wain LV, 2011
rs11953630	5	LOC101927697 - EBF1	SBP, DBP, HTN	0.6 mmHg decrease	protective	Ehret GB, 2011; Kato N, 2015
rs13178964	5	LOC105379111 - RAB9BP1	SBP	[2.09-4.75] mmHg decrease	protective	He J, 2013
rs1421811	5	NPR3	BP	[0.44-0.94] mmHg decrease	protective	Simino J, 2014
rs7729447	5	NPR3	BP	[0.26-0.66] mmHg increase	harmful	Simino J, 2014
rs1173766	5	NPR3 - LOC340113	DBP, SBP	[0.41-0.85] mm Hg increase	harmful; protective	Kato N, 2011; Kato N, 2015
rs1173771	5	NPR3 - LOC340113	BP, SBP, DBP, HTN	[0.19-0.37] mmHg increase	harmful; harmful; protective	Wain LV, 2011; Ehret GB, 2011; Kato N, 2015
rs822127	5	PLCXD3 - TCP1P2	DBP	[NR] mmHg decrease	protective	Salvi E, 2017
rs13359291	5	PRDM6	SBP	[0.4-0.66]	harmful	Kato N, 2015

				mmHg increase		
rs9687065	5	SH3TC2	DBP	[0.18-0.33] mmHg increase	harmful	Kato N, 2015
rs6453204	5	SV2C	BP	[NR]	NA	Schneider BP, 2014
rs805303	6	BAG6	SBP, DBP, HTN	[NR] mmHg increase	harmful	Ehret GB, 2011
rs9370524	6	COL21A1	DBP	[NR] mmHg increase	harmful	Salvi E, 2017
rs9266359	6	DHFRP2	SBP, DBP	[0.24-0.64] unit increase	harmful	Lu X, 2015
rs1799945	6	HFE	SBP, DBP, HTN	[NR] mmHg increase	harmful	Ehret GB, 2011
rs6910741	6	HIST1H2APS2 - SLC17A2	BP	[0.36-0.86] mmHg decrease	protective	Simino J, 2014
rs198846	6	HIST1H4C - HIST1H1T	BP	[0.35-0.61] mmHg decrease	protective	Wain LV, 2011
rs12195230	6	KLHL32	BP	[1.1-2.48] mmHg increase	harmful	Simino J, 2014
rs16890334	6	LOC105377865 - LOC107986613	BP	[1.95-4.45] mmHg decrease	protective	He J, 2013
rs6924906	6	LOC105377871	BP	[0.31-0.71] unit decrease	protective	Franceschini N, 2013
rs13209747	6	LOC105377992 - LOC105377989	BP	[0.44-1.26] unit increase	harmful	Franceschini N, 2013
rs2876449	6	LOC105378027	SBP	[NR] mmHg decrease	protective	Salvi E, 2017
rs12195036	6	LOC105378117	BP	[1.91-4.31] mmHg decrease	protective	Simino J, 2014
rs675026	6	OPRM1	HTN	[1.11-1.3]	NA	Lettre G, 2011
rs17080102	6	PLEKHG1	BP	[0.53-1.51] unit decrease	protective	Franceschini N, 2013
rs11750990	6	RNU2-8P - SLC25A5P7	SBP	[NR] mmHg increase	harmful	Salvi E, 2017
rs7751419	6	SAYSD1 - KCNK5	HTN	unit increase	harmful	Bis JC, 2015
rs2021783	6	TNXB	SBP, DBP, HTN	[0.44-0.92] unit increase	harmful	Lu X, 2015

rs1563788	6	ZNF318	SBP	[0.39-0.63] mmHg increase	harmful	Kato N, 2015
rs17135875	7	FAM185A, FBXL13	BP	[1.67-3.95] mmHg decrease	protective	He J, 2013
rs17477177	7	LOC102724339 - RNA5SP236	BP	[0.31-0.53] mmHg decrease	protective	Wain LV, 2011
rs10951933	7	PKD1L1	DBP	[NR] mmHg increase	harmful	Salvi E, 2017
rs17428471	7	RPL35P4 - LOC107986733	BP	[0.73-1.67] unit increase	harmful	Franceschini N, 2013
rs7801190	7	SLC12A9	HTN	[1.19-1.44]	NA	Lettre G, 2011
rs12541063	8	LOC101927845	BP	[0.48-1.14] mm of mercury decrease	protective	Kelly TN, 2013
rs2925663	8	LOC101929528 - UBXN2B	SBP	[NR] mmHg decrease	protective	Salvi E, 2017
rs13253998	8	LOC102724874 - LOC105375911	SBP	[NR] mmHg decrease	protective	Salvi E, 2017
rs10504249	8	LOC105375856	BP	[2.02-4.42] mmHg increase	harmful	He J, 2013
rs2627282	8	LOC105377787, LOC105377786	BP	[1.39-3.19] mmHg decrease	protective	He J, 2013
rs11775334	8	MSRA	HTN	[0.04-0.12] log odds increase	harmful	Levy D, 2009
rs2071518	8	NOV	BP	[0.21-0.41] mmHg increase	harmful	Wain LV, 2011
rs2702888	8	RPL23AP96 - DEFA6	BP	[0.83-1.89] mmHg decrease	protective	Simino J, 2014
rs2198596	8	SGCZ	DBP	[NR] mmHg decrease	protective	Salvi E, 2017
rs11784910	8	ZDHHC2	SBP, DBP	[NR] mmHg increase	harmful	Salvi E, 2017
rs3118867	9	DAPK1	BP, HTN	[0.31-0.67]	protective	Simino J, 2014

				mmHg decrease		
rs4841895	9	LOC100506532	BP	[0.5-1.12] mmHg increase	harmful	Simino J, 2014
rs17755650	9	LOC107987026 - MTAP	DBP	[NR] mmHg increase	harmful	Salvi E, 2017
rs1530440	10	C10orf107	DBP	[0.27-0.51] mm Hg decrease	protective	Newton-Cheh C, 2009
rs4590817	10	C10orf107	BP	[0.45-0.71] mmHg increase	harmful	Wain LV, 2011
rs12416687	10	C10orf32-ASMT	BP	[0.39-0.79] mmHg decrease	protective	Simino J, 2014
rs4409766	10	C10orf32-ASMT, C10orf32	SBP, DBP, HTN	[0.95-1.53] unit increase	harmful	Lu X, 2015
rs11014166	10	CACNB2	SBP, DBP, HTN	[0.05-0.13] log odds increase	harmful	Levy D, 2009
rs12258967	10	CACNB2	BP	[0.33-0.53] mmHg decrease	protective	Wain LV, 2011
rs11191548	10	CNNM2	BP, SBP, HTN	[0.92-1.40] mm Hg increase	harmful	Newton-Cheh C, 2009; Wain LV, 2011, Ehret GB, 2011; Kato N, 2011; Kato N, 2015
rs1004467	10	CYP17A1	SBP	[0.74-1.36] mm Hg increase	harmful	Levy D, 2009
rs3824755	10	CYP17A1	BP	[0.3-0.7] mm of mercury decrease	protective	Kelly TN, 2013
rs603788	10	KCNMA1	BP	[1.04-2.42] mmHg increase	harmful	Simino J, 2014
rs7088591	10	LOC105378314 - MRPS35P3	BP	[0.87-2.01] mm of mercury decrease	protective	Kelly TN, 2013
rs2782980	10	LOC105378492	BP	[0.23-0.45] mmHg decrease	protective	Wain LV, 2011
rs11191593	10	NT5C2	BP	[0.50-0.82] mmHg increase	harmful	Wain LV, 2011; Kelly TN, 2013

rs932764	10	PLCE1	SBP, DBP, HTN	[NR] mmHg increase	harmful	Ehret GB, 2011
rs9663362	10	PLCE1	BP	[0.18-0.36] mmHg decrease	protective	Wain LV, 2011
rs11816631	10	SFRP5 - LOC107984260	BP	[1.23-2.75] mmHg increase	harmful	Simino J, 2014
rs4373814	10	SLC39A12 - CACNB2	SBP, DBP, HTN	[NR] mmHg decrease	protective	Ehret GB, 2011
rs11037965	11	ALX4 - LOC105376645	BP	[0.83-1.97] mmHg decrease	protective	He J, 2013
rs633185	11	ARHGAP42	BP, SBP, DBP, HTN	[0.22-0.43] mmHg decrease	protective; harmful	Wain LV, 2011; Ehret GB, 2011; Kato N, 2015
rs7129220	11	CAND1.11	BP, SBP, DBP	[0.23-0.53] mmHg decrease	protective	Wain LV, 2011; Ehret GB, 2011
rs4601790	11	EHBP1L1	BP	[0.012-0.028] mmHg decrease per 1 year increase in age	harmful	Simino J, 2014
rs1943466	11	GRAMD1B	HTN	[NR]	NA	Schneider BP, 2014
rs10832417	11	KCNQ1OT1, KCNQ1	BP	[0.64-1.46] mmHg decrease	protective	He J, 2013
rs11222084	11	LOC646383	BP	[0.24-0.44] mmHg increase	harmful	Wain LV, 2011
rs2196122	11	OR51H1 - OR51H2P	BP	[1.17-2.65] mmHg increase	harmful	Simino J, 2014
rs11041530	11	OVCH2	BP	[0.86-1.84] unit decrease	protective	Franceschini N, 2013
rs11024074	11	PLEKHA7	DBP	[0.19-0.47] mm Hg decrease	protective	Levy D, 2009
rs381815	11	PLEKHA7	SBP, HTN	[0.43-0.87] mm Hg increase	harmful	Levy D, 2009; Wain LV, 2011
rs1401454	11	SOX6	BP	[0.24-0.86] unit increase	harmful	Franceschini N, 2013
rs4757391	11	SOX6	SBP, DBP, HTN	[0.59-1.17] unit increase	harmful	Lu X, 2015
rs17249754	12	ATP2B1	BP, SBP, DBP,	[0.27-0.52]	harmful;	Wain LV, 2011; Kato N,

			HTN	mmHg increase	protective	2011; Lu X, 2015; Kelly TN, 2013; Kato N, 2015
rs2681472	12	ATP2B1	SBP, DBP, HTN	[0.11-0.19] log odds increase	harmful	Levy D, 2009; Kato N, 2015
rs2681492	12	ATP2B1	SBP	[0.60-1.10] mm Hg increase	harmful	Levy D, 2009
rs653178	12	ATXN2	BP, SBP, DBP	[0.36-0.56] mm Hg decrease	protective	Newton-Cheh C, 2009; Wain LV, 2011; Kato N, 2015
rs11066280	12	HECTD4	BP, SBP, DBP, HTN	[1.31-1.81] mm Hg increase	harmful	Kato N, 2011; Lu X, 2015; Kato N, 2015
rs12579720	12	LOC100506393	DBP	[0.24-0.4] mmHg decrease	protective	Kato N, 2015
rs35444	12	LOC102723639 - LOC105370003	BP, SBP, DBP	[0.38-0.88] mm Hg increase	harmful	Kato N, 2011; Lu X, 2015; Kato N, 2015
rs11067763	12	LOC105370003	SBP, DBP, HTN	[0.61-1.01] unit increase	harmful	Lu X, 2015
rs2384550	12	LOC107984437 - LOC102723639	BP, DBP	[0.23-0.47] mm Hg decrease	protective; harmful	Levy D, 2009; Wain LV, 2011
rs7960884	12	OVOS2 - LOC107987168	SBP	[NR] mmHg increase	harmful	Salvi E, 2017
rs4842666	12	POC1B - ATP2B1	BP	[0.46-0.96] mmHg increase	harmful	Simino J, 2014
rs3184504	12	SH2B3	SBP, DBP	[0.38-0.78] mm Hg increase	harmful	Levy D, 2009; Ehret GB, 2011; Kato N, 2015
rs2315885	13	MIR5007 - HNF4GP1	BP	[0.84-1.98] mm of mercury increase	harmful	Kelly TN, 2013
rs8002688	13	PIBF1	BP	[1.37-2.71] mmHg increase	harmful	He J, 2013
rs11158609	14	NEDD8, NEDD8-MDP1	SBP	NA	NA	Taylor JY, 2016
rs10143078	14	SYNJ2BP,	BP	[2.47-5.65]	protective	Simino J, 2014

		SYNJ2BP-COX16		mmHg decrease		
rs177848	14	TTC6	DBP	[NR] mmHg decrease	protective	Salvi E, 2017
rs6495122	15	CPLX3 - ULK3	DBP	[0.28-0.52] mm Hg increase	harmful	Levy D, 2009
rs1378942	15	CSK	BP, SBP, DBP	[0.35-0.51] mm Hg increase	harmful; protective	Newton-Cheh C, 2009; Wain LV, 2011,; Ehret GB, 2011; Kato N, 2015
rs2521501	15	FES	BP, SBP, DBP, HTN	[0.22-0.46] mmHg increase	harmful; protective	Wain LV, 2011; Ehret GB, 2011; Kato N, 2015
rs1550576	15	LOC107984724 - ALDH1A2	HTN	[NR]	NA	Adeyemo A, 2009
rs16962897	16	DNAAF1	SBP	[NR] mmHg decrease	protective	Salvi E, 2017
rs1862746	16	LOC101927605	SBP	NA	NA	Taylor JY, 2016
rs11646213	16	LOC101928392 - CDH13	HTN	[1.15-1.43]	NA	Org E, 2009
rs2030114	16	LOC102723323 - LOC107984892	BP	[2.28-4.00] mmHg decrease	protective	He J, 2013
rs4150161	16	TAF1C	SBP	[NR] mmHg increase	harmful	Salvi E, 2017
rs13333226	16	UMOD	HTN	[1.10-1.19]	NA	Padmanabhan S, 2010
rs11867410	17	APOH - RNA5SP444	BP	[2.43-5.49] mmHg decrease	protective	He J, 2013
rs11657217	17	ENPP7	DBP	[NR] mmHg decrease	protective	Salvi E, 2017
rs17608766	17	GOSR2	BP, SBP	[0.40-0.67] mmHg decrease	protective	Wain LV, 2011; Ehret GB, 2011
rs16948048	17	LOC102724596	DBP	[0.21-0.41] mm Hg increase	harmful	Newton-Cheh C, 2009
rs747685	17	NXN	BP	[0.91-2.09] mmHg increase	harmful	Simino J, 2014
rs747687	17	NXN	DBP	[0.86-1.88] mmHg increase	harmful	Simino J, 2014

rs12946454	17	PLCD3	SBP	[0.37-0.77] mm Hg increase	harmful	Newton-Cheh C, 2009
rs8065772	17	PRKCA - CACNG5	SBP	NA	NA	Taylor JY, 2016
rs8078051	17	TTYH2	SBP	NA	NA	Taylor JY, 2016
rs12940887	17	ZNF652	BP	[0.16-0.35] mmHg increase	harmful	Wain LV, 2011
rs403814	18	L3MBTL4	HTN	[1.07-1.23]	NA	Liu X, 2016
rs1792738	18	LOC105372132 - LOC105372135	SBP	NA	NA	Taylor JY, 2016
rs2217560	18	LOC105372189 - CBLN2	HTN	[1.59-2.45]	NA	Germain M, 2013
rs1157477	18	LOC339298	SBP	NA	NA	Taylor JY, 2016
rs7233332	18	RAB31	BP	[0.013-0.033] mmHg increase per 1 year increase in age	harmful	Simino J, 2014
rs16964543	19	ZNF536	HTN	unit decrease	protective	Bis JC, 2015
rs1327235	20	C20orf187	BP, SBP, DBP	[0.17-0.35] mmHg increase	harmful; protective	Wain LV, 2011; Ehret GB, 2011; Kato N, 2015
rs1887320	20	C20orf187	SBP, DBP	[0.51-1.05] unit increase	harmful	Lu X, 2015
rs2273359	20	NELFCD	HTN	[NR] mm Hg increase	harmful	Turner ST, 2013
rs16982520	20	ZNF831	HTN	[0.09-0.17] log odds decrease	protective	Levy D, 2009
rs6015450	20	ZNF831	BP, SBP, DBP, HTN	[0.21-0.49] mmHg increase	harmful	Wain LV, 2011; Ehret GB, 2011
rs1735151	21	IGSF5	HTN	[1.09-1.24]	NA	Lettre G, 2011
rs1475591	21	UBE3AP2 - TIAM1	HTN	[1.10-1.27]	NA	Lettre G, 2011

rs7286472	**22**	**LARGE - LOC105373010**	**BP**	**[1.39-3.11] mmHg decrease**	**protective**	**He J, 2013**
rs130318	22	PARVB	HTN	[NR]	NA	Schneider BP, 2014

SNP: single nucleotide polymorphism identifier based on Human Genome Assembly GRCh37, Chr: chromosome, SBP: systolic blood pressure, DBP: diastolic blood pressure, HTN: hypertension, [NR]: not reported, NA: not available

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