This author's PDF version corresponds to the article as it

appeared upon acceptance. Fully formatted PDF versions will be

made available soon.

The association of blood pressure with estimated urinary sodium,

potassium excretion and their ratio in hypertensive, normotensive,

and hypotensive Chinese adults

doi: 10.6133/apjcn.202002/PP.0001 Published online: February 2020

Running title: Blood pressure and urinary sodium vs potassium

Ying Li PhD^{1†}, Lu Yin PhD^{2†}, Yaguang Peng PhD³, Xiaoyun Liu, PhD², Xia Cao PhD¹, Yaqin Wang PhD¹, Pingting Yang PhD¹, Xiaohui Li PhD⁴, and Zhiheng Chen MD¹

[†]Co-first authors

¹Department of Health Management, The Third Xiangya Hospital, Central South University, Changsha, China

²Medical Research & Biometrics Center, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

³Center for Clinical Epidemiology and Evidence-based Medicine, Beijing Children's Hospital, Capital Medical University, National Center for Children Health, Beijing, China

⁴Department of Pharmacology, Xiangya School of Pharmceutical Science, Central South University, Changsha, Hunan, China

Authors' email addresses and contributions:

Ying Li, E-mail: lydia0312@csu.edu.cn. Telephone number: +86073188618389. Lu Yin, E-mail: yinlu@mrbc-nccd.com. Telephone number: +8613691166577. Yaguang Peng, E-mail: plwumi@aliyun.com. Telephone number: +8613810968993. Xiaoyun Liu, E-mail: liuxiaoyun@mrbc-nccd.com. Telephone number: +86073188618389. Yaqin Wang, E-mail: 269380030@qq.com. Telephone number: +86073188618389. Pingting Yang, E-mail: 446238213@qq.com. Telephone number: +86073188618389. Xiaohui Li, E-mail: xiaohuili@csu.edu.cn. Telephone number: +86073188618389. Ziaohui Li, E-mail: 37618190@qq.com. Telephone number: +86073188618389.

Corresponding Author: Prof Zhiheng Chen, Department of Health Management, The Third Xiangya Hospital Affiliated with Central South University, Changsha, Hunan Province, China. Email: 37618190@qq.com

ABSTRACT

Background and Objectives: Low sodium and high potassium intake is reported to be a risk of hypertension. However, it is uncertain whether these associations can be generalized to those without hypertension. This study is to evaluate the associations of systolic and diastolic blood pressure (SBP and DBP, respectively) with estimated urinary sodium excretion (eUNaE), estimated urinary potassium excretion (eUKE) and their ratio (Na/K ratio) among hypertensive, normotensive, and hypotensive Chinese individuals. Methods and Study Design: A large institution-based cross-sectional study was conducted at the Third Xiangya Hospital, Changsha between August 2017 and November 2018. Spot urine samples were collected to test urinary sodium, potassium, and creatinine excretions for each participant. The Kawasaki formula was used to estimate 24-hour urinary sodium and potassium excretions. Results: A total of 26,363 eligible subjects were used to analyze the associations of blood pressure with eUNaE, eUKE, and their ratio. 27.3% (n=7,201) of participants were diagnosed with hypertension, 5.4% (n=1,427) were diagnosed with hypotension, and the remaining of 17,735 participants were normotensive. A significant increase in SBP and DBP was related to the Na/K ratio increase in hypertensive and normotensive subgroups (all $p_{trend} < 0.01$), but the association was not significant for DBP among hypotensive individuals (*p*_{trend}=0.58). Stronger associations of SBP with the Na/K ratio were observed in older people *p*_{interaction}<0.01) and females (pinteraction<0.0001), but the same trend was not observed for DBP (pinteraction=0.10 and 0.88, respectively). Conclusions: High potassium and low sodium intake were further confirmed to reduce blood pressure in hypotensive, normotensive, and hypertensive individuals.

Key Words: systolic blood pressure, diastolic blood pressure, estimated urinary sodium excretion, estimated urinary potassium excretion

INTRODUCTION

"Low sodium and high potassium intake" is recommended as the one of primary prevention and control strategies to reduce the risk of hypertension and consequential cardiovascular diseases,¹⁻⁷ especially in China.⁸⁻¹⁰ The average salt intake was 12 g/day in Chinese adults based on the National Dietary Survey conducted in 2002,¹¹ and another survey involving 20 provinces revealed that salt intake decreased 22% from 2000 at 11.8 g/day to 2009-2011 at 9.2 g/day,¹⁰ all of these intake values exceeded the recommended daily maximum intake of salt at 5 g/day by the World Health Organization and 6 g/day by the Chinese Society of Nutrition.^{12,13} The National Dietary Survey in 2002 classified four salt regions based on daily sodium intake: heavy-salt regions (≥ 8 g), moderate-salt regions (7 to 8 g), light-salt regions (6 to 7 g), and low-salt regions (< 6 g).^{11,14} Although the PURE-China results between 2005 and 2009 involving 12 provinces did not show an expected trend based on this salt-region classification, less sodium intake and more potassium intake was confirmed to reduce blood pressure (BP), which could be generalized across various salt-intake regions, even light- and low-salt regions (<7 g/day salt intake).⁹

Several prospective cohort studies have reported U-shaped associations between estimated urinary sodium excretion (eUNaE) and cardiovascular disease morbidity and mortality,^{7,15-18} among which a pooled analysis of data from four studies revealed that compared with the risk associated with moderate sodium excretion of 4-4.99 g/day, high sodium excretion of ≥ 5 g/day was associated with an increased risk of cardiovascular diseases in hypertensive populations, but not in the normotensive population.¹⁷ Therefore, sodium restriction is more important for those suffering from hypertension. A meta-analytic review involving 34 randomized trials assessing the effects of a modest reduction in salt intake for at least 4 weeks observed important reductions in blood pressure in both hypertensive and normotensive individuals, irrespective of sex and ethnic group.¹⁹ A prospective cohort study involving 18 countries found a steeper slope of the BP-eUNaE association among hypertensive people than among normotensive people.8 It is uncertain whether these associations among those with and without hypertension can be generalized to Chinese individuals with a high sodium intake level. Hence, we used an institution-based cross-sectional study to evaluate the associations of blood pressure with eUNaE, estimated urinary potassium excretion (eUKE), and their ratio (estimated urinary sodium vs. potassium excretion (Na/K ratio)) in hypertensive, normotensive, and hypotensive individuals, based on data from the Third Xiangya Hospital located in Changsha, China.

MATERIALS AND METHODS

Study design and participants

Our study was based on physical examination institution-based cross-sectional study in the Third Xiangya Hospital, Changsha, China, which offers primary health services, including physical examination, blood and urine measurements, ultrasound on the thyroid and carotid artery, bone mineral density measurement and other specific services at the client's request²⁰ This study utilized a health physical examination registry system without random sampling to control the potential sources of bias. All individuals (N=27,837) who attended a routine health

check-up in the Health Management Center between August 2017 and November 2018 provided a random urine samples on the day of physical examination or the next day to test sodium, potassium, and creatinine excretions. Participants with missing values of age, blood pressure, weight, height, eUNaE, or eUKE were excluded. Additionally, those aged <18 or >80 years, with SBP <70 mmHg or >260 mmHg, with DBP <40 mmHg or >140 mmHg, eUNaE >12 g/day, or eUKE >4 g/day were removed from the analysis. Informed consent and the protocol of the overall physical examination, as well as the contents of salt intake in the study were reviewed and approved by the institutional review board at The Third Xiangya Hospital (No. 2018-S393).

Physical examination and laboratory measurements

Based on the Guidelines for Blood Pressure Measurement in China,²¹ subjects had to rest for at least 5 minutes prior to measurement without smoking, exercising, eating, or climbing stairs within 30 minutes. An appropriate size cuff was selected and centered over the brachial artery. First, blood pressure (BP) readings were taken on both arms using an OMRON automatic digital BP monitor (OMRON HBP-9021, OMRON Healthcare, Scarborough, ON, Canada). Second, the arm with the higher BP was chosen for the measurement of BP twice at one-minute intervals. Both systolic and diastolic BPs were recorded. The means of the two measurements were used for our analyses. Finally, a third measurement was conducted to calculate the mean of three measurement values if the difference between the first two BP results was more than 5 mmHg.

Blood samples were collected according to the relevant guidelines in the Third Xiangya Hospital. All blood and urine samples were measured using 7600 and 7170 Hitachi automatic biochemical analyzer. Fasting blood samples were collected to test fasting serum glucose (FSG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) using LEADMAN test kits (Beijing LEADMAN Biochemical Co., Ltd. China), as well as serum creatinine (SCr) using Wako L-Type Creatinine M kits (Wako Pure Chemical Industries, Ltd. Japan).

Urine collection was performed for each participant according to the following guidelines: 1) a labeled urine container was provided for each subject to collect his/her mid-stream urine sample; 2) after urine collection, the lids of the containers were screwed tightly; and 3) the samples were transferred to the Department of Clinical Laboratory to test for sodium, potassium, and creatinine within 2 hours. Sodium and potassium were examined by ion

5

selective electrode method, and creatinine was examined by a dynamic enzymatic method (Beijing LEADMAN Biochemical Co., Ltd. China).

Numerous studies have explored methods for estimating 24-hour urinary sodium excretion from spot urine samples, including the Kawasaki method,²² the INTERSALT method,²³ and the Tanaka method,²⁴ all of which are common methods used in clinical and epidemiological studies. These three methods have been evaluated and validated in a Chinese population, but all of the methods underestimated true 24-hour urinary sodium excretion. Compared to the other two approaches, the Kawasaki equation had the lowest mean difference compared to 24-h urinary sodium excretion.²⁵ Therefore, we ultimately chose the Kawasaki method to estimate salt intake in the current study.

Confounding factors

Written informed consent forms were signed by each participant before the interview, physical examination and sample collection. The National Unified Physical Examination Questionnaire was used to assess sociodemographic characteristics, alcohol use, cigarette smoking, and self-reported disease history (such as hypertension, diabetes, stroke, cancer, and coronary artery diseases, et al.). A physical examination was conducted for each participant to collect weight, height, hip circumference (HC), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse by trained physicians or nurses. Statistical analyses

Continuous variables are shown as the mean \pm standard deviation (SD), and categorical variables are shown as percentages (%) and numbers (n). Those with SBP/DBP \ge 140/90 mmHg, self-reported hypertension history or blood pressure medication use were defined as hypertensive individuals; SBP/DBP < 90/60 mmHg was defined as hypotensive individuals, and the remaining of participants were defined as normotensive individuals. Multivariable linear regressions were performed to evaluate the changes and their 95% confidence intervals (CIs) of SBP and DBP by eUNaE, eUKE, the Na/K ratio among hypertensive, normotensive, and hypotensive individuals adjusted for age, sex, body mass index, smoking status, and alcohol use. In assessing associations of the Na/K ratio with blood pressure, the influence of sex (female or male), age (<45 years, 45-55 years, or >55 years), body mass index (BMI, <18.5 kg/m², 18.5-25 kg/m², or >25 kg/m²), and hypertension status (yes or no) was investigated using tests of interaction adjusted for the above-mentioned covariates. The effect of sodium or potassium excretion on blood pressure was further assessed at various levels of

eUNaE and eUKE. The Statistical Analysis System (SAS 9.4 for Windows; SAS Institute Inc., Cary, NC, USA) was used for the overall statistical analyses in our study.

RESULTS

A total of 27,837 individuals who attended routine health check-ups between August 2017 and November 2018 in the Health Management Center provided random urine samples on the day of the physical examination or the next day to test sodium, potassium, and creatinine excretion; among these participants, 232 were excluded due to ages not within 18-80 years (6 did not provide their ages, 64 were younger than 18 years, and 124 were older than 80 years old). Of the remaining 27,643 individuals aged 18-80 years, 386 were removed from the analysis due to missing values of blood pressure, and one was removed due to implausible SBP/DBP values (reasonable SBP within 70-260 mmHg, or DBP within 40-140 mmHg). Additionally, 804 were excluded because of missing values of weight and height, 3 for lack of urine collection, 10 for eUNaE >12 g/day, and 76 for eUKE >4 g/day. Finally, 26,636 individuals were included in the analyses (see Supplementary Figure 1).

Overall, the mean age of 26,363 eligible participants was 46.4 ± 11.8 years old (range 18-80 years old). A total of 57.0% (n=15,027) were males. A total of 27.3% were diagnosed as hypertensive individuals, 5.4% as hypotensive individuals, and 67.3% as normotensive individuals. Those with hypertension (53.3±10.7 years) were much older than those with normotension (43.9±11.1 years) and hypotension (41.9±11.6 years; *p*_{trend}<0.001). In total, 33.8% of hypertensive individuals were self-reported current alcohol users, and this value was much higher than that among normotensive and hypotensive individuals (33.8%, 31.6%, and 14.9%, respectively; *p*_{trend}<0.001), and 24.5% of hypertensive and 24.7% of normotensive individuals were current smokers; these values were much higher than that among hypotensive individuals (14.9%). Hypertensive individuals were more likely to have higher BMI, waist circumference (WC), SBP, DBP, FSG, SCr, TC, TG, LDL-C, and eUNaE than normotensive and hypotensive individuals (all *p*_{trend}<0.01), while those suffering from hypertension had lower HDL-C levels (*p*_{trend}<0.01). More detailed results are presented in Table 1.

Figure 1 illustrates the association of SBP and DBP with eUNaE, eUKE, and the Na/K ratio in hypertensive, normotensive, and hypotensive individuals after adjusting for age, sex, BMI, smoking status, and alcohol use. As shown in Figure 1A, a dose-response trend of SBP was observed with eUNaE increase among hypertensive (β =2.1473, *p*_{trend}<0.0001), normotensive (β =0.6737, *p*_{trend}<0.0001), and hypotensive people (β =1.018, *p*_{trend}<0.0001). As

shown in Figure 1B, a similar dose-response trend was also observed for DBP in hypertensive (β =1.0240, p_{trend} <0.0001) and normotensive individuals (β =0.1113, p_{trend} =0.0346), while this trend was not significant in those with hypotension (β =0.1364, p_{trend} =0.0909). A significant decrease in SBP was observed for each increase in eUKE in hypertensive individuals (β =-2.6948, p_{trend} <0.0001), normotensive people (β =-0.9343, p_{trend} <0.0001), and hypotensive individuals (β =-1.1026, p_{trend} =0.0400) (Figure 1C), while this trend was found for DBP only in hypertensive (β =-1.6602, p_{trend} <0.0001) and normotensive individuals (β =-0.8426, p_{trend} <0.0001). No significance was shown for hypotensive individuals (β =-0.0956, p_{trend} =0.6319) (Figure 1D). Figure 1E illustrates the obvious dose-response trend of SBP with the Na/K ratio in hypertensive people (β =3.4297, p_{trend} <0.0001), normotensive individuals (β =1.6114, p_{trend} <0.0001). However, this positive association of DBP was observed in Figure 1F only for hypertensive (β =1.6816, p_{trend} <0.0001) and normotensive people (β =0.5487, p_{trend} <0.0001), but not for hypotensive individuals (β =0.0678, p_{trend} =0.5778).

Figure 2 illustrates the forest plots of changes in SBP and DBP per unit increase of the ratio of estimated urinary sodium to potassium excretion across various subgroups. The eUNa/K ratio was more strongly associated with increased SBP (increment of 3.43 mmHg; 95% CI, 2.91-3.95) and DBP (increment of 1.68 mmHg; 95% CI, 1.33-2.04) in persons with hypertension than in those without hypertension (SBP: 1.51 mmHg; 95% CI, 1.26-1.77; DBP: 0.60 mmHg; 95% CI, 0.41-0.80; both pinteraction<0.001). There was a significant trend of SBP according to age, with a steeper slope of association with the eUNa/K ratio in persons older than 55 years of age (3.88 mmHg; 95% CI, 3.23-4.53 per unit increase of eUNa/K) than in those 45 to 55 years of age (2.66 mmHg; 95% CI, 2.21-3.11) or those aged<45 years (1.71 mmHg; 95% CI, 1.35-2.08; *pinteraction*<0.001), but this significant trend was not observed for DBP (*p*_{interaction}=0.8841). A stronger association was found for SBP in females (3.19 mmHg; 95% CI, 2.74-3.63) than males (2.32 mmHg; 95% CI, 1.99-2.65; *pinteraction*<0.001), but not for DBP (pinteraction=0.1032). A significant trend of SBP was found according to BMI (*p*_{interaction}<0.001), with the steepest slope of association with the eUNa/K ratio found among those with normal BMI (3.04 mmHg; 95% CI, 2.64-3.45), compared with the slope of the association of those who were underweight (1.04 mmHg; 95% CI, -0.20 to 2.29) and overweight (2.68 mmHg; 95% CI, 2.30-3.06), while no significant association was observed for DBP (*p*_{interaction}=0.7323).

After adjustment for covariates, the highest SBP and DBP values were observed in the group with the highest eUNaE and the lowest eUKE values (compared with the group with

the lowest eUNaE and highest eUKE values, 9.72 mmHg for SBP with $p_{interaction}=0.0131$ and 6.29 mmHg for DBP with $p_{interaction}=0.0008$; Figure 3).

DISCUSSION

Our study further confirmed the effects of sodium restriction and potassium addition on reducing blood pressure in hypertensive, normotensive, and hypotensive individuals, although the associations of DBP with eUNaE, eUKE, and the Na/K ratio were not significant in hypotensive individuals. A larger change in SBP per unit increase in the Na/K ratio was observed in females, older adults, and normal-weight and overweight people, but this trend was not observed for DBP. Hence, sodium restriction and potassium addition may be effective in controlling blood pressure, regardless of hypertensive, normotensive, or hypotensive status.

The Chinese dietary is well known as a high-sodium and low-potassium diet.^{8,23,26-30} The Chinese Dietary Guidelines recommended no more than 6g/d of salt intake beginning in 2007. In recent years, sodium restriction strategies have been proposed in China, including strengthening salt reduction health education, issuing salt-limiting spoons, and enforcing the General Principles of Nutrition Labeling of Prepackaged Foods.^{4,31-33} As a result, the mean daily salt intake decreased from 12.0 grams in 2002 to 9.6 grams in 2012 based on a dietary questionnaire survey.^{14,30} As shown in a famous prospective urban and rural epidemiological study (PURE) involving in 12 administrative regions between 2005 and 2009 in China, a salt intake of approximately 14.3 grams was estimated using a single fasting urine specimen for China, and this value is much higher than the intake in other PURE countries.^{8,9} Our study also estimated salt intake using spot urine specimens between 2017 and 2018 and obtained a daily intake value of 8.4-10.8 grams/day in Hunan Province,³⁴ which is much lower than that determined in PURE-China. However, the salt intake from all these studies is higher than the maximum salt intake recommended by current guidelines.^{35,36} In view of this, the General Office of the State Council issued a National Nutrition Plan (2017-2030) that regards "Three Reductions" as the focus of the national nutrition work over the next 13 years, including salt intake reduction.³⁷ Therefore, we have reasons to believe that salt restriction in China has achieved initial success, but the task remains arduous.

It is not surprising that a positive association exists between estimated sodium excretion and blood pressure. Previous studies demonstrated an increase in blood pressure for every 1g increase in eUNaE of 1.46-2.11 mmHg for SBP and 0.54-0.78 mmHg for DBP.^{8,23} Interestingly, however, higher sodium excretion was not associated with the risk of the

primary composite outcome of the population without hypertension.¹⁷ In the current study, we calculated the associations between eUNaE and blood pressure in hypertensive, normotensive, and hypotensive individuals, and demonstrated that a significant increase in SBP was related to higher eUNaE in all three subgroups, but a more significant association was found in the hypertensive subgroup. Low potassium excretion seemed to be a global problem, with a mean level of approximately 2 g/day, similar to that observed in PURE-China⁹ and our study. Potassium intake levels in China were still much lower than the recommended adequate intake levels,^{36,38} but were within the range recommended by China.¹⁴ Therefore, extensive attention may not have been paid to potassium addition strategies by the Chinese government and the Chinese population in the past 10 years. Potential effectiveness of potassium intervention on controlling blood pressure at different levels of salt intake has been observed in the PURE-China study,⁹ which suggested that high potassium intake. Hence, potassium addition in the diet may decrease the risk of high blood pressure, even if sodium intake is still high.

Males had higher sodium excretion (4.5 vs 3.9 g/day) and blood pressure (SBP: 126.2 vs 118.9 mmHg; DBP: 78.6 vs 71.0 mmHg) than females in our study, which was consistent with previous studies conducted in China.4,9,28,39 Our study also found lower levels of sodium excretion and blood pressure among females and males than the PURE-China study conducted between 2005 and 2009 (sodium: 6.1 vs 5.4 g/day; SBP: 135.1 vs 132.3 mmHg; DBP: 84.1 vs 82.0 mmHg).⁹ The main reason might be the younger participants and professionals were enrolled in the physical examination, including a predominance of males, which was different from traditional epidemiological studies (mostly females and housewives).^{8,17,40} Another reason might be related to preliminary achievements of salt restriction in China over the past decades. China is a large country with a high prevalence of hypertension, and the prevention and control of hypertension has caused a heavy economic burden. In the current study, we found that the salt intake of people undergoing physical examinations was notably high, which partly caused the hypertension. In the next step, we recommend that salt restriction-related health education be strengthened. In addition, it is particularly recommended that the country introduce policies to limit the salt content of packaged food.

Our study had several limitations. First, only spot urine samples were collected for each participant at a random time on one day (approximately 90% were the second fasting urine samples), and these samples were used to estimate of 24-hour urinary excretion using the

Kawasaki formula.²² Although this formula was less biased than the INTERSALT and Tanaka methods,²³⁻²⁵ our estimates may not represent actual urinary sodium and potassium intake levels. Second, we only had one institution of physical examination in Changsha, Hunan Province, China, though the institution is the largest institution in South Central China. Hence, our results may not be generalizable to China. Third, physical activity level is an important confounding factor affecting blood pressure, but no adequate information of physical activity levels was collected in questionnaires in the physical examination. Finally, only 1,427 hypotensive individuals were included in the analysis of the association of blood pressure with eUNaE, eUKE, and their ratio, which may not have provided enough power to test their potential effects of sodium and potassium intake on blood pressure. Larger sample sizes are needed.

Conclusions

Although sodium intake might have decreased in the Chinese diet over the past 10 years, low potassium intake seemed not to be improved. Our results further confirm that less sodium intake and higher potassium intake result in a decrease in blood pressure and the risk of possible cardiovascular diseases. In addition to sodium restriction, potassium addition should be generalized into Chinese diet.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

This study is funded by the National Natural Science Foundation of China (81973324, 81503071), Hunan Provincial Key R & D plans (2018SK2093), as well as the New Xiangya Talent Project of The Third Xiangya Hospital of Central South University (JY201709).

REFERENCES

- Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ. 2007;334:885-8.
- Mu J, Liu Z, Liu F, Xu X, Liang Y, Zhu D. Family-based randomized trial to detect effects on blood pressure of a salt substitute containing potassium and calcium in hypertensive adolescents. Am J Hypertens. 2009;22:943-7.
- 3. Aaron KJ, Sanders PW. Role of dietary salt and potassium intake in cardiovascular health and disease: a review of the evidence. Mayo Clin Proc. 2013;88:987-95.

- Du S, Batis C, Wang H, Zhang B, Zhang J, Popkin BM. Understanding the patterns and trends of sodium intake, potassium intake, and sodium to potassium ratio and their effect on hypertension in China. Am J Clin Nutr. 2014;99:334-43.
- Noubiap JJ, Bigna JJ, Nansseu JR. Low sodium and high potassium intake for cardiovascular prevention: evidence revisited with emphasis on challenges in sub-Saharan Africa. J Clin Hypertens (Greenwich). 2015;17:81-3.
- 6. Rebholz CM, Chen J, Zhao Q, Chen JC, Li J, Cao J et al. Urine angiotensinogen and salt-sensitivity and potassium-sensitivity of blood pressure. J Hypertens. 2015;33:1394-400.
- 7. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med. 2014;371:612-23.
- 8. Mente A, O'Donnell MJ, Rangarajan S, McQueen MJ, Poirier P, Wielgosz A et al. Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med. 2014;371:601-11.
- Yin L, Deng G, Mente A, Sun Y, Liu X, Zhang X et al. Association patterns of urinary sodium, potassium, and their ratio with blood pressure across various levels of salt-diet regions in China. Sci Rep. 2018;8:6727.
- 10. Hipgrave DB, Chang S, Li X, Wu Y. Salt and Sodium Intake in China. JAMA. 2016;315:703-5.
- 11. Zhai F, Yang X. Report of National Nutrition and Health Survey of China Residents in 2002: Part 2: Diet and Nutrition Intake. Beijing, China. 2006.
- WHO. Guideline: Sodium intake for adults and children. Geneva: World Health Organization (WHO); 2012.
- 13. Chinese Soclety of Nutrition. Dietary Guidelines for Chinese Residents 2016. Beijing: People's Medical Publishing House (PMPH); 2016.
- Wang L. The First Report-2002 Comprehensive Report of Chinese Nutrition and Health Status. Beijing: People's Medical Publishing House; 2005.
- Pfister R, Michels G, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Estimated urinary sodium excretion and risk of heart failure in men and women in the EPIC-Norfolk study. Eur J Heart Fail. 2014;16:394-402.
- 16. Saulnier PJ, Gand E, Hadjadj S, Group SS. Sodium and cardiovascular disease. N Engl J Med. 2014;371:2135-6.
- 17. Mente A, O'Donnell M, Rangarajan S, Dagenais G, Lear S, McQueen M et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. Lancet. 2016;388:465-75.
- Stolarz-Skrzypek K, Kuznetsova T, Thijs L, Tikhonoff V, Seidlerova J, Richart T et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA. 2011;305:1777-85.
- 19. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ. 2013;346:f1325.

- 20. Wang YQ, Wang CF, Zhu L, Yuan H, Wu LX, Chen ZH. Ideal cardiovascular health and the subclinical impairments of cardiovascular diseases: a cross-sectional study in central south China. BMC Cardiovasc Disord. 2017;17:269.
- 21. Wang W, Zhang WZ, Sun NL, Lin JX, Chen LY, Wu KG et al. Guidelines for blood pressure measurement in China. Chin J Hyperten. 2011;19:1101-15.
- 22. Kawasaki T, Itoh K, Uezono K, Sasaki H. A simple method for estimating 24 h urinary sodium and potassium excretion from second morning voiding urine specimen in adults. Clin Exp Pharmacol Physiol. 1993;20:7-14.
- 23. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. BMJ. 1988;297:319-28.
- 24. Tanaka T, Okamura T, Miura K, Kadowaki T, Ueshima H, Nakagawa H et al. A simple method to estimate populational 24-h urinary sodium and potassium excretion using a casual urine specimen. J Hum Hypertens. 2002;16:97-103.
- 25. Peng Y, Li W, Wang Y, Chen H, Bo J, Wang X et al. Validation and assessment of three methods to estimate 24-h urinary sodium excretion from spot urine samples in Chinese adults. PLoS One. 2016;11:e0149655.
- 26. Ge Z, Guo X, Chen X, Tang J, Yan L, Ren J et al. Association between 24 h urinary sodium and potassium excretion and the metabolic syndrome in Chinese adults: the Shandong and Ministry of Health Action on Salt and Hypertension (SMASH) study. Br J Nutr. 2015;113:996-1002.
- 27. O'Donnell MJ, Yusuf S, Mente A, Gao P, Mann JF, Teo K et al. Urinary sodium and potassium excretion and risk of cardiovascular events. JAMA. 2011;306:2229-38.
- 28. Yan L, Bi Z, Tang J, Wang L, Yang Q, Guo X et al. Relationships Between Blood Pressure and 24-Hour Urinary Excretion of Sodium and Potassium by Body Mass Index Status in Chinese Adults. J Clin Hypertens (Greenwich). 2015;17:916-25.
- 29. Yan L, Guo X, Wang H, Zhang J, Tang J, Lu Z et al. Population-based association between urinary excretion of sodium, potassium and its ratio with albuminuria in Chinese. Asia Pac J Clin Nutr. 2016;25:785-97.
- Yu D, He Y, Fang H, Xu X, Wang X, Yu W et al. Salt intake among Chinese adults in 2010-2012. Zhonghua Yu Fang Yi Xue Za Zhi. 2016;50:217-20. (In Chinese)
- 31. Li N, Yan LL, Niu W, Yao C, Feng X, Zhang J et al. The effects of a community-based sodium reduction program in rural China a cluster-randomized trial. PLoS One. 2016;11:e0166620.
- 32. McLaren L, Sumar N, Barberio AM, Trieu K, Lorenzetti DL, Tarasuk V et al. Population-level interventions in government jurisdictions for dietary sodium reduction. Cochrane Database Syst Rev. 2016;9:CD010166.
- 33. Wang X, Li X, Vaartjes I, Neal B, Bots ML, Hoes AW et al. Does education level affect the efficacy of a community based salt reduction program? - A post-hoc analysis of the China Rural Health Initiative Sodium Reduction Study (CRHI-SRS). BMC Public Health. 2016;16:759.

- 34. Yang P, Chen Z, Yin L, Peng Y, Li X, Cao X et al. Salt intake assessed by spot urine on physical examination in Hunan, China. Asia Pac J Clin Nutr. 2019;28:845-56. doi: 10.6133/apjcn.201912_28(4).0022.
- 35. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S76-99.
- Institute of Medicine. Dietary reference intakes for water, potassium, sodium, chloride, and sulfate.
 Washington, DC: The National Academies Press; 2005.
- 37. The State Council. National Nutrition Plan (2017-2030). Beijing, China. [cited 2017/07/13]; Available at http://english.www.gov.cn/policies/latest_releases/2017/07/13/content_281475725038850.htm.
- Diet, nutrition and the prevention of chronic diseases. World Health Organ Tech Rep Ser. 2003;916:iviii, 1-149.
- 39. Chen X, Guo X, Ma J, Zhang J, Tang J, Yan L et al. Urinary sodium or potassium excretion and blood pressure in adults of Shandong province, China: preliminary results of the SMASH project. J Am Soc Hypertens. 2015;9:754-62.
- 40. Brown IJ, Dyer AR, Chan Q, Cogswell ME, Ueshima H, Stamler J, Elliott P, Group IC-OR. Estimating 24-hour urinary sodium excretion from casual urinary sodium concentrations in Western populations: the INTERSALT study. Am J Epidemiol. 2013;177:1180-92

13

Characteristics [†]	Total	Hypertensive	Normotensive	Hypotensive	†
(mean±SD)	(N=26,363)	(n=7,201)	(n=17,735)	(n=1,427)	ptrend*
Age (years)	46.4±11.8	53.3±10.7	43.9±11.1	41.9±11.6	< 0.001
BMI (kg/m^2)	24.2±3.3	25.3±3.3	23.9±3.2	22.1±2.5	< 0.001
BMI categories % (n)					< 0.001
<18.5	2.6 (697)	1.2 (84)	3.0 (534)	5.5 (79)	
18.5-24.9	58.9 (15,538)	46.1 (3,318)	62.3 (11,050)	82.0 (1,170)	
25.0-29.9	34.0 (8,955)	45.4 (3,266)	31.1 (5,515)	12.2 (174)	
≥30.0	4.4 (1,173)	7.4 (533)	636 (3.6)	0.3 (4)	
SBP (mmHg)	123.0±16.0	137.3±17.6	119.0±10.8	101.4±8.3	< 0.001
DBP (mmHg)	75.3±11.4	84.3±12.5	73.2±7.8	56.0±2.9	< 0.001
Waist (cm)	82.1±10.0	86.0±9.5	81.1±9.8	74.7±7.6	< 0.001
Pulse (beats/minute)	79.4±11.6	79.9±12.2	79.5±11.4	75.3±10.4	0.376
FSG (mmol/L)	5.59±1.35	6.13±1.91	5.41 ± 1.00	5.16±0.82	< 0.001
SCr (mmol/L)	73.1±20.6	76.3±29.6	72.6±15.7	63.1±13.5	< 0.001
TC (mmol/L)	5.02±0.97	5.16 ± 1.05	4.99±0.94	4.72±0.90	< 0.001
TG (mmol/L)	1.81 ± 1.70	2.13 ± 1.98	1.74±1.61	1.14±0.89	< 0.001
LDL-C (mmol/L)	2.85±0.83	2.89 ± 0.91	2.84±0.80	2.71±0.75	0.001
HDL-C (mmol/L)	1.36±0.31	1.31±0.29	1.37±0.31	1.50±0.32	< 0.001
Estimated UNa (g/day) §	4.26±1.17	4.33±1.24	4.26±1.15	3.89±1.04	0.007
Estimated UK (g/day) §	2.11±0.46	2.08 ± 0.46	2.13±0.46	2.02 ± 0.42	< 0.001
Estimated UCr (g/day) §	1.37±0.39	1.36 ± 0.37	1.39 ± 0.39	1.10 ± 0.27	< 0.001
Salt intake (g/day) ³	10.8±3.0	11.0±3.1	10.8 ± 2.9	9.9 ± 2.6	0.007
Male sex % (n)	57.0 (15,027)	64.4 (4,639)	57.2 (10,137)	17.6 (251)	< 0.001
Current alcohol users % (n)	31.3 (7,539)	33.8 (2,277)	31.6 (5074)	14.9 (188)	< 0.001
Current smokers % (n)	24.2 (5,815)	25.4 (1,707)	24.7 (3,972)	10.8 (136)	0.536
Self-reported diabetes % (n)	2.9 (776)	9.7 (701)	0.4 (74)	0.1 (1)	< 0.001
Self-reported stroke % (n)	0.3 (73)	0.8 (59)	0.1 (14)	0 (0)	< 0.001
Self-reported CHD % (n)	1.0 (267)	2.9 (211)	0.3 (53)	0.2 (3)	< 0.001
Self-reported dyslipidemia % (n)	2.6 (695)	5.8 (415)	1.5 (268)	0.8 (12)	< 0.001

Table 1. Characteristics by hypertensive, normotensive, and hypotensive subgroups

SD: standard deviance; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FSG: fasting serum glucose; SCr: serum creatinine; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; UNa: urinary sodium excretion; UK: urinary potassium excretion; UCr: urinary creatinine excretion; CHD: coronary heart diseases.

[†]Sum may not always add up to total because of mission values.

 p_{trend} were obtained using generalized linear models for continuous variables and Mantel-Haenszel Chi-square trend test for categorical variables.

[§]24-hour urinary sodium, potassium, and creatinine were estimated using Kawasaki formula 22.



Figure 1. Adjusted associations of blood pressure with eUNaE, eUKE, and Na/K ratio in hypertensive, normotensive, and hypotensive individuals[†]. SBP, systolic blood pressure; DBP, diastolic blood pressure; eUNaE, estimated urinary sodium excretion; eUKE, estimated urinary potassium excretion; Na/K ratio, ratio for estimated urinary sodium to potassium excretion. [†]Adjusted for age, gender, body mass index, smoking status, alcohol use.



Figure 2. Forest plots of changes in systolic and diastolic blood pressure per unit increase of ratio for estimated urinary sodium to potassium excretion^{\dagger}. [†]Adjusted for age, gender, body mass index, smoking status, alcohol use.



Figure 3. Mean systolic and diastolic blood pressure according to estimated urinary sodium and potassium excretion^{\dagger}. [†]Adjusted for age, gender, body mass index, smoking status, alcohol use.



Supplementary figure 1. Flow chart of participant selection. SBP: systolic blood pressure; DBP: diastolic blood pressure; eUNaE: estimated urinary sodium excretion; eUKE: estimated urinary potassium excretion.