ARTICLE

Association of blood pressure with estimates of 24-h urinary sodium and potassium excretion from repeated single-spot urine samples

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Abstract

While the association between 24-h urinary sodium and potassium excretion with blood pressure is well established, the relationships of these ions to spot urine measurements are unclear. Our purpose is to assess the association between blood pressure and the estimated 24-h sodium and potassium excretion from repeated single-spot urine samples. Spot urine and blood pressure were collected annually during a 5-year period from 4360 Japanese workers with ages ranging from 19 to 55 years. Estimates of 24-h sodium and potassium excretion were based on Tanaka's formula. Overall, a single standard deviation increase in the estimated sodium excretion (36.5 mmol/day) was associated with a 1.3 mmHg higher systolic blood pressure and a 0.8 mmHg higher diastolic blood pressure ($P < 0.001$). A single standard deviation increase in estimated potassium excretion (8.9 mmol/day) was associated with a 1.1 mmHg lower systolic blood pressure and a 0.7 mmHg lower diastolic blood pressure ($P < 0.001$). As a combined measure of the excretion of both electrolytes, the estimated 24-h sodium-to-potassium ratio was positively associated with both blood pressures ($P < 0.001$). Associations of blood pressure with sodium and the sodium-to-potassium ratio increased with age and were stronger in men compared to women. Associations with potassium and the sodium-to-potassium ratio were stronger in individuals who were overweight. The findings provide evidence for an association between blood pressure and the estimated 24-h sodium and potassium excretion from repeated single-spot urine samples. As convenient measures of dietary intake for each electrolyte, repeated spot urine samples may be useful for assessing hypertension risk, especially in men, older individuals, and overweight individuals.

Keywords Sodium · Potassium · Blood pressure · Spot urine · Association study

Introduction

The association of dietary sodium (Na) and potassium (K) intake with elevated blood pressure (BP) is well-established [1–6]. Reducing Na intake can lead to significant reductions in BP, while higher K intake helps lower BP. A 24-h urine collection is considered to be the gold standard procedure for estimating an individual's daily Na intake [7, 8].

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However, a 24-h urinary assessment is burdensome. Because of low-response rates and undetected under collection, bias in determining the total volumes excreted is not uncommon [8, 9]. In large population-based studies, 24-h collections can also be costly and impractical, especially for the return of large quantities of urine to the research clinic.

As an alternative to the collection of urine over a 24-h period, spot urine sampling is a more convenient and affordable method for measuring the intake of Na and K. Unfortunately, single-spot urine samples are often considered poor estimates of electrolytic excretion over a 24-h period [10]. Whether an analysis of repeated measurements of spot urine estimates for the amount of electrolytes excreted over a 24-h period helps to clarify the value of using single-spot urine samples is unknown. To the best of our knowledge, there are no studies of the association between BP and estimates of 24-h urinary Na and K excretion or the sodium/potassium (Na/K) ratio from repeated measures of single-spot urine samples. Our purpose for this study is to examine this association using spot urine samples that were collected annually over a 5-year period from a representative sample of Japanese workers.

Methods

Study design and enrollment

The current study is based on previously collected data from the High-Risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP), which was a 5-year lifestyle intervention trial that was conducted from 1999 to 2004 to improve cardiovascular risk factor profiles across a broad spectrum of companies found in Japan and other developed countries (which included companies as diverse as a chemical factory and electrical appliance manufacturer as well as a life insurance company and a research laboratory). Details of the study design and methods have been described elsewhere [11, 12]. In brief, employees from 12 companies were divided into lifestyle intervention and control groups (6 companies each). For the high-risk strategy, all participants with high-normal or high BP, hypercholesterolemia, or impaired glucose tolerance received standardized individual counseling by trained nurses with expert knowledge for 6 months of the study period. For the population strategy, the intervention group was exposed to health promotion procedures in group settings with structured presentations, health campaigns, and improvements to their working environment that focused on nutrition, physical activity, and smoking.

There were 5975 participants (2704 in the intervention group and 3271 in the control group) with ages from 19 to 56 years who were enrolled at some time during the 5-year course of the study. After initial enrollment (1999–2000), four additional medical examinations were given on an annual basis. Each visit included a physical examination and a lifestyle survey. Except for the second examination, spot urine specimens were also collected. In this study, we used data from 4474 participants who received at least three of the first, third, fourth, and fifth examinations. Participants who took an anti-hypertensive medication (43) or had a history of diabetes (71) at any examination were excluded. The final available sample was 4360 participants. Other than the intervention, no participants were receiving dietary therapy. Informed consent was obtained from the participants. A safety hygiene monitoring committee for each company examined and approved the study plan and provided monthly oversite. Approval of the study was obtained from the Institutional Review Board of Shiga University of Medical Science.

Data collection

At each examination, sitting BP was measured twice by a nurse after a 5-min rest using a validated automated sphygmomanometer (Nippon Colin, BP-103iII, Japan) [13]. The average value of the two recordings was used in the analysis. Hypertension was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg [14].

Casual spot urine samples from each participant were collected following a standardized protocol for the determination of Na and K excretion levels [11]. As health-checkups were performed in the morning or early afternoon, most participants provided samples at that time. Estimates of 24-h urinary excretion of Na and K from the spot urine samples is based on the formula reported by Tanaka [15]. Both spot urine and 24-h estimates of the Na/K ratio are considered in this report.

Body-mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Standardized questionnaires were administered to assess lifestyle habits and medical history. Alcohol intake was calculated as the total amount consumed in a weekly period (g/week). Smoking status was classified as current and nonsmoker. A measure of physical activity was based on a physical activity index and expressed as minutes of metabolic equivalents per week [16].

Statistical analysis

Means of the estimated 24-h excretion of Na, K, and spot urine as well as estimated Na/K ratios were presented for each examination and adjusted for sex, intervention group, and age. To estimate the effects of Na and K excretion and the Na/K ratios on BP, linear mixed-effects regression models for data with repeated measures were used to calculate the mean difference in systolic and diastolic BP per

Table 1 Characteristics of the HIPOP-OHP study participants by examination

Characteristics	Exam 1 1999–2000	Exam 3 2001–2002	Exam 4 2002–2003	Exam 5 2003–2004
Number of participants	4174	4157	4111	3806
Men, n (%)	3291 (78.9)	3247 (78.1)	3227 (78.5)	2950 (77.5)
Age (years)	36.7 ± 8.5	38.6 ± 8.5	39.7 ± 8.5	40.8 ± 8.5
BMI (kg/m^2)	22.3 ± 2.9	22.5 ± 2.9	22.6 ± 2.1	22.6 ± 3.0
Systolic BP (mmHg)[a]	112.7 ± 11.7	114.1 ± 12.9	114.0 ± 13.6	114.7 ± 14.0
Diastolic BP (mmHg)[a]	68.2 ± 8.7	69.8 ± 9.6	69.6 ± 9.9	70.3 ± 10.4
Na excretion (mmol/day)[a]	156.0 ± 36.9	156.4 ± 36.6	155 ± 36.5	153.5 ± 35.8
K excretion (mmol/day)	41.9 ± 9	42.3 ± 8.9	42.2 ± 8.9	41.8 ± 8.9
Estimated Na/K ratio[a]	3.8 ± 0.9	3.8 ± 0.9	3.8 ± 0.9	3.8 ± 1.0
Spot urinary Na/K ratio[a]	3.3 ± 2.0	3.2 ± 2.0	3.2 ± 2.2	3.2 ± 2.1
Hypertension, n (%)	0 (0)	184 (4.4)	224 (5.5)	259 (6.8)
Current smoker, n (%)	1908 (45.7)	1814 (43.6)	1743 (42.4)	1560 (41.0)
Alcohol intake (g/week)	110 ± 196	112 ± 193	113 ± 194	108 ± 191
PAI (METS min/week)	2099 ± 1077	2023 ± 979	1971 ± 969	2098 ± 945

Values are mean ± standard deviation unless stated otherwise

BMI body-mass index, *BP* blood pressure, *Na* sodium, *K* potassium, *PAI* physical activity index, *METS* metabolic equivalents

[a] Significant difference between exams 1 and 5 after adjustment for sex, intervention group, and time-dependent age: $P < 0.001$ for systolic BP, diastolic BP, Na excretion, and estimated Na/K ratio, $P = 0.003$ for spot urinary Na/K ratio, and $P = 0.350$ for K excretion

standard deviation (SD) change in Na and K excretion and the Na/K ratios (including 95% confidence intervals). Individual-specific random intercepts were used to account for the correlation among repeated outcome measurements. To adjust the correlation among random intercepts, the unstructured covariance matrix was applied. Models were further adjusted for additional confounders, including year of examination and other time-varying covariates (BMI, smoking status, alcohol consumption, and physical activity). In the assessment of the effects of Na and K on BP, adjustments were also made for the other electrolytes. Tests for interactions due to varying effects across sex, age, and BMI were also conducted. Separate assessments were made for men and women and within different age groups (<35, ≥35 to <45, and ≥45 years) and levels of BMI (<25 and ≥25 kg/m^2). Analyses used SAS statistical software (version 9.4; SAS Institute). All statistical tests were two-sided.

Results

Table 1 describes the characteristics of the participants across the four examinations used in this report (1999–2004). At the first exam, the mean age was 36.7 years. Nearly, 80% of the participants were men. Relative to the first exam, mean systolic and diastolic BP were 2 mmHg higher at the last examination ($P < 0.001$). Although the sample was without hypertension at exam 1, the percent of participants with hypertension increased consistently to

6.8% by exam 5 ($P < 0.001$). Among the Na and K electrolytes, Na excretion declined by 2.5 mmol/day between exams 1 and 5 ($P < 0.001$). While not apparent in Table 1, possibly because of large sample sizes, a significant decline was observed for the estimated Na/K ratio ($P < 0.001$). There was a tendency for the spot urinary Na/K ratio to also decline (from 3.3 to 3.2 between exams 1 and 5, $P = 0.003$). Compared to the estimated Na/K ratio, the SD for the spot urine estimate was more than double the SD for the estimated ratio at each exam. Mean K excretion remained constant in the course of follow-up (approximately 42 mmol/day). Differences between the other characteristics between exams 1 and 5 were not significant. Differences in blood pressure and Na and K excretion between the intervention and the control groups in the course of follow-up were modest.

Relationships between BP and the 24-h estimates of Na and K excretion (along with the Na/K ratios) are shown in Table 2. In a fully adjusted model that accounts for sex, intervention group, age, smoking and drinking status, physical activity, and BMI (Model 3), a 1 SD increase in estimated Na excretion (36.5 mmol/day) corresponded with a 1.3 mmHg increase in systolic BP ($P < 0.001$). Increases in systolic BP on the order of 1.0–1.2 mmHg were observed for a 1 SD increase in the estimated and spot urinary Na/K ratio. In contrast, a 1 SD increase in estimated K excretion (8.9 mmol/day) corresponded with a significant 1.1 mmHg decline in systolic BP. Similar findings were observed for diastolic BP. Although absolute differences in diastolic BP

Table 2 Mean BP (mmHg) difference for 1 standard deviation increase[a] in estimated 24-h urinary Na, K, Na/K ratio, and spot urinary Na/K ratio

	Model 1[b]		Model 2[c]		Model 3[d]	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Systolic BP						
Estimated Na[e]	1.6	(1.4–1.8)	1.6	(1.4–1.8)	1.3	(1.2–1.5)
Estimated K[f]	−0.9	(−1.1 to −0.7)	−0.9	(−1.1 to −0.7)	−1.1	(−1.3 to −0.9)
Estimated Na/K ratio	1.3	(1.1–1.4)	1.3	(1.1–1.4)	1.2	(1.0–1.3)
Spot urinary Na/K ratio	1.2	(1.0–1.3)	1.2	(1.0–1.3)	1.0	(0.9–1.2)
Diastolic BP						
Estimated Na[e]	1.0	(0.9, 1.1)	1.0	(0.9, 1.1)	0.8	(0.7, 0.9)
Estimated K[f]	−0.6	(−0.7 to −0.4)	−0.6	(−0.7 to −0.5)	−0.7	(−0.8 to −0.5)
Estimated Na/K ratio	0.8	(0.7–0.9)	0.8	(0.7–0.9)	0.7	(0.6–0.8)
Spot urinary Na/K ratio	0.7	(0.6–0.8)	0.7	(0.6–0.8)	0.6	(0.5–0.7)

All differences are statistically significant ($P < 0.001$)

CI confidence interval, *BP* blood pressure, *Na* sodium, *K* potassium; *BMI*, body-mass index

[a]One standard deviation = 36.5 mmol/day for estimated 24-h urinary Na, 8.9 mmol/day for estimated 24-h urinary K, 0.93 for estimated urinary Na/K, and 2.1 for spot urinary Na/K ratio

[b]Model 1: Adjusted for sex, intervention group, and time-dependent age

[c]Model 2: Adjusted for model 1 covariates plus time-dependent smoking status, drinking status, and physical activity

[d]Model 3: Adjusted for model 2 covariates plus time-dependent BMI

[e]Models were additionally adjusted for K excretion

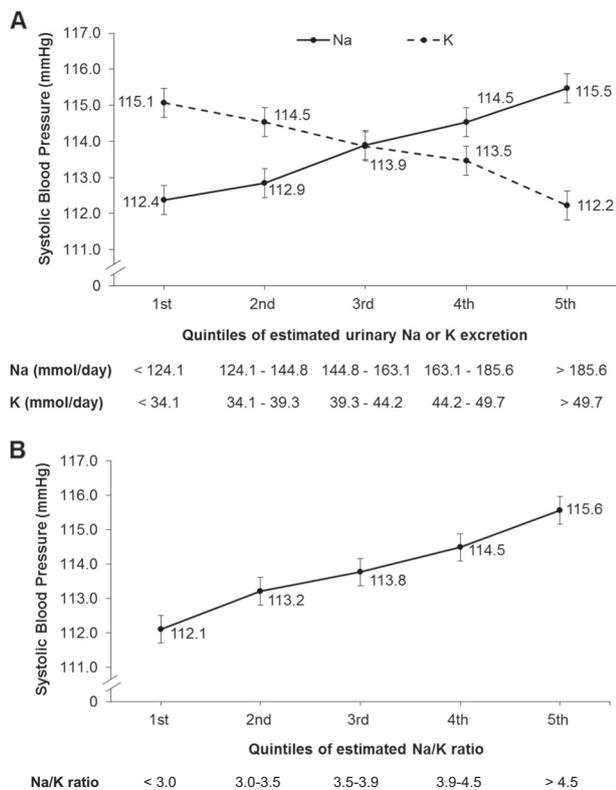[f]Models were additionally adjusted for Na excretion

were smaller than they were for systolic BP, associations with estimated Na and K excretion and each of the Na/K ratios were all significant. Corresponding to a 1 SD increase in estimated Na and either ratio, diastolic BP increased from 0.6 to 0.8 mmHg. Diastolic BP declined by 0.7 mmHg for a 1 SD increase in estimated K excretion. The association of the estimated Na excretion with systolic and diastolic BP is independent of estimated K excretion values. Similarly, the association involving estimated K excretion is independent of estimated Na values.

As depicted in Fig. 1, consistent differences in BP occurred across the different groups for the estimated Na, K, and Na/K ratios. For estimated 24-h Na excretion (Fig. 1a), systolic BP was 3.1 mmHg higher in the fifth versus the first quintile. The average Na excretion in the fifth quintile was >3 SD higher than in the first quintile (1 SD = 36.5 mmol/day). For estimated K excretion, systolic BP was 2.9 mmHg lower in the first versus the first quintile. Additionally, systolic BP was 3.5 mmHg higher in the first versus the first quintile for the estimated Na/K ratio (Fig. 1b). All trends were statistically significant ($P < 0.001$). The results for the estimated Na/K ratio (Fig. 1b) were nearly identical for the spot urine Na/K ratio. The results for diastolic BP were similar (Supplementary Figure 1).

Additional analyses were performed for the association of BP change with a 1 SD increase in each urinary electrolyte excretion measure according to sex, age group, and level of BMI (Fig. 2). Tests for interactions were included.

As seen in Fig. 2a, the association between estimated Na excretion and systolic BP was stronger in men than in women ($P = 0.001$ for interaction). Associations became increasingly stronger with advancing age ($P < 0.001$ for interaction). Associations across BMI groups were nearly identical but remained significant within a BMI group. In contrast, for the association between estimated K excretion and systolic BP (Fig. 2b), there were no significant interactions involving sex and age. The association between systolic BP and estimated K excretion, however, was significantly increased in subjects who were overweight ($P = 0.018$). Associations within a BMI group were also significant.

Unlike excretion of Na and K, the association of the estimated Na/K ratio with systolic BP differed significantly across sex, age, and BMI group (Fig. 2c). The associations were significantly stronger in men, in individuals with an age >45 years, and in participants who are overweight (BMI ≥ 25 kg/m^2). The associations that BP has with estimated 24-h Na and K excretion levels (Fig. 2a, b) had joint roles in this result. Levels of Na excretion seemed to drive the different sex and age relationships that the Na/K ratio has with BP, whereas levels of K seemed to drive the different relationships observed between BMI groups. Associations were nearly identical for the spot urine Na/K ratio. Similar patterns were observed for diastolic BP (Supplementary Figure 2).
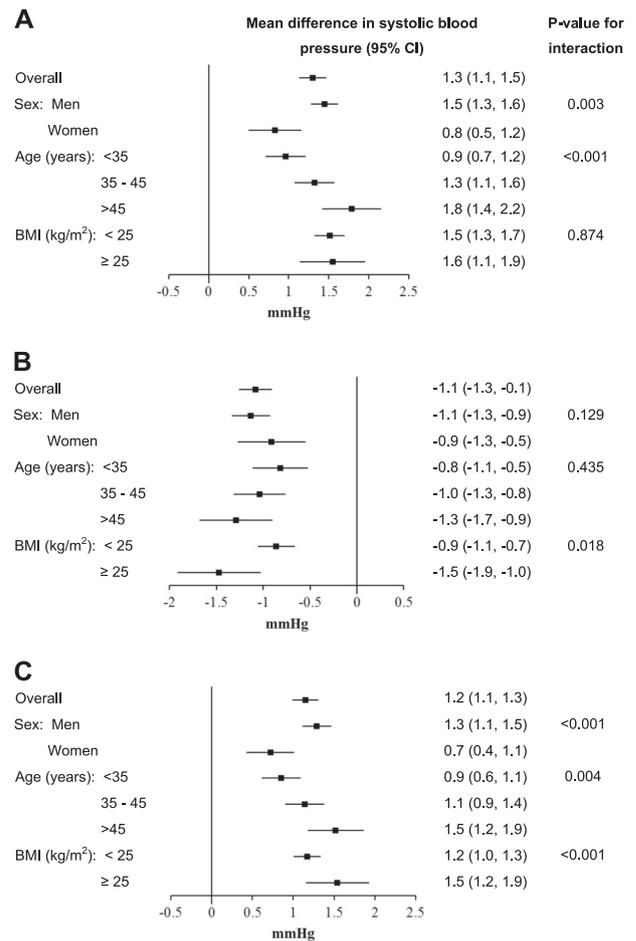
| Na (mmol/day) | < 124.1 | 124.1 - 144.8 | 144.8 - 163.1 | 163.1 - 185.6 | > 185.6 |
| K (mmol/day) | < 34.1 | 34.1 - 39.3 | 39.3 - 44.2 | 44.2 - 49.7 | > 49.7 |

| Na/K ratio | < 3.0 | 3.0-3.5 | 3.5-3.9 | 3.9-4.5 | > 4.5 |

Fig. 1 Mean systolic BP according to quintiles of estimated urinary Na and K excretion levels (**a**) and the estimated Na/K ratio (**b**). The analyses were adjusted for sex, intervention group, age, smoking and drinking status, physical activity, and body-mass index. The results for the estimated Na/K ratio (panel B) are nearly identical to those for the spot urine Na/K ratio. BP blood pressure, Na sodium, K potassium. Vertical bars indicate 95% confidence intervals

Fig. 2 Mean difference in systolic BP per 1 standard deviation increase in estimated Na excretion (**a**), estimated K excretion (**b**), and the estimated Na/K ratio (**c**) divided by sex, time-dependent age group, and time-dependent BMI. The overall estimated mean differences were adjusted for sex, intervention group, age, smoking and drinking status, physical activity, and body-mass index. Within-group differences were adjusted for the other covariates used in the adjustment for the overall differences. The results for the estimated Na/K ratio (panel C) are nearly identical to those for the spot urine Na/K ratio. BP blood pressure, Na sodium, K potassium, BMI body-mass index

Discussion

Based on analyses from repeated measurements of urinary electrolytes and BP from a large sample of Japanese participants from diverse work environments, we found significant and positive associations of BP with estimated Na excretion and Na/K ratios that were estimated or determined from spot urine samples. In contrast, the estimated K excretion was inversely related to BP. While the associations of estimated Na excretion and Na/K ratios with systolic BP were stronger among older participants and more noticeable in men than in women, there was no effect modification by age or sex on relationships with estimated K excretion. Although the association of systolic BP with estimated Na excretion was unrelated to BMI, the effects of the Na/K ratio and estimated K excretion on systolic BP were noticeably stronger in overweight individuals (BMI ≥ 25 kg/m^2) versus those who were leaner.

Our results support previous findings from epidemiological studies on the opposing relationship that BP has with urinary Na and K excretion [1, 4, 5]. While the directions of

the association are generally the same, the magnitude of reported findings can differ. In the INTERSALT study, a 100 mmol/day higher Na excretion was associated with a 3.1 mmHg higher systolic BP. The corresponding value in our study was 3.9 mmHg. The INTERSALT findings were also based on the collection of urine over a 24-h period [1]. Results from our analyses show comparable estimates with a recent meta-analysis of randomized controlled trials in which a 100 mmol/day reduction in Na intake corresponded with a decline in systolic BP of 3.8 mmHg [6]. For estimated K excretion, the magnitude of the overall inverse association with BP in the current report was also greater than the findings from the INTERSALT study [1]. There was at least one consistency in that our results showed a

comparable estimated effect of urinary K excretion on BP that was comparable to results from the INTERSALT study that was conducted in Japan [17]. A separate study in middle-aged Japanese women also found a similar inverse relationship between estimated K excretion and BP to the relationship reported in this study [18].

Our finding of an association between estimated 24-h Na excretion with systolic BP is also comparable to the Dietary Approaches to Stop Hypertension (DASH) study [19]. Systolic BP declined 3.9 mmHg in the DASH diet group for each 100 mmol/day reduction in salt intake. The intake of K was higher in the DASH diet group compared to our study participants. DASH participants were also largely over-weight (BMI ≥ 25 kg/m^2) compared to our much leaner Japanese sample. Nevertheless, we also found that being overweight strengthens the association between estimated K excretion and each of the Na/K ratios with systolic BP [20]. A study from China also indicates that BMI can modify the relationship between BP and both urinary Na and K [21]. An effect of race on salt sensitivity has also been considered an important influence on the association between urinary electrolytes and BP [22–24]. Studies on gene polymorphism have shown that Asians might be more likely to be salt sensitive than Caucasians [23, 25]. Moreover, increasing K intake might also help suppress the occurrence and severity of salt sensitivity [22]. A greater effect of K on BP observed in this study and other Japanese samples may indicate that for a population with a high Na diet and salt sensitivity, intervention strategies focusing on increasing the con-sumption of dietary K in participants who are K deficient could be worthwhile.

As a combined measure of electrolytic intake, the urinary Na/K ratio has attracted increased attention for its higher reliability of measurement than spot urinary Na or K con-centrations, which is largely due to its independence from urinary creatinine. In addition, estimates of the 24-h Na/K ratio from multiple spot urine samples correlated well with ratios based on daily urinary output, and these correlations were better compared to those of single Na or K excretion and other ratios, including Na/creatinine and K/creatinine [26–28].

Our findings of an increased association of the Na/K ratio with BP in men as well as in individuals with an age >45 years and in individuals who are overweight (BMI ≥ 25 kg/m^2) warrants emphasis. In all of these groups, the adverse consequences of having an elevated BP and a greater risk of cardiovascular disease is more apparent compared to women and those who are young or lean. The stronger association in men is similar to population-based findings from the United States [29] but different from INTERSALT [30], the DASH-Sodium trial [19] and Trials of Hyperten-sion Prevention (TOHP) [31]. Comparisons between our findings and these studies are difficult to make since the study populations and the methods of measuring urinary electrolyte excretion are different. Additionally, the inter-vention approach for salt reduction basically included population strategies in the HIPOP-OHP study that were compared to the DASH-Sodium and TOHP trials. The effectiveness of this intervention approach was not espe-cially remarkable. The differences in sodium excretion and blood pressure during the course of the study were modest. Therefore, measurements of urinary electrolyte excretion and blood pressure were considered as observational data in the current study. Finally, separate versions of Tanaka's formula were not created for men and women [15]. Whether using the same formula in both sexes is important is unknown. Further studies are needed to explain the influ-ence of sex on the association between urinary electrolyte excretion and BP.

As with many large-scale surveys, our study has strengths and weaknesses. Although the participants are employed and relatively young, work environments repre-sent a broad cross-section of companies that exist in Japan and other developed countries. Having access to partici-pants at places of employment is an asset for collecting and completing questionnaires and medical records. However, the generalizability of our working population-based study may be limited. For example, the small number of indivi-duals with hypertension in this study may hinder compar-ison to an earlier report that focused entirely on hypertensive subjects [32]. In addition, the relative absence of participants with sodium intakes lower than 2500 mg/day may also influence the interpretation of the results. For example, the INTERSALT study has shown that low-salt intake population-based samples can have low blood pres-sure and nearly no increase in blood pressure with age [1].

The precision in our findings might also be stronger than in other studies with only a single-spot urine collection since repeated measurement of urinary excretion para-meters, BP, and other variables in the current study was continued annually. However, as spot urines were mostly collected in the morning or early afternoon, we were unable to assess the influence of diurnal variations in urinary electrolyte excretion on our findings [33]. Additionally, the estimation of 24-h Na and K intake from a spot urine spe-cimen derived from a simple formula has its limitations. Such formulas (including Tanaka's) often overestimate excretion at lower intake levels and underestimate intake at higher levels [34–37]. This bias cannot be removed by using the repeated formula-based estimates for urinary electrolyte excretion. While multiple urine samples can improve the precision of the estimate of overall population electrolyte excretion levels, the precision in monitoring individual values is uncertain [15]. Nevertheless, collection of spot urine samples can provide a less costly and less cumbersome method for monitoring electrolyte excretion

levels and assessing hypertension risk and its burden for the formulation of health intervention policies in broad population-based settings.

In summary, our study shows that the estimated 24-h excretion of Na and, K, and the Na/K ratio from repeated single-spot urine samples have significant associations with BP. For estimated Na and the Na/K ratio, associations were more pronounced in men and participants >45 years of age. In contrast, the relationship between BP and estimated K excretion was consistently strong regardless of sex and age. While the relationship persisted in leaner individuals (BMI $< 25 \, kg/m^2$), it was significantly stronger in those who were overweight. As surrogate measures of dietary intake of Na and K, our findings support the use of the more convenient collection of single-spot urine samples versus 24-h urinary excretions. As measures to help assess hypertension risk at the population level, they might be useful, especially in groups who tend to be at a higher risk of cardiovascular disease, including men, samples who reach middle-adulthood (>45 years of age), and in those who are overweight.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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