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# Discrepant acute effect of saline loading on blood pressure, urinary sodium and potassium according to salt intake level: EpiSS study

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## Abstract

Acute dietary salt intake may cause an elevation in blood pressure (BP). The study aimed to assess the acute effect of saline loading on BP in subjects with different levels of salt intake. This study is based on the baseline survey of systemic epidemiology of salt sensitivity study. The sodium excretion in the 24-hour urine was calculated for estimating the level of salt intake. Subjects were performed an acute oral saline loading test (1 L), and data of 2019 participants were included for analyses. Multivariate linear regression and stratified analyses were performed to identify associations between 24-hour urinary sodium (24hUNa) with BP changes. Due to saline loading, systolic BP (SBP), pulse pressure, and urinary sodium concentration were significantly increased, while diastolic BP, heart rate, and urinary potassium concentration were significantly decreased. The SBP increments were more significant in subjects with lower salt intake, normotensives, elders, males, smokers, and drinkers. There was a significant linear negative dose-response association between SBP increment with 24hUNa ($\beta$ = −0.901, 95% CI: −1.253, −0.548), especially in lower salt intake individuals ($\beta$ = −1.297, 95% CI: −2.338, −0.205) and hypertensive patients ($\beta$ = −1.502, 95% CI: −2.037, −0.967). After excluding patients who received antidiabetic or antihypertensive medicines, the effects of negative associations weakened but remained significantly. In conclusion, acute salt loading leads to an increment in SBP, and the increased SBP was negatively related with 24hUNa. This study indicated avoiding acute salt loading was important for escaping acute BP changes, especially in lower salt intake populations.

## 1 | INTRODUCTION

Large epidemiology studies suggest that high-salt diet is an important trigger for blood pressure (BP) elevation, including the International Cooperative Study on Salt, Other Factors, and Blood Pressure (Intersalt) study,[1] and the Prospective Urban and Rural Epidemiology (PURE) study.[2] Accordingly, it has been long known that eating on a low-sodium diet would help prevent and control

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hypertension. The prevention and control of hypertension in China (2018) recommended a salt intake of less than 6 g/day,[3] and The World Health Organization population target for salt intake is 5 g/day.[4] However, very few populations fulfill these recommendations, and people may have an acute dietary salt intake occasionally, which could lead to an elevation in BP.

Some researchers reported that excessive acute salt intake might be harmful for organic, animal studies reported a high-salt intake intervention was associated with increased post-infarct arrhythmias,[5] accelerated post-infaction ventricular remodeling, and elevated mortality rate.[6] Moreover, the association between saline loading with atrial natriuretic peptide (ANP),[7] renal vascular resistance,[8] circulating angiotensin II concentration,[9] renal sodium excretion,[10] and urinary dopamine and noradrenaline [11] had been long explored in human previously, which were related to the incidence of hypertension and BP mediation.

An acute administration of sodium could suppresses plasma renin activity (PRA)[12,13] and then produce hypertension.[14] It is well known that the synthesis and release of renin is inversely related to salt intake. Increasing the NaCl concentration at the macula densa suppressed the renin release.[15] Isaksson and colleagues found that the plasma renin concentration fell with a half-life of 4.6 h during the 48 h of intravenous salt loading experiment.[16] In contrast, the stimulation of longer lasting reductions of salt intake will induce the reversible transformation to renin-producing cells of the preglomerular vascular smooth muscle cells.[17,18] Recent research indicated that intestinal flora could modulate BP by regulating the synthesis of intestinal-derived corticosterone in high-salt-induced hypertension.[19] The elevation of plasma sodium could increase BP, and Suckling and colleagues found that a 1-mmol/L increase in plasma sodium was associated with a 1.91-mmHg increase in systolic BP (SBP).[20]

There were differences in the response of individuals to the acute salt loading. A previous study had demonstrated that women, hypertensives, and elders had increased salt sensitivity of BP by conducting dietary salt intervention trial.[21] However, there were few population-based epidemiological studies focused on BP response to acute saline loading in people with different salt intake levels. We hypothesized that the variations of BP after acute oral saline in subjects with different levels of salt intake are different. Thus, this study aimed to assess the acute effect of saline loading on BP, and the associations of BP changes with 24-hour urinary sodium excretion in subjects with different levels of salt intake.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

All participants in this study were derived from the baseline survey of the systemic epidemiology of salt sensitivity (EpiSS) study. EpiSS is a study aimed to uncover both the genetic and environmental factors of salt sensitivity of blood pressure. This study was registered in the Chinese Clinical Trial Registry (No: ChiCTR1900024725, http://www.chictr.org.cn/index.aspx). The protocol for selection of the subjects, sample collection, and measurement methods have been described in detail previously,[22] including the inclusion and exclusion criteria for subjects, questionnaire survey, anthropometric measurements, urine (spot and 24 hours), and blood sample collection. Briefly, participants aged 35 to 70 years were recruited voluntarily from five community health centers in Beijing and six community health centers in Liaoning Province during July 2014 and July 2016. Patients with hypertension and diabetes were required to stop the intake of all antihypertensive and antidiabetic drugs for at least 24 h. In addition, pregnant women, self-adherence to a low-sodium diet people, patients with secondary stage and above hypertension [SBP >160 mmHg and (or) diastolic BP (DBP) >100 mmHg], and individuals with clinical diagnosis of cardiovascular disease, kidney disease, liver disease, or malignant tumors were excluded.

### 2.2 | Saline loading protocol

There are two mainstream intervention for acute saline loading, oral saline, and intravenous saline. In the EpiSS study, all participants were subjected to the oral saline loading test, which was the first stage of the Modified Sullivan's acute oral saline load and diuresis shrinkage test (MSAOSL-DST).[23-26] The saline loading test was performed in the morning with a stable room temperature 20–24°C, and participants fasted 8 ± 2 h before test. The test was divided into three steps. First, baseline BP was measured after taking a rest at least 15 min, and blood and spot urine samples were obtained at baseline. Second, subjects were asked to take 1000 ml of 0.9% saline solution orally within 30 min. Third, the second time BP was measured, and spot urine samples were obtained after two hours from the time each individual finished drinking the saline.

### 2.3 | Data collection and variables

Questionnaires were completed through a face-to-face interview, and information including age, sex, smoking status, alcohol consumption status, dietary habits, and self-reported chronic disease were collected. Considering the effect of antihypertensive or antidiabetic medication on urine sodium and potassium in hypertensive and diabetic patients, we also summarized antihypertensive drugs including calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor inhibitors (ARB), diuretic, beta-blockers, the compound preparation and Chinese patent medicine, and antidiabetic drugs including biguanides, sulfonylureas, thiazolidinediones, glinides, alpha-glycosidase inhibitors, and insulin.

The anthropometric measurements included height, weight, and waist and hip circumference. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m), and waist-to-hip ratio (WHR) as the ratio of waist circumference (cm) to hip circumference (cm). BMI was grouped

according to the Working Group on Obesity in China[27]: normal weight (BMI < 24.0 kg/m$^2$), overweight (BMI 24.0 to < 28.0 kg/m$^2$), and obesity (BMI ≥ 28.0 kg/m$^2$).

Seated BP, including SBP and DBP, was measured after at least 15-min rest with an automatic sphygmomanometer (Omron HEM-7118, Japan).[28] BP measurement was carried out twice with a 1 min interval, and the average of the two readings was used in data analysis. If the difference between the two values was greater than five mmHg, then a third measurement was taken, and the mean value of the last two measurements was considered as the final BP. In addition, the pulse pressure (PP) was equal to final SBP value minus DBP value. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or current use of antihypertensive medications.[29]

The urinary sodium and potassium concentrations in the spot urine sample (1 ml) and 24-hour urine sample were measured by a Cobas C8000 analyzer (Roche, Basel, Switzerland). The daily sodium and potassium intake were estimated by the 24-hour urinary sodium (24hUNa) and potassium (24hUK). And 24-hour urinary sodium-to-potassium ratio (24hUNa/K) is defined as moles of sodium divided by moles of potassium. Each participant was given a 5 L plastic container with a lid to collect 24-hour urine samples. The 24-hour urine sample was collected one week after MSAOSL-DST, during which the subjects were on a normal diet. A urine volume of more than 500 ml was considered as effective sample.[30] The daily salt consumption (indicated by e24hSalt) was estimated by the following formula:

$$\text{e24hSalt}\,(\text{g/day}) = \frac{24\text{hUNaC} \times 24\text{hUV} \times \text{M}\,(\text{NaCl})}{1000}$$

e24hSalt, estimated 24-hour salt intake.

24hUNaC, 24-hour urinary $Na^+$ excretion concentration value (mmol/L).

24hUV, 24-hour urine volume (L).

M, molar mass (g/mol).

## 2.4 | Statistical analysis

All statistical analyses were performed using SPSS 24.0 for Windows (SPSS, Inc, Chicago, IL, USA). Two-tailed and $p < .05$ indicated a statistically significant difference. Data were expressed as mean ± standard deviation (SD) for normally distributed data, median ± inter-quartile range (IQR) for non-normally distributed data, and numbers (percentages) for categorical variables. Normally distributed data were analyzed using a Student's t tests and non-normally distributed data using a Wilcoxon rank sum test. Changes of SBP, DBP, PP, heart rate (HR), spot urinary sodium concentration (UNaC), and spot urinary potassium concentration (UKC) before and after acute oral saline loading were calculated. The paired-samples Wilcoxon test was conducted to compare variables measured after saline loading and baseline. The Mann-Whitney U test and Kruskal-Wallis test were applied to compare the changes of SBP, DBP, PP, HR, UNaC, and UKC between different groups. Multiple linear regression analyses were performed for BP changes and 24hUNa, 24hUK, 24hUNa/K after adjusting for age, sex, BMI, fasting blood glucose (FBG), current smoking, and drinking. Stratified analysis was performed by age, sex, BMI, level of salt consumption, hypertension status, diabetes status, smoking, and drinking. Subjects with e24h-Salt ≥ 8.00 g/day (median) were classified into group of higher salt intake, and < 8.00 g/day were classified into group of lower salt intake.

According to the Guidelines for the Prevention and Treatment of Hypertension in China (Revised Edition, 2018) [3] and the Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2017),[31] antidiabetic medications and antihypertensive drugs such as ACEI, ARB, and diuretic can interfere both in the measurement of sodium from a sample spot and in the determination of salt intake. Therefore, we performed sensitive analysis to examine whether these therapies could influence the association between BP changes and 24hUNa, 24hUK, 24hUNa/K.

# 3 | RESULTS

## 3.1 | Study population and baseline characteristics

The characteristics of all participants and that classified by salt intake level or hypertension were presented in Table 1. A total of 2019 participants (58.13 ± 7.49 years, 542 males) were included in this study, in which 1040 (51.51%) were hypertensive patients. And 374 (35.96%) hypertensive patients claimed to limit their dietary salt intake to control BP level. The distribution of e24hSalt, 24hUNa, 24hUK, and 24hUNa/K was all left skewed (Figure 1), with the median (IQR) of 8.00 (5.27–11.41) g/day, 3.14 (2.07–4.49) g/day, 1.67 (1.15–2.27) g/day, and 3.28 (2.31–4.38), respectively.

## 3.2 | Changes of variables after acute saline loading

After saline loading, SBP and PP increased significantly by 8.12 and 11.67 mmHg, while DBP and HR decreased by 3.55 mmHg and −2.25 bpm, respectively (Table 2). The changes varied between different characteristic groups (Table 3). The increment of SBP was greater in subjects with lower salt intake compared to those with high-salt intake (8.99 ± 11.21 vs. 7.25 ± 12.92 mmHg, $p = .001$). More significant increased SBP was found in normotensives, elders, males, smokers, and drinkers. The decrement of DBP showed no significant difference between high- and low-salt intake groups (−3.50 ± 6.74 vs. −3.60 ± 6.87 mmHg, $p = .854$), while it decreased more significantly in females, normal weight people (BMI < 24 kg/m$^2$), non-smokers, and non-drinkers (Table 3). Subgroup analyses showed that the increment of SBP was also greater in subjects with lower salt intake compared to those with high-salt intake, in subgroups of hypertensives, youngers, females, obese people (BMI ≥ 28 kg/m$^2$), non-diabetics, non-smokers, and drinkers (Figure 2).

**TABLE 1** Characteristics of the participants classified by salt intake levels or hypertension

| Variables | Total | Lower salt intake | Higher salt intake | $p^1$ | Hypertension | Normotension | $p^2$ |
|---|---|---|---|---|---|---|---|
| Number (%)[b] | 2019 | 1009 (49.98) | 1010 (50.02) | - | 1040 (51.51) | 979 (48.49) | - |
| Age (years)[b] | 59 (54–63) | 60 (54–64) | 59 (53–63) | .002 | 60 (55–64) | 58 (52–63) | <.001 |
| Sex (male, *n*, %)[a] | 542 (26.84) | 239 (23.69) | 303 (30.00) | .001 | 307 (29.50) | 235 (24.00) | .005 |
| BMI ($kg/m^2$)[b] | 25.92 (23.84–28.13) | 25.44 (23.34–27.34) | 26.45 (24.59–28.72) | <.001 | 26.83 (24.88–29.02) | 25.11 (22.99–26.94) | <.001 |
| WHR[b] | 0.89 (0.85–0.93) | 0.89 (0.85–0.92) | 0.89 (0.86–0.93) | <.001 | 0.90 (0.86–0.94) | 0.88 (0.84–0.91) | <.001 |
| e24hSalt (g/day)[b] | 8.00 (5.27–11.41) | 5.27 (3.81–6.60) | 11.41 (9.59–14.21) | <.001 | 8.94 (6.28–12.33) | 6.90 (4.57–10.46) | <.001 |
| 24hUNa (g/day)[b] | 3.14 (2.07–4.49) | 2.07 (1.50–2.59) | 4.49 (3.77–5.59) | <.001 | 3.52 (2.47–4.95) | 2.71 (1.80–4.11) | <.001 |
| 24hUK (g/day)[b] | 1.67 (1.15–2.27) | 1.29 (0.91–1.80) | 2.044 (1.58–2.60) | <.001 | 1.77 (1.25–2.32) | 1.54 (1.07–2.21) | <.001 |
| 24hUNa/K[b] | 3.28 (2.31–4.38) | 2.58 (1.82–3.55) | 3.93 (3.03–5.10) | <.001 | 3.50 (2.43–4.59) | 3.02 (2.12–4.19) | <.001 |
| FBG (mmol/L)[b] | 5.42 (4.99–6.18) | 5.36 (4.96–5.96) | 5.51 (5.00–6.43) | <.001 | 5.62 (5.07–6.47) | 5.27 (4.91–5.86) | <.001 |
| TC (mmol/L)[b] | 5.04 (4,35–5.72) | 5.05 (4.37–5.72) | 5.03 (4.32–5.73) | .993 | 5.00 (4.21–5.70) | 5.08 (4.47–5.76) | .273 |
| TG (mmol/L)[b] | 1.63 (1.13–2.49) | 1.61 (1.13–2.49) | 1.64 (1.12–2.49) | .874 | 1.69 (1.18–2.53) | 1.54 (1.09–2.41) | .057 |
| HDL-C (mmol/L)[b] | 1.44 (1.13–2.40) | 1.41 (1.12–2.40) | 1.47 (1.14–2.40) | .347 | 1.48 (1.13–2.40) | 1.39 (1.13–2.40) | .572 |
| LDL-C (mmol/L)[b] | 2.27 (1.54–2.97) | 2.30 (1.58–2.96) | 2.25 (1.52–2.98) | .803 | 2.29 (1.50–3.09) | 2.25 (1.58–2.87) | .015 |
| Diabetes (*n*, %)[a] | 320 (15.85) | 128 (12.69) | 176 (17.43) | .003 | 225 (21.63) | 95 (9.70) | <.001 |
| Current smoking (yes, *n*, %)[a] | 304 (15.06) | 465 (46.09) | 491 (48.61) | .255 | 174 (16.73) | 130 (13.28) | .030 |
| Current drinking (yes, *n*, %)[a] | 956 (47.35) | 118 (11.69) | 202 (20.00) | <.001 | 498 (44.04) | 458 (46.78) | .620 |

*Note:* $p < .05$ was considered statistically significant; $p^1$, compared between lower salt intake and higher salt intake; $p^2$, compared between hypertension and normotension.

Abbreviations: 24hUK, 24-hour urinary potassium excretion; 24hUNa, 24-hour urinary sodium excretion; 24hUNa/K, 24-hour urinary sodium-to-potassium ratio; BMI, body mass index; e24hSalt, estimated 24-hour salt intake; FBG, fasting blood glucose; HDL-C, high density lipoprotein-cholesterol; Higher salt intake, subjects whose e24hSalt ≥ 8.00 g/day; LDL-C, Lower salt intake, subjects whose e24hSalt < 8.00 g/day (median); TC, total cholesterol; TG, triglycerides; WHR, waist-to-hip ratio.

[a]Statistical testing by chi-square test.

[b]Statistical testing by Mann-Whitney U test.

The UNaC and UKC also changed due to saline loading, the mean level of UNaC was significantly increased by 7.06 mmol/L, while UKC was significantly decreased by 25.06 mmol/L (Table 2). In total, the increment of UNaC was more significant in hypertensives, non-diabetics, and drinkers; and the decrement of UKC was more significant in normotensives and non-drinkers (Table 3). In addition, there was no difference in UNaC elevation between the lower salt intake subjects and high-salt intake participants in all subgroups; and individuals with lower salt intake in elders observed more obvious UKC decrement than higher salt intake subjects (Figure 2).

## 3.3 | The association of BP changes with 24hUNa, 24hUK, and 24hUNa/K

The variables of 24hUNa, 24hUK, and 24hUNa/K were divided into five quintiles, and the association between BP changes and electrolyte level was analyzed (Figure 3). There was significant downward trend in SBP increment according to 24hUNa five quintiles ($Q_1$ = 9.36, $Q_2$ = 9.30, $Q_3$ = 8.61, $Q_4$ = 7.36, $Q_5$ = 5.97 mmHg, $p_{\text{for trend}} < .001$), and 24hUNa/K ($Q_1$ = 9.20, $Q_2$ = 8.78, $Q_3$ = 8.41, $Q_4$ = 6.78, $Q_5$ = 7.42, $p_{\text{for trend}} < .001$). The average decrement of DBP showed no significant trend in five 24hUNa, 24hUK, and 24hUNa/K quintiles ($p > .05$).

Table 4 described the associations of BP changes with 24hUNa, 24hUK, and 24hUNa/K per one-unit increase adjusted for sex, age, BMI, FBG, smoking, and drinking. Totally, after saline loading, there was a significant linear negative dose-response association between SBP increment with 24hUNa ($\beta$ = −0.901, 95% confidence interval (CI): −1.253, −0.548; $p < .001$) and 24hUNa/K ($\beta$ = −0.571, 95% CI: −0.890, −0.255; $p < .001$), respectively.

Stratified analysis was performed by age, sex, BMI, salt intake level, hypertension, diabetes, current smoking, and drinking (Table 4, Figure 4, Figures S1 and S2). The negative association between SBP increment with 24hUNa in subgroup of lower salt intake seems more stronger ($\beta$ = −1.297, 95% CI: −2.338, −0.205; $p = .020$) than that in subgroup of higher salt intake ($\beta$ = −0.978, 95% CI: −1.565, −0.390; $p = .001$, Table 4).

In patients with hypertension, SBP increment due to saline loading decreased by 1.502 mmHg (95% CI: −2.037, −0.967; $p < .001$), and 1.293 mmHg (95% CI: −1.789, −0.797; $p < .001$) for every 1 g increase in 24hUNa and 1 unit increase of 24hUNa/K, increased by 1.646 mmHg (95% CI: 0.538, 2.754; $p = .004$) for every 1 g increase

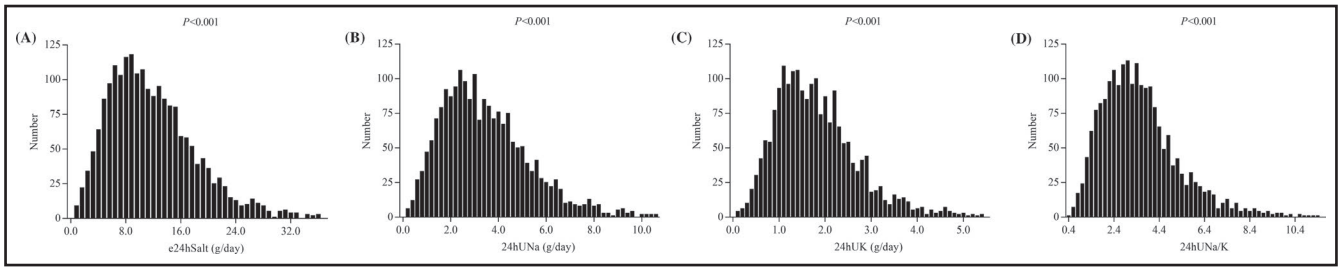


**FIGURE 1** The distribution of e24hSalt, 24hUNa, 24hUK, and 24hUNa/K. e24hSalt, estimated 24-hour salt intake; 24hUNa, 24-hour urinary sodium excretion; 24hUK, 24-hour urinary potassium excretion; 24hUNa/K 24-hour urinary sodium-to-potassium ratio. Statistical testing by normality test. $p < .05$ was considered statistically significant

**TABLE 2** Variation of blood pressure and spot urinary electrolyte concentrations after acute saline loading

| Variables | Baseline | After saline loading | Changes | *Z* | *p* |
|---|---|---|---|---|---|
| SBP (mmHg) | 122.87 ± 19.98 | 130.99 ± 18.09 | 8.12 ± 12.12 | −21.19 | <.001 |
| DBP (mmHg) | 77.21 ± 11.04 | 73.66 ± 10.88 | −3.55 ± 6.81 | −22.31 | <.001 |
| PP (mmHg) | 45.66 ± 15.00 | 57.33 ± 13.55 | 11.67 ± 10.46 | −33.94 | <.001 |
| HR (bpm) | 74.43 ± 10.59 | 72.18 ± 9.98 | −2.25 ± 6.67 | −11.71 | <.001 |
| UNaC (mmol/L) | 131.41 ± 49.03 | 138.47 ± 52.00 | 7.06 ± 53.08 | −6.64 | <.001 |
| UKC (mmol/L) | 68.22 ± 36.02 | 43.16 ± 25.03 | −25.06 ± 35.65 | −38.00 | <.001 |

*Note:* Changes, variables measured after saline loading minus variables measured at baseline time, *Z*, statistic. Compared between variables measured after saline loading and that measured at baseline time. $p < .05$ was considered statistically significant. Statistical testing by paired-samples Wilcoxon test.

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure; UKC, spot urinary potassium concentration; UNaC, spot urinary sodium concentration.

of 24hUK (Table 4). In normotensive participants, SBP increment insignificantly changed by 0.246 mmHg (95% CI: −0.190, 0.683; $p = .269$) in 24hUNa and −0.786 mmHg (95% CI: −1.645, 0.072; $p = .073$) in 24hUK for every 1 g increase, while significantly increased by 0.434 mmHg (95% CI: 0.056, 0.812; $p < .001$) for every 1 unit increase of 24hUNa/K (Table 4).

Furthermore, with every 1-g increase in 24hUNa, the average SBP increments of individuals in most subgroups significantly decreased, except for normal weight people (BMI < 24 kg/m$^2$) (Figure 4A). The negative associations between 24hUNa with both SBP elevation and PP increment in elders, males, obese people (BMI ≥ 28 kg/m$^2$), diabetes patients, smokers, and non-drinkers were significantly stronger than the corresponding subgroups (Figure 4A,C). However, the correlations of DBP changes with 24hUNa in most subgroups were insignificant (Figure 4B). In addition, the results of relationships between BP changes with 24hUK and 24hUNa/K were showed in supplement (Figure S1 and S2), respectively.

## 3.4 | Sensitive analysis

The association between BP changes and 24hUNa, 24hUK, and 24hUNa/K was analyzed after excluding patients who received antidiabetic drugs (99 patients were excluded) or antihypertensive drugs inclusive of ACEI (62 patients were excluded), ARB (132 patients were excluded), diuretic (18 patients were excluded), or the compound preparation (119 patients were excluded) contain one or more of these three medicines.

After excluding these subjects, the linear negative dose-response association between SBP increment with 24hUNa became weaker ($\beta = -0.579$, 95% CI: −0.966, −0.192; $p = .003$, Table S1) than that in total population ($\beta = -0.901$). This phenomenon also appeared in the associations between SBP increment with 24hUK ($\beta = 0.216$, 95% CI: −0.561, 0.993; $p = .586$) and 24hUNa/K ($\beta = -0.322$, 95% CI: −0.664, 0.020; $p = .065$). Furthermore, the negative associations between SBP increment with 24hUNa in both subgroup of lower salt intake ($\beta = -1.062$, 95% CI: −2.203, 0.079; $p = .068$) and subgroup of higher salt intake ($\beta = -0.606$, 95% CI: −1.277, 0.066; $p = .077$, Table S1) turned to be insignificant.

In 697 hypertensive patients, SBP increment significantly decreased by 1.104 mmHg (95% CI: −1.769, −0.440; $p = .001$) for every 1 g increase in 24hUNa, insignificantly increased by 1.294 mmHg (95% CI: −0.044, 2.633; $p = .058$) for every 1 g increase in 24hUK, and significantly decreased by 1.055 mmHg (95% CI: −1.651, −0.459; $p = .001$) for every 1 unit increase of 24hUNa/K. In 939 normotensive subjects, SBP increment insignificantly changed by 0.208 mmHg (95% CI: −0.240, 0.656; $p = .363$) in 24hUNa and −0.795 mmHg (95% CI: −1.677, 0.087; $p = .077$) in 24hUK for every 1 g increase, while significantly increased by 0.418 mmHg (95% CI: 0.033, 0.803; $p = .033$) for every 1 unit increase of 24hUNa/K (Table S1).

**TABLE 3** Comparison of changes of blood pressure and spot urinary electrolyte concentrations in different groups

| Variables | ΔSBP (mmHg) | ΔDBP (mmHg) | ΔPP (mmHg) | ΔHR (bpm) | ΔUNaC (mmol/L) | ΔUKC (mmol/L) |
|---|---|---|---|---|---|---|
| Age (years)[a] | | | | | | |
| <60 | 7.72 ± 11.62* | −3.50 ± 6.81 | 11.22 ± 9.97* | −2.40 ± 6.48 | 8.53 ± 55.38 | −24.96 ± 37.22 |
| ≥60 | 8.55 ± 12.64 | −3.61 ± 6.81 | 12.16 ± 10.94 | −2.05 ± 5.72 | 4.49 ± 50.46 | −25.17 ± 33.89 |
| Sex[a] | | | | | | |
| Male | 8.99 ± 11.96* | −2.94 ± 7.07* | 11.93 ± 10.35 | −1.65 ± 6.66 | 3.99 ± 48.70 | −22.43 ± 30.58 |
| Female | 7.80 ± 12.17 | −3.78 ± 6.69 | 11.58 ± 10.49 | −2.45 ± 5.98 | 8.19 ± 54.57 | −26.03 ± 37.30 |
| BMI (kg/m$^2$)[b] | | | | | | |
| <24 | 8.61 ± 10.64 | −4.10 ± 6.45* | 12.71 ± 9.05* | −3.33 ± 6.51* | 0.11 ± 52.75* | −28.67 ± 38.15 |
| 24 ≤ BMI<28 | 8.48 ± 12.21 | −3.10 ± 6.85 | 11.58 ± 10.67 | −2.01 ± 5.96 | 7.74 ± 52.92 | −23.80 ± 34.59 |
| ≥28 | 6.96 ± 13.30 | −3.82 ± 7.02 | 10.78 ± 11.29 | −1.46 ± 5.98 | 12.97 ± 53.01 | −23.66 ± 34.71 |
| e24hSalt (g/day)[a] | | | | | | |
| Lower salt intake | 8.99 ± 11.21* | −3.50 ± 6.74 | 12.49 ± 9.56** | −2.33 ± 6.31 | 6.72 ± 52.01 | −24.99 ± 37.22 |
| Higher salt intake | 7.25 ± 12.92 | −3.60 ± 6.87 | 10.85 ± 11.22 | −2.17 ± 6.02 | 7.41 ± 54.16 | −25.13 ± 34.02 |
| Current smoking[b] | | | | | | |
| Yes | 9.99 ± 11.58* | −2.19 ± 6.78** | 12.19 ± 9.83 | −1.49 ± 6.03 | 8.55 ± 52.75 | −23.11 ± 33.37 |
| No | 7.79 ± 12.19 | −3.79 ± 6.78 | 11.58 ± 10.56 | −2.39 ± 6.18 | 6.80 ± 53.15 | −25.41 ± 36.04 |
| Current drinking[b] | | | | | | |
| Yes | 8.80 ± 11.93* | −3.09 ± 6.80* | 11.89 ± 10.20 | −2.25 ± 6.23 | 11.30 ± 52.70* | −21.61 ± 30.20** |
| No | 7.51 ± 12.27 | −3.97 ± 6.78 | 11.48 ± 10.68 | −2.25 ± 6.15 | 3.25 ± 53.15 | −28.16 ± 39.68 |
| Diabetic status[b] | | | | | | |
| Diabetics | 9.23 ± 13.01 | −3.08 ± 7.15 | 12.31 ± 10.74 | −2.74 ± 5.91 | 1.21 ± 48.87* | −25.72 ± 33.70 |
| Non-diabetic | 7.91 ± 11.94 | −3.64 ± 6.74 | 11.55 ± 10.40 | −2.16 ± 6.21 | 8.17 ± 53.78 | −24.94 ± 36.01 |
| Hypertensive status[b] | | | | | | |
| Hypertensive | 6.23 ± 13.63** | −3.77 ± 6.91 | 10.00 ± 11.74** | −1.67 ± 6.26* | 10.10 ± 50.33* | −23.60 ± 32.86* |
| Normotensive | 10.13 ± 9.91 | −3.32 ± 6.69 | 13.45 ± 8.54 | −2.76 ± 6.05 | 3.84 ± 55.70 | −26.62 ± 38.34 |
| Medicines[b] | | | | | | |
| Taking | 7.54 ± 13.49 | −3.49 ± 6.56 | 11.02 ± 11.27 | −1.94 ± 5.74 | 9.61 ± 50.12 | −24.57 ± 34.66 |
| Not taking | 8.26 ± 11.78 | −3.57 ± 6.86 | 11.83 ± 10.25 | −2.32 ± 6.27 | 6.46 ± 53.75 | −25.18 ± 35.89 |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; e24hSalt, estimated 24-hour salt intake; Higher salt intake, subjects whose e24hSalt ≥ 8.00 g/day. Medicines, antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors, diuretic, and the compound preparation), and antidiabetic drugs (biguanides, sulfonylureas, thiazolidinediones, glinides, alpha-glycosidase inhibitors, and insulin); HR, heart rate; Lower salt intake, subjects whose e24hSalt < 8.00 g/day (median); PP, pulse pressure; SBP, systolic blood pressure; UKC, spot urinary potassium concentration; UNaC, spot urinary sodium concentration; Δ, changes after saline loading.

[a]Statistical testing by Mann-Whitney U test.

[b]Statistical testing by Kruskal-Wallis test.

*$p < .05$.

**$p < .001$.

## 4 | DISCUSSION

In the present study, a total of 2019 participants were performed an acute oral saline loading test. Our results showed that the SBP, PP, and UNaC were significantly increased, while DBP, HR, and UKC were significantly decreased after saline loading. The increment of SBP was more significant in subjects with lower salt intake, normotensives, elders, males, smokers, and drinkers. Stratified analyses showed that individuals with lower salt intake in hypertensives, youngers, females, obese people, non-diabetics, non-smokers, and drinkers observed higher SBP elevation than those with higher salt intake. There was a significant linear negative dose-response association between the SBP increment and 24hUNa or 24hUNa/K, especially in subjects with lower salt intake and hypertensive patients.

Few population-based studies focused on BP response to acute saline loading. In this study, we found SBP significantly increased by 8.12 mmHg, but DBP significantly decreased 3.55 mmHg. These findings consistent with previous data, Brown CM and colleagues conducted oral saline trail on nine young healthy subjects, and observed that SBP increased by 3 mmHg.[32] Rasmussen and colleagues conducted isotonic sodium loading test and showed 6 mmHg SBP elevation in eight subjects.[33] Sharma and colleagues conducted an

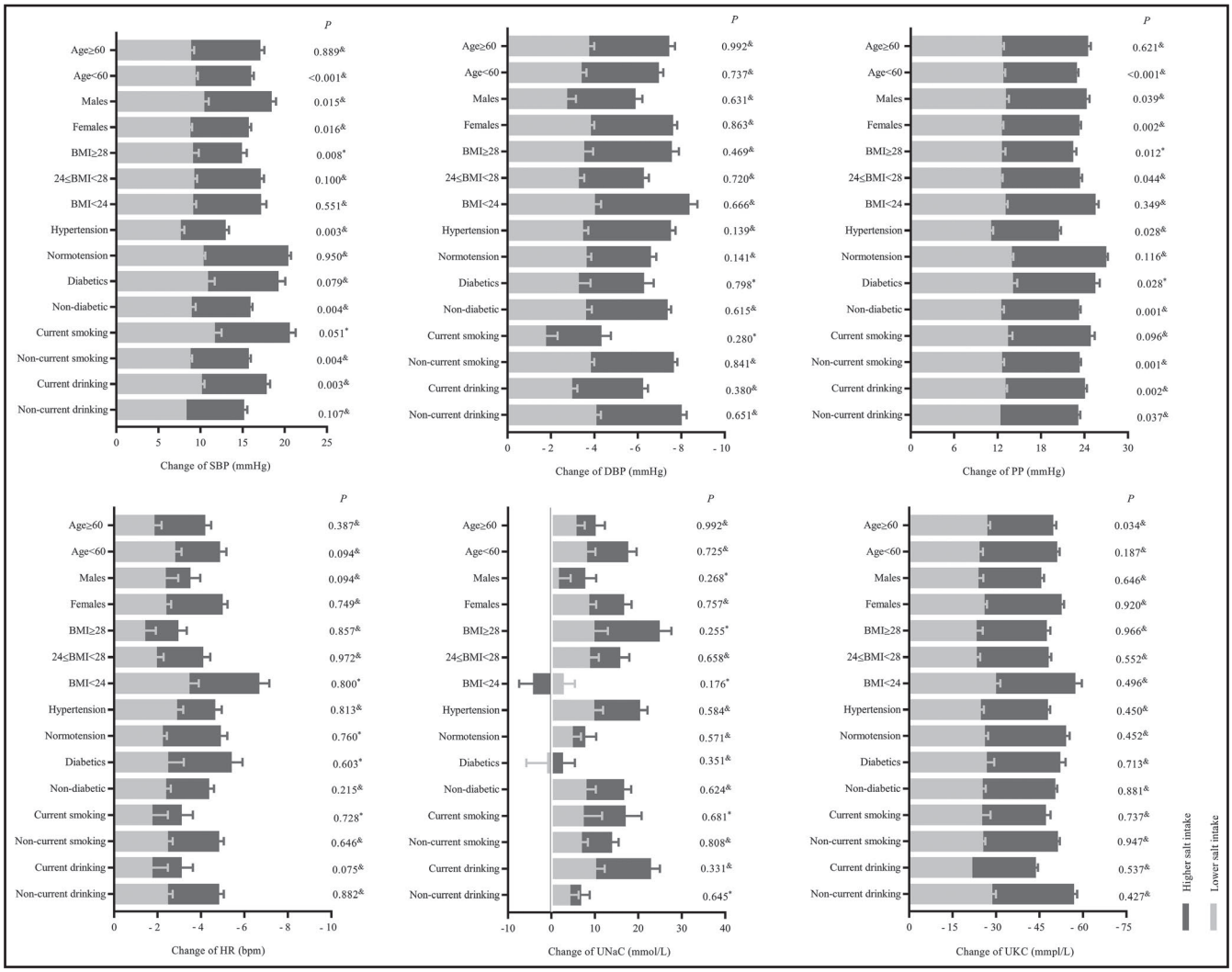


**FIGURE 2** The changes in blood pressure and spot urinary electrolyte concentrations of individuals with lower and higher salt intake levels in subgroups. BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure; UKC, spot urinary potassium concentration; UNaC, spot urinary sodium concentration. Horizontal bars indicate standard error. Lower salt intake, e24hSalt < 8.00 g/day (median); Higher salt intake, 24hSalt ≥ 8.00 g/day. Comparing the changes between lower salt intake individuals and higher salt intake subjects in subgroups, respectively. &, Statistical testing by Mann-Whitney U test; *Statistical testing by independent samples t test. $p < .05$ was considered statistically significant

intravenous saline trail in 22 healthy men and found that SBP increased by 4 mmHg, while DBP decreased by 2 mmHg.[34] Mak and colleagues recruited 13 healthy normotensive subjects to perform a dietary trial, and 2 L of normal saline was intravenous at the end of 1 week low-salt diet. They found DBP significantly decreased 5 mmHg and HR decreased 2 bpm.[35]

It is easy to understand the elevation of SBP after saline loading since the pathophysiological link between sodium intake and rise in BP has been widely studied. High-salt intake, salt retention, and/or volume overload can lower the activity of the renin-angiotensin-aldosterone system and cause hypertension.[36] Acute oral saline also leading an increase in extracellular fluid, it might stimulate the secretion of catecholamine and activate the sympathetic nervous system, through increasing vascular smooth muscle contraction leading to increase BP in response to acute saline loading.[37,38]

Drinking 1 L normal saline could elevate the circulating volume and longer the diastole, which directly leads to decreased HR. In addition, the prolong diastole contributes to the blood flow from the aorta to the peripheral vessels increased, and blood flow remained in aorta decreased, thus reducing DBP. These physiological process can be mainly caused by the cardiopulmonary receptor, which was an important mechanism in the control of blood volume homeostasis.[39] On the one hand, the atrial wall is stretched, causing atrial receptors to become excited, which further results in sympathetic inhibition and vagal excitation, reducing HR and BP.[40] On the other hand, atrial distention stimulates the release of atrial natriuretic peptide (ANP).[41] ANP interferences with the baroreflex control of circulation and induces rapid reduction of HR by increases the activity of vagal afferents thereby inhibiting renal sympathetic nerve activity.[42] Also, ANP leads to the rapid changes

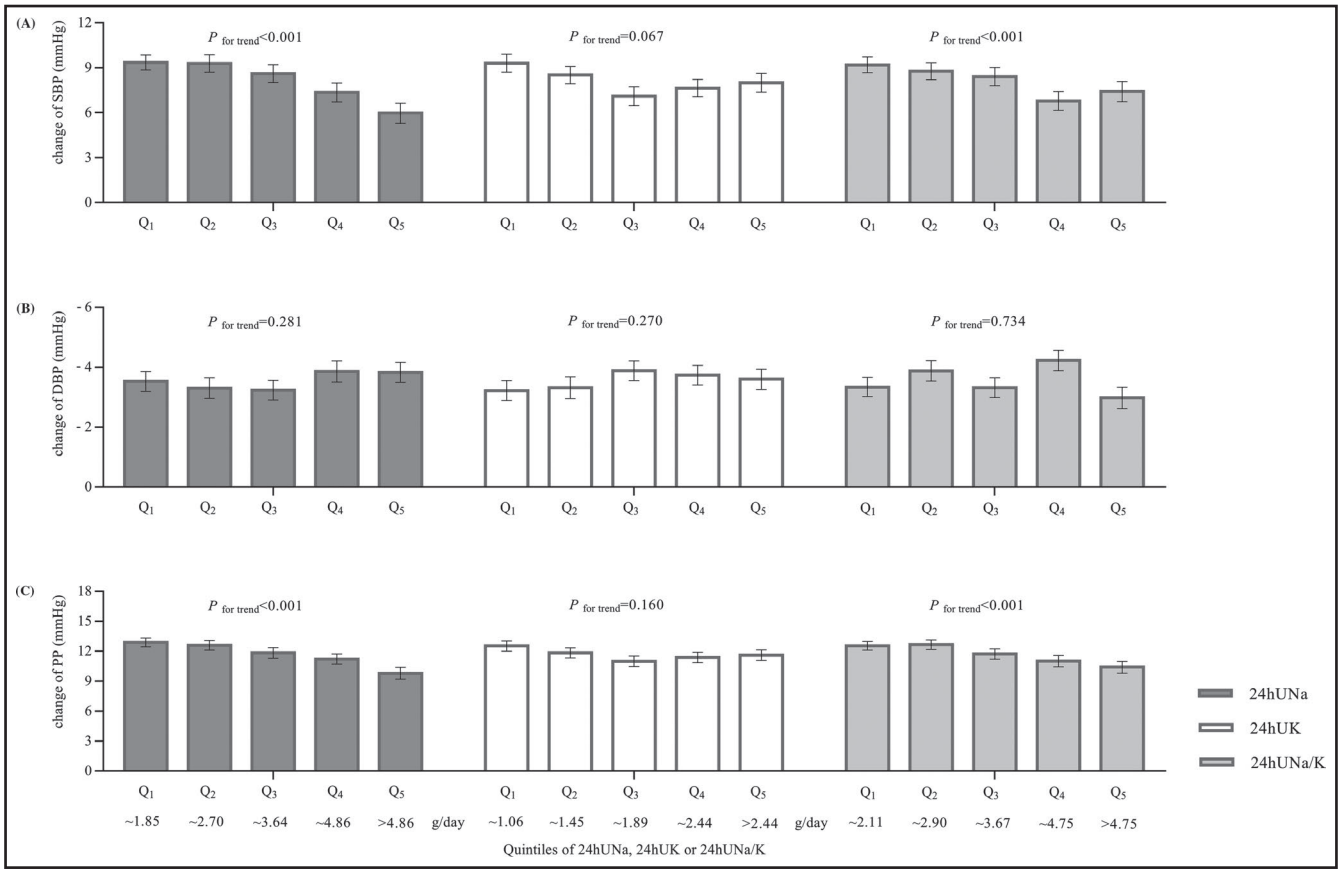


**FIGURE 3** Average variations of blood pressure according to quintiles of 24hUNa, 24hUK, and 24hUNa/K. 24hUK, 24-hour urinary potassium excretion; 24hUNa, 24-hour urinary sodium excretion; 24hUNa/K 24-hour urinary sodium-to-potassium ratio; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure. Vertical bars indicate standard error. Statistical testing by Mann-kendall trend test. $p < .05$ was considered statistically significant

of DBP by direct vasorelaxation [43-45] and fluid shift from the intravascular to the interstitial space.[46,47]

The BP response of individuals to the acute saline loading could be varied. We found that the influence of drinking 1 L saline on SBP in lower salt intake individuals and normotensives was more obvious. The slope of the negative association between sodium excretion and SBP increment became steeper in the individuals with lower salt intake both in total population and hypertensive patients. In normotensive subjects, there was no difference in SBP between lower and higher salt intake individuals. This phenomenon consistent with the result that the SBP increment significantly decreased by 1.502 mmHg for every 1 g increase in 24hUNa in hypertension patients, but insignificantly changed by 0.246 mmHg in normotensives.

The interrelationship between total body $Na^+$, salt intake, fluid balance, and BP has been proposed.[48] It is well known that arginine vasopressin (AVP) decreases renal water excretion [49,50] and increases BP.[51] Kanbay and Coll illustrated that the acute effect of salt supplementation on BP increase is dependent on plasma osmolality.[52] Individuals with high dietary sodium result in the increased plasma sodium concentration,[53] which stimulates the AVP release [54] and induces the elevation of BP.[55] A wealth of data has confirmed that high-salt intake could increase the BP level [20,56] and lead to hypertension.[57] Therefore, normotensives often have a lower salt diet. Due to the self-protection response after the rapid increase in blood volume, a higher basic BP also result in lower elevation after saline loading. The acute saline loading test was equivalent to a rapid ingestion of 9 g NaCl, the effect on the circulating levels of $Na^+$ and plasma osmolality was more dramatic in low-sodium diet individuals [58] and normotensives, and this may explain the difference in SBP elevation in people with different salt intake levels and BP levels.

As expected, in the present study, the mean level of UNaC was significantly increased after saline loading. However, UKC was significantly decreased. This is probably mainly due to the role of $Na^+$-$K^+$-ATPase. The $Na^+$-$K^+$ pump is an electrogenic transmembrane ATPase situated in the outer plasma membrane of the cells,[59] which helps to maintain osmotic equilibrium and membrane potential in cells.[60] The $Na^+$- $K^+$-ATPase could pump 3 $Na^+$ out of the cell and 2 $K^+$ that into the cell, for every single ATP consumed.[61] Saline loading may contribute to a higher $Na^+$ content in the body, and in order to increase the urinary sodium excretion, the activity of $Na^+$- $K^+$-ATPase on the membrane of renal tubules would be increased.

Some strengths and limitations of the current study should be acknowledged. This is the first epidemiologic study based on general population to focus on the association between salt intake with the variations of BP after acute saline loading, and the sample size was much larger than any previous data,[62-64] which made

**TABLE 4** Multiple linear regression analyses of variations of blood pressure with 24hUNa, 24hUK, and 24hUNa/K

| | Total (*N* = 2019) | Lower salt intake (*N* = 1009) | Higher salt intake (*N* = 1010) | Hypertension (*N* = 1040) | Normotension (*N* = 979) |
|---|---|---|---|---|---|
| **Change of BP** | ***β* (95% CI)** | ***β* (95% CI)** | ***β* (95% CI)** | ***β* (95% CI)** | ***β* (95% CI)** |
| ΔSBP | | | | | |
| 24hUNa[a] (g/day) | −0.901 (−1.253, −0.548)** | −1.297 (−2.388, −0.205)* | −0.978 (−1.565, −0.390)* | −1.502 (−2.037, −0.967)** | 0.246 (−0.190, 0.683) |
| 24hUK[a] (g/day) | 0.589 (−0.130, 1.308) | 0.571 (−0.513, 1.654) | 0.600 (−0.397, 1.597) | 1.646 (0.538, 2.754)* | −0.786 (−1.645, 0.072) |
| 24hUNa/K[b] | −0.571 (−0.890, −0.255)** | −0.538 (−1.014, −0.062)* | −0.259 (−0.769, 0.251) | −1.293 (−1.789, −0.797)** | 0.434 (0.056, 0.812)* |
| ΔDBP | | | | | |
| 24hUNa[a] (g/day) | −0.178 (−0.377, 0.022) | −0.331 (−0.987, 0.326) | −0.229 (−0.544, 0.086) | −0.362 (−0.639, −0.086)* | 0.115 (−0.178, 0.408) |
| 24hUK[a] (g/day) | 0.034 (−0.372, 0.440) | 0.171 (−0.481, 0.823) | −0.071 (−0.606, 0.463) | 0.264 (−0.310, 0.837) | −0.253 (−0.829, 0.323) |
| 24hUNa/K[b] | −0.066 (−0.246, 0.113) | −0.525 (−0.939, −0.111)* | −0.190 (−0.627, 0.247) | −0.304 (−0.56, −0.048)* | 0.223 (−0.03, 0.477) |
| ΔPP | | | | | |
| 24hUNa[a] (g/day) | −0.723 (−1.028, 0.418)** | −0.966 (−1.902, −0.030)* | −0.749 (−1.260, −0.237)* | −1.140 (−1.603, −0.676)** | 0.131 (−0.246, 0.508) |
| 24hUK[a] (g/day) | 0.555 (−0.067, 1.177) | 0.399 (−0.530, 1.328) | 0.671 (−0.198, 1.540) | 1.382 (0.422, 2.343)* | −0.533 (−1.274, 0.208) |
| 24hUNa/K[b] | −0.505 (−0.780, −0.229)** | −0.013 (−0.267, 0.242) | −0.069 (−0.376, 0.237) | −0.989 (−1.419, −0.56)** | 0.211 (−0.116, 0.537) |

*Note:* Statistical testing by multiple linear regression analyses, adjust for age, sex, body mass index, fasting blood glucose, current smoking, and drinking.

Abbreviations: 24hUK, 24-hour urinary potassium excretion; 24hUNa, 24-hour urinary sodium excretion; 24hUNa/K, 24-hour urinary sodium-to-potassium ratio; DBP, diastolic blood pressure; Higher salt intake, subjects whose e24hSalt ≥ 8.00 g/day; Lower salt intake, subjects whose estimated 24-hour salt intake (e24hSalt) < 8.00 g/day (median); PP, pulse pressure; SBP, systolic blood pressure; Δ, changes after saline loading.

[a]24hUNa and 24hUK were added in the same model;

[b]24hUNa/K was added in another model.

*$p < .05$;

**$p < .001$.

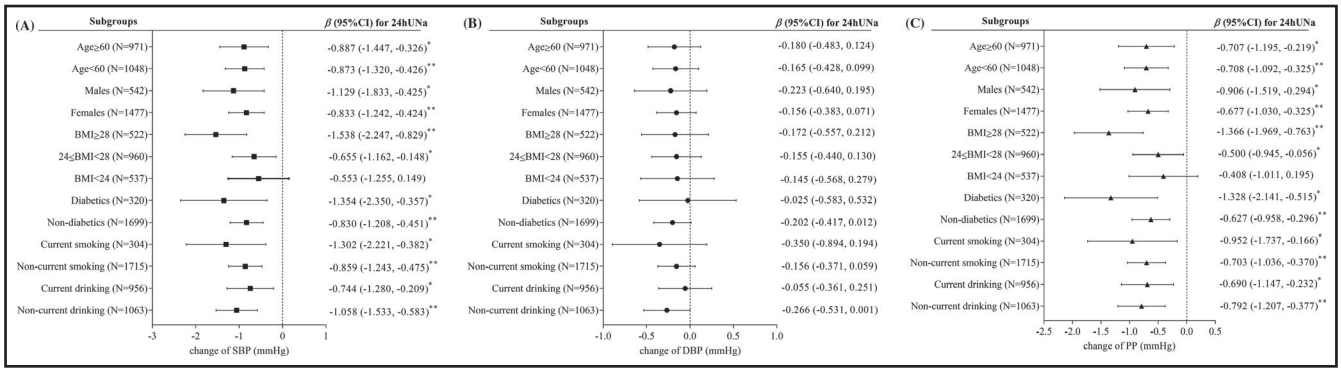


**FIGURE 4** Multivariable linear regression of changes of SBP, DBP, and PP with 24hUNa in subgroups. 24hUNa, 24-hour urinary sodium excretion; BMI, body mass index; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure. Statistical analysis by multivariable linear regression analyses, and the model was adjusted by 24-hour urinary potassium excretion, age, sex, BMI, fasting blood glucose, smoking, and drinking. $p < .05$ was considered statistically significant. *$p < .05$; **$p < .001$

the result of statistical analysis more persuasive. Our results emphasized the importance of keeping stable lower sodium diet and avoiding acute salt loading for escaping acute changes in blood pressure levels. Some scholars claimed that acute salt loading has adverse cardiovascular effects [65]; therefore, we developed a set of strict inclusion criteria for study subjects, and there was no side effect occurred during saline loading. The limitations are as follows: though 24-hour urine collection remains the gold standard for estimating sodium intake, studies indicate that not all dietary sodium are recovered from urine potentially leading to underestimates in dietary intakes; only one 24-hour urine sample tested once per participant may not represent the actual level of daily intake; the sodium intervention in this study was oral saline, and the other method including intravenous saline and dietary salt intervention trial were not included; urine sodium and potassium could affect by renal function, but we did not take it into concern due to lack of data; participants were all from two cities in northern China, which may affect the extrapolation of results.

## 5 | CONCLUSIONS

In conclusion, after acute saline solution, the SBP elevations were more obvious in lower salt intake individuals, normotensives, elders, males, smokers, and drinkers. There was a significant linear negative dose-response association between the SBP increment with 24hUNa, and the association between the increased SBP to daily urinary sodium excretion was more obvious in subjects with lower salt intake than those with higher salt intake. This study has dietary implications and indicated avoiding acute salt loading was important for escaping acute BP changes, especially in lower salt intake populations.

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### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

### AUTHOR CONTRIBUTION

All authors completed the sample collection together. Wenjuan Peng analyzed the data and wrote the paper. In addition, both Ling Zhang and Wenjuan Peng revised the paper.

### ETHICAL APPROVAL

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the Ethics Committee of Capital Medical University. Written informed consent was obtained from all subjects.

### DATA AVAILABILITY STATEMENT

Some or all data, models, or code generated or used during the study are available from the corresponding author by request.

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### REFERENCES

1. Elliott P, Stamler J, Nichols R, et al. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. *BMJ*. 1996;312(7041):1249-1253.
2. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. *N Engl J Med*. 2014;371(7):601-611.
3. Guidelines for the prevention and treatment of hypertension in china (Revised Edition, 2018). *Chin J Cardiol*. 2019;24(01):24-56.
4. WHO Guidelines Approved by the Guidelines Review Committee. *Guideline: Sodium Intake for Adults and Children*. Geneva: World Health Organization; 2012.
5. Baldo MP, Teixeira AK, Rodrigues SL, Mill JG. Acute arrhythmogenesis after myocardial infarction in normotensive rats: influence of high salt intake. *Food Chem Toxicol*. 2012;50(3–4):473-477.

6. Forechi L, Baldo MP, Araujo IB, Nogueira BV, Mill JG. Effects of high and low salt intake on left ventricular remodeling after myocardial infarction in normotensive rats. *J Am Soc Hypertens*. 2015;9(2):77-85.
7. Hsieh BS, Wang TC, Chen YM, Wu KD. Blood pressure, circulating atrial natriuretic peptide and sodium excretion responses during acute saline infusion in patients with essential hypertension. *J Formosan Med Assoc*. 1994;93(7):576-581.
8. Textor SC, Turner ST. Renal vascular response to sodium loading in sons of hypertensive parents. *Hypertension*. 1991;17(6_pt_2):982-988.
9. Duggan KA, Ye VZ. Mechanisms underlying the decrease in circulating angiotensin II concentration after sodium loading. *Clin Exp Pharmacol Physiol*. 1998;25(10):818-819.
10. Widgren BR, Herlitz H, Hedner T, et al. Blunted renal sodium excretion during acute saline loading in normotensive men with positive family histories of hypertension. *Am J Hypertens*. 1991;4(7 Pt 1):570-578.
11. Chan TYK, Critchley JAJH, Ho CS, et al. Urinary dopamine and noradrenaline outputs during large acute changes in oral salt intake in healthy Chinese subjects. *J Auton Pharmacol*. 1994;14(5):317-323.
12. Thurau K, Schnermann J. The sodium concentration in the macula densa cells as a regulating factor for glomerular filtration (micropuncture experiments). *Klin Wochenschr*. 1965;43:410-413.
13. Thurau K, Schnermann J. The sodium concentration in the macula densa cells as a regulating factor for glomerular filtration (Micropuncture experiments). *Klin Wochenschr*. 1965;43:410-413.
14. Kotchen TA, Luke RG, Ott CE, Galla JH, Whitescarver S. Effect of chloride on renin and blood pressure responses to sodium chloride. *Ann Intern Med*. 1983;98(5 Pt 2):817-822.
15. Skøtt O, Briggs JP. Direct demonstration of macula densa-mediated renin secretion. *Science*. 1987;237(4822):1618-1620.
16. Isaksson GL, Stubbe J, Lyngs Hansen P, Jensen BL, Bie P. Salt sensitivity of renin secretion, glomerular filtration rate and blood pressure in conscious Sprague-Dawley rats. *Acta Physiol (Oxf)*. 2014;210(2):446-454.
17. Machura K, Neubauer B, Steppan D, Kettl R, Groβ A, Kurtz A. Role of blood pressure in mediating the influence of salt intake on renin expression in the kidney. *Am J Physiol Renal Physiol*. 2012;302(10):F1278-F1285.
18. Sequeira López MLS, Pentz ES, Nomasa T, Smithies O, Gomez RA. Renin cells are precursors for multiple cell types that switch to the renin phenotype when homeostasis is threatened. *Dev Cell*. 2004;6(5):719-728.
19. Yan X, Jin J, Su X, et al. Intestinal flora modulates blood pressure by regulating the synthesis of intestinal-derived corticosterone in high salt-induced hypertension. *Circ Res*. 2020;126(7):839-853.
20. Suckling RJ, He FJ, Markandu ND, MacGregor GA. Dietary salt influences postprandial plasma sodium concentration and systolic blood pressure. *Kidney Int*. 2012;81(4):407-411.
21. Shukri MZ, Tan JW, Manosroi W, et al. Biological sex modulates the adrenal and blood pressure responses to angiotensin II. *Hypertension*. 2018;71(6):1083-1090.
22. Qi H, Liu B, Guo C, et al. Effects of environmental and genetic risk factors for salt sensitivity on blood pressure in northern China: the systemic epidemiology of salt sensitivity (EpiSS) cohort study. *BMJ Open*. 2018;8(12):e023042.
23. Sullivan JM. Salt sensitivity. Definition, conception, methodology, and long-term issues. *Hypertension*. 1991;17(1_Suppl):I61.
24. Galletti F, Ferrara I, Stinga F, Iacone R, Noviello F, Strazzullo P. Evaluation of a rapid protocol for the assessment of salt sensitivity against the blood pressure response to dietary sodium chloride restriction. *Am J Hypertens*. 1997;10(4 Pt 1):462-466.
25. Liu Z, Qi H, Liu B, et al. Genetic susceptibility to salt-sensitive hypertension in a Han Chinese population: a validation study of candidate genes. *Hyperten Res*. 2017;40(10):876-884.
26. Mu J, Zheng S, Lian Q, Liu F, Liu Z. Evolution of blood pressure from adolescents to youth in salt sensitivies: a 18-year follow-up study in Hanzhong children cohort. *Nutr J*. 2012;11:70.
27. Chen C, Lu FC. The guidelines for prevention and control of overweight and obesity in Chinese adults. *Biomed Environ Sci*. 2004;17(Suppl):1-36.
28. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension*. 2005;45(1):142-161.
29. Joint Committee for Guideline Revision. Chinese guidelines for prevention and treatment of hypertension-A report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. *J Geriatr Cardiol*. 2019;16(3):182-241.
30. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA*. 2011;305(17):1777-1785.
31. Guidelines for the prevention and treatment of type 2 diabetes in China (2017). *Chin J Pract Intern Med*. 2018;38(04):292-344.
32. Brown CM, Barberini L, Dulloo AG, Montani JP. Cardiovascular responses to water drinking: does osmolality play a role? *Am J Physiol Regul Integr Comp Physiol*. 2005;289(6):R1687-R1692.
33. Rasmussen MS, Simonsen JA, Sandgaard NC, Hoilund-Carlsen PF, Bie P. Mechanisms of acute natriuresis in normal humans on low sodium diet. *J Physiol*. 2003;546(Pt 2):591-603.
34. Sharma AM, Schorr U, Cetto C, Distler A. Dietary v intravenous salt loading for the assessment of salt sensitivity in normotensive men. *Am J Hypertens*. 1994;7(12):1070-1075.
35. Mak GS, Sawaya H, Khan AM, et al. Effects of subacute dietary salt intake and acute volume expansion on diastolic function in young normotensive individuals. *Eur Heart J Cardiovasc Imaging*. 2013;14(11):1092-1098.
36. Richardson SI, Freedman BI, Ellison DH, Rodriguez CJ. Salt sensitivity: a review with a focus on non-Hispanic blacks and Hispanics. *J Am Soc Hypertens*. 2013;7(2):170-179.
37. Esler M, Jennings G, Korner P, et al. Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension*. 1988;11(1):3-20.
38. Huang BS, Amin MS, Leenen FH. The central role of the brain in salt-sensitive hypertension. *Curr Opin Cardiol*. 2006;21(4):295-304.
39. Hainsworth R. Cardiovascular control from cardiac and pulmonary vascular receptors. *Exp Physiol*. 2014;99(2):312-319.
40. Colombari DS, Colombari E, Lopes OU, Cravo SL. Afferent pathways in cardiovascular adjustments induced by volume expansion in anesthetized rats. *Am J Physiol Regul Integr Comp Physiol*. 2000;279(3):R884-R890.
41. Volpe M, Cuocolo A, Vecchione F, Mele AF, Condorelli M, Trimarco B. Vagal mediation of the effects of atrial natriuretic factor on blood pressure and arterial baroreflexes in the rabbit. *Circ Res*. 1987;60(5):747-755.
42. Thorén P, Mark AL, Morgan DA, O'Neill TP, Needleman P, Brody MJ. Activation of vagal depressor reflexes by atriopeptins inhibits renal sympathetic nerve activity. *Am J Physiol*. 1986;251(6 Pt 2):H1252-H1259.
43. Kleinert HD, Volpe M, Odell G, et al. Cardiovascular effects of atrial natriuretic factor in anesthetized and conscious dogs. *Hypertension*. 1986;8(4):312-316.
44. Currie M, Geller D, Cole B, et al. Bioactive cardiac substances: potent vasorelaxant activity in mammalian atria. *Science*. 1983;221(4605):71-73.
45. Saito Y. Roles of atrial natriuretic peptide and its therapeutic use. *J Cardiol*. 2010;56(3):262-270.

46. Almeida FA, Suzuki M, Maack T. Atrial natriuretic factor increases hematocrit and decreases plasma volume in nephrectomized rats. *Life Sci*. 1986;39(13):1193-1199.
47. Huxley VH, Tucker VL, Verburg KM, Freeman RH. Increased capillary hydraulic conductivity induced by atrial natriuretic peptide. *Circ Res*. 1987;60(2):304-307.
48. Guyton AC, Coleman TG, Cowley AW, Liard JF, Norman RA, Manning RD. Systems analysis of arterial pressure regulation and hypertension. *Ann Biomed Eng*. 1972;1(2):254-281.
49. Bankir L. Antidiuretic action of vasopressin: quantitative aspects and interaction between V1a and V2 receptor-mediated effects. *Cardiovasc Res*. 2001;51(3):372-390.
50. Stockand JD. Vasopressin regulation of renal sodium excretion. *Kidney Int*. 2010;78(9):849-856.
51. Cowley AW Jr, Monos E, Guyton AC. Interaction of vasopressin and the baroreceptor reflex system in the regulation of arterial blood pressure in the dog. *Circ Res*. 1974;34(4):505-514.
52. Kanbay M, Aslan G, Afsar B, et al. Acute effects of salt on blood pressure are mediated by serum osmolality. *J Clin Hypertens*. 2018;20(10):1447-1454.
53. 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.
54. Bourque CW. Central mechanisms of osmosensation and systemic osmoregulation. *Nat Rev Neurosci*. 2008;9(7):519-531.
55. Fujiwara Y, Tanoue A, Tsujimoto G, Koshimizu TA. The roles of V1a vasopressin receptors in blood pressure homeostasis: a review of studies on V1a receptor knockout mice. *Clin Exp Nephrol*. 2012;16(1):30-34.
56. Wenner MM, Paul EP, Robinson AT, Rose WC, Farquhar WB. Acute NaCl loading reveals a higher blood pressure for a given serum sodium level in African American Compared to Caucasian Adults. *Front Physiol*. 2018;9:1354.
57. Kurokawa T, Zha X, Ito H, et al. Underlying mechanisms of urine storage dysfunction in rats with salt-loading hypertension. *Life Sci*. 2015;141:8-12.
58. He FJ, Macgregor GA. Salt intake, plasma sodium, and worldwide salt reduction. *Ann Med*. 2012;44(Suppl 1):S127-S137.
59. Skou JC. The influence of some cations on an adenosine triphosphatase from peripheral nerves. *Biochim Biophys Acta*. 1957;23(2):394-401.
60. Kopec W, Loubet B, Poulsen H, Khandelia H. Molecular mechanism of Na(+), K(+)-ATPase malfunction in mutations characteristic of adrenal hypertension. *Biochemistry*. 2014;53(4):746-754.
61. Pivovarov AS, Calahorro F, Walker RJ. Na/K-pump and neurotransmitter membrane receptors. *Invert Neurosci*. 2018;19(1):1.
62. Chan TYK, Critchley JAJH, Ho CS, et al. Renal kallikrein-kinin system, but not renal dopamine system, mediates the natriuretic response to intravenous saline infusion in healthy Chinese subjects. *J Auton Pharmacol*. 2000;20(1):37-45.
63. Lang CC, Choy AM, Turner K, Tobin R, Coutie W, Struthers AD. The effect of intravenous saline loading on plasma levels of brain natriuretic peptide in man. *J Hypertens*. 1993;11(7):737-741.
64. Ishimitsu T, Nishikimi T, Matsuoka H, et al. Behaviour of adrenomedullin during acute and chronic salt loading in normotensive and hypertensive subjects. *Clin Sci*. 1996;91(3):293-298.
65. Tzemos N, Lim PO, Wong S, Struthers AD, MacDonald TM. Adverse cardiovascular effects of acute salt loading in young normotensive individuals. *Hypertension*. 2008;51(6):1525-1530.


## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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