Spot urine sodium measurements do not accurately estimate dietary sodium intake in chronic kidney disease[1,2]

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ABSTRACT

Background: Sodium intake influences blood pressure and proteinuria, yet the impact on long-term outcomes is uncertain in chronic kidney disease (CKD). Accurate assessment is essential for clinical and public policy recommendations, but few large-scale studies use 24-h urine collections. Recent studies that used spot urine sodium and associated estimating equations suggest that they may provide a suitable alternative, but their accuracy in patients with CKD is unknown.

Objective: We compared the accuracy of 4 equations [the Nerbass, INTERSALT (International Cooperative Study on Salt, Other Factors, and Blood Pressure), Tanaka, and Kawasaki equations] that use spot urine sodium to estimate 24-h sodium excretion in patients with moderate to advanced CKD.

Design: We evaluated the accuracy of spot urine sodium to predict mean 24-h urine sodium excretion over 9 mo in 129 participants with stage 3–4 CKD. Spot morning urine sodium was used in 4 estimating equations. Bias, precision, and accuracy were assessed and compared across each equation.

Results: The mean age of the participants was 67 y, 52% were female, and the mean estimated glomerular filtration rate was 31 ± 9 mL · min^{-1} · 1.73 m^{-2}. The mean ± SD number of 24-h urine collections was 3.5 ± 0.8/participant, and the mean 24-h sodium excretion was 168.2 ± 67.5 mmol/d. Although the Tanaka equation demonstrated the least bias (mean: −8.2 mmol/d), all 4 equations had poor precision and accuracy. The INTERSALT equation demonstrated the highest accuracy but derived an estimate only within 30% of mean measured sodium excretion in only 57% of observations. Bland-Altman plots revealed systematic bias with the Nerbass, INTERSALT, and Tanaka equations, underestimating sodium excretion when intake was high.

Conclusion: These findings do not support the use of spot urine specimens to estimate dietary sodium intake in patients with CKD and research studies enriched with patients with CKD. The parent data for this study come from a clinical trial that was registered at clinicaltrials.gov as NCT00785629. *Am J Clin Nutr* 2016;104:298–305.

Keywords: 24-hour urine, chronic kidney disease, sodium intake, spot urine, hypertension, cardiovascular disease

INTRODUCTION

Excess sodium intake in persons with chronic kidney disease (CKD)[8] is associated with hypertension and proteinuria, and existing studies suggest that sodium reduction produces clinically significant improvements in these endpoints (1–5). Although higher blood pressure and proteinuria are markers of CKD progression and cardiovascular disease events, data from epidemiologic studies with the use of 24-h urine sodium excretion as a marker of dietary sodium intake have reported conflicting results on CKD progression and cardiovascular disease events in CKD, with some studies suggesting that there are benefits from lower sodium intake, and others suggesting harm (3, 6–11). Current international clinical practice guidelines recommend that individuals with CKD limit their sodium intake to <90 mmol/d (2069 mg/d) (12), but these data are based largely on expert opinion and extrapolation from studies conducted in the general population. Data availability is limited by the complexity of 24-h urine collections, which require substantial effort from the individual, are challenging and expensive in large epidemiologic studies, and are fraught with errors from under- and overcollection (13). Surveys and 24-h dietary recalls constitute alternative methods of data collection; however, these methods may introduce substantial error and systematic bias because they depend heavily on self-report (14–17).

Prior studies have demonstrated that multiple 24-h urine collections are required to determine usual sodium intake (18,

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[2] Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[8] Abbreviations used: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INTERSALT, International Cooperative Study on Salt, Other Factors, and Blood Pressure; LoA, limits of agreement; PNT, Phosphate Normalization Trial; P_{30}, percentage of estimated sodium excretion values within 30% of the measured 24-h sodium excretion.

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19). Given the technical difficulties and challenges, few large-scale epidemiologic studies have obtained even a single 24-h urine collection, and many fewer have collected multiple samples from the same individual over time (8, 20, 21). Many more have obtained spot urine specimens (22, 23). In an effort to develop a reliable method of estimating sodium intake that does not require multiple 24-h urine collections and is not prone to the errors of collection accuracy or recall, researchers have published numerous equations that attempt to estimate sodium intake with the use of spot urine samples (24–26). These equations, however, were developed and validated in the healthy general population, and their accuracy in CKD populations is unknown. How well spot urine specimens may reflect usual dietary intake is uncertain, given both the potential for circadian changes in sodium excretion throughout the day and changes in diet over time. Moreover, 2 were developed in a Japanese general population setting, a population with a much higher sodium intake than that of the United States (27). Nerbass et al. (28) recently developed a CKD-specific equation; however, to the best of our knowledge, this equation has not been validated externally. Furthermore, it is uncertain whether this equation has improved accuracy compared with the others developed in the general population when applied to persons with CKD.

The Phosphate Normalization Trial (PNT) was designed to test the effect of intestinal phosphate binders on serum phosphate concentrations in patients with moderate to advanced CKD. The design and primary results have been published previously (29). In this trial, participants provided multiple 24-h urine collections over 9 mo, and also provided spot urine specimens. This unique resource provides an opportunity to test the accuracy of equations that estimate 24-h urine sodium excretion from spot urine specimens and compare the performance of different equations in patients with CKD. Therefore, the aim of this study was to evaluate and compare the performance of 4 different equations that estimate 24-h urine sodium excretion from spot urine specimens in a population with moderate to advanced CKD.

METHODS

Study population

The study design of the PNT has been described previously (29). Briefly, participants with an estimated glomerular filtration rate (eGFR) between 20 and 45 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} were recruited from a large clinical practice in Denver, Colorado. Major exclusion criteria included serum phosphate concentrations $<$3.6 or $\geq$6.0 mg/dL, parathyroid hormone concentrations $\geq$500 pg/mL, or active use of intestinal phosphate binders, vitamin D, or cinacalcet at enrollment. An eligibility criterion was that participants not make any intentional changes in their diet for the duration of the study. No recommendations regarding sodium intake were provided through the study protocol.

From 2009 to 2010, 148 participants were recruited and randomly assigned to 1 of 3 commercially available phosphate binders or placebo and treated for 9 mo. Of the 148 participants, 19 were excluded from the present analysis because of missing spot urine specimens, resulting in a final sample size of 129. These 129 participants were similar in age, sex, BMI, and eGFR to those not meeting this criterion (data not shown).

Study measurements

All 24-h and spot urine chemistries were performed by a single laboratory, Litholink Corporation. All other laboratory assessments used in this analysis were performed by Quest Diagnostics. Age, sex, race/ethnicity, comorbidities, and medication use were obtained by self-report. Body weight was measured with participants wearing light clothing and no shoes, and height was measured by stadiometer. Height and weight were used to calculate BMI. Blood pressure was measured twice by sphygmomanometer and averaged. The 4-variable Modification of Diet in Renal Disease study equation was used to calculate eGFR (30).

Description of 4 estimating equations

We used the 4 previously published sodium excretion estimating equations to estimate 24-h urine sodium excretion based on spot urine sodium measurements (24–26, 28), as shown in **Figure 1**. The Nerbass equation was developed in a population of individuals with stage 3 CKD from the United Kingdom (28). The INTERSALT (International Cooperative Study on Salt, Other Factors, and Blood Pressure) equation was developed in a sample of individuals aged 20–59 y from 29 North American and European populations (1, 24). The Tanaka and Kawasaki equations both were developed in Japanese populations (25, 26); the Tanaka equation was developed in the 3 Japanese populations included in the INTERSALT (18). The Kawasaki equation, by original design, evaluated the second morning urine void. Although we evaluated spot morning urine specimens, whether or not they were the first, second, or subsequent void of the morning was not recorded in the data set.

All participants were provided detailed instructions on accurate collection of 24-h urine collections. Collections were obtained at baseline and repeatedly during follow-up in the trial. Urine sodium, creatinine, and volume were recorded. We multiplied urine sodium by urine volume to derive the sodium excretion rate (mmol/d), and averaged each individual's multiple 24-h urine sodium excretion rates as our gold standard measure of usual dietary sodium intake. We also multiplied urine creatinine by urine volume to derive the urine creatinine excretion rate, which is an indicator of collection accuracy (31). This was used in sensitivity analyses to determine whether results were similar in a subset of urine collections with high collection accuracy, as described below.

Ethics

Written informed consent was obtained from all participants at the time of the study. The clinical trial (NCT00785629) was approved by the Schulman Institutional Review Board (Cincinnati, Ohio). This secondary data analysis of de-identified data was considered exempt by the University of California San Diego Institutional Review Board.

Statistical analysis

For descriptive purposes, we divided participants into 2 groups on the basis of a mean measured 24-h urine sodium excretion of $\leq$148 compared with $>$148 mmol/d (3400 mg/d), which is

Nerbass

$$\text{Estimated sodium excretion}\left(\frac{\text{mmol}}{\text{day}}\right) = -68.65 + 1.824 \times \text{weight (kg)} + 0.482 \times \text{spot sodium}\left(\frac{\text{mmol}}{\text{L}}\right)$$

Intersalt

$$\text{Estimated sodium excretion}\left(\frac{\text{mmol}}{\text{day}}\right) =$$

If male:

$$25.46 + 0.46 \times \text{spot sodium}\left(\frac{\text{mmol}}{\text{L}}\right) - 2.75 \times \frac{88.4\left(\frac{\mu\text{mol creatinine} \times \text{dL}}{\text{mg creatinine} \times \text{L}}\right)}{1000\left(\frac{\mu\text{mol creatinine}}{\text{mmol creatinine}}\right)} \times \text{spot creatinine}\left(\frac{\text{mg}}{\text{dL}}\right) - 0.13 \times 20\left(\frac{\text{mmol K}}{\text{L}}\right)$$

$$+4.1 \times \text{BMI}\left(\frac{\text{kg}}{\text{m}^2}\right) + 0.26 \times \text{age (yrs)} + 0.00 \times \text{age}^2\text{(yrs)}$$

If female:

$$5.07 + 0.34 \times \text{spot sodium}\left(\frac{\text{mmol}}{\text{L}}\right) - 2.16 \times \frac{88.4\left(\frac{\mu\text{mol creatinine} \times \text{dL}}{\text{mg creatinine} \times \text{L}}\right)}{1000\left(\frac{\mu\text{mol creatinine}}{\text{mmol creatinine}}\right)} \times \text{spot creatinine}\left(\frac{\text{mg}}{\text{dL}}\right) - 0.09 \times 20\left(\frac{\text{mmol K}}{\text{L}}\right)$$

$$+2.39 \times \text{BMI}\left(\frac{\text{kg}}{\text{m}^2}\right) + 2.35 \times \text{age (yrs)} + 0.03 \times \text{age}^2\text{(yrs)}$$

Tanaka

$$\text{Estimated sodium excretion}\left(\frac{\text{mmol}}{\text{day}}\right) =$$

$$21.98 \times \left\{\frac{\text{spot sodium}\left(\frac{\text{mmol}}{\text{L}}\right)}{10\left(\frac{\text{dL}}{\text{L}}\right) \times \text{creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)} \times \left[-2.04 \times \text{age (yrs)} + 14.89 \times \text{weight (kg)} + 16.14 \times \text{height (cm)} - 2244.45\right]\right\}^{0.392}$$

Kawasaki

$$\text{Estimated sodium excretion}\left(\frac{\text{mmol}}{\text{day}}\right) =$$

If male:

$$16.3 \times \sqrt{\frac{\text{spot sodium}\left(\frac{\text{mmol}}{\text{L}}\right)}{10\left(\frac{\text{dL}}{\text{L}}\right) \times \text{creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)} \times \left[-12.63 \times \text{age (yrs)} + 15.12 \times \text{weight (kg)} + 7.39 \times \text{height (cm)} - 79.90\right]}$$

If female:

$$16.3 \times \sqrt{\frac{\text{spot sodium}\left(\frac{\text{mmol}}{\text{L}}\right)}{10\left(\frac{\text{dL}}{\text{L}}\right) \times \text{creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)} \times \left[-4.72 \times \text{age (yrs)} + 8.58 \times \text{weight (kg)} + 5.09 \times \text{height (cm)} - 74.50\right]}$$

FIGURE 1 Equations used to estimate 24-h sodium excretion from spot urine sodium samples. yrs, years.

approximately the national mean sodium intake in the United States (32). Continuous variables were reported as means ± SDs, and categorical variables were reported as *n* (%), as appropriate. Differences by mean 24-h urine sodium excretion groups were assessed with *t* tests for continuous variables and a chi-square test for categorical variables. The INTERSALT equation requires measurement of spot urine potassium concentrations, which were not available in the PNT. We therefore imputed a spot urine potassium concentration of 20 mmol/L for all individuals.

Spearman correlation coefficients were used to assess the correlations between spot urine sodium and mean measured 24-h sodium excretion, as well as correlations between estimates from each of the 4 estimating equations and mean measured 24-h sodium excretion.

We explored the bias, precision, and accuracy of the estimated sodium excretion with each equation compared with mean measured 24-h sodium excretion. Bias was assessed as the mean difference of estimated and mean measured 24-h sodium excretion. Systematic bias was depicted graphically with the use of Bland-Altman plots, plotting the individual observation difference (estimated − measured) against the individual observation mean of estimated and measured 24-h sodium excretion (33). Spearman correlations between the individual observation difference and the individual observation mean were used to quantify objectively systemic bias. Precision was evaluated as the width of the 95% limits of agreement (LoAs; mean ± 1.96 SDs) of the mean difference. Accuracy was evaluated as the percentage of estimated sodium excretion values within 30% of

the measured 24-h sodium excretion (P_{30}) and as the absolute value of the percentage difference of mean measured 24-h sodium excretion [|(estimated − measured) × 100/measured|].

We performed a rank order analysis with the use of rank quartiles to classify participants into 4 categories of sodium excretion based on the equation-predicted estimates. We then compared the percentage of individuals who fell within the same quartile on the basis of mean 24-h urine sodium excretion measurements. This was done to investigate whether, even if bias and precision were low, the estimating equations would perform well enough to allow researchers to rank-order individuals into low, moderate, and high sodium intake categories with the use of spot urine specimens in large epidemiologic studies.

Finally, sensitivity analyses were conducted to evaluate the potential impact of higher or lower eGFR, diuretic use, and 24-h urine collection quality. To assess 24-h sample collection quality, we calculated each individual's mean 24-h urine creatinine excretion rate, which is a marker of collection accuracy and should be constant in individuals over time (31). When any individual 24-h creatinine excretion rate was >30% of the mean or <70% of the mean creatinine excretion rate, the individual 24-h urine was excluded, and the remainder of collections were used to define the 24-h urine sodium excretion in the sensitivity analysis.

All statistical analyses were conducted with the use of SAS version 9.3.

RESULTS

Among the 129 study participants, mean age was 67 y, 52% were female, and mean eGFR was 31 ± 9 mL · min^{-1} · 1.73 m^{-2}. On average, participants provided 3.5 ± 0.8 24-h urine collections [median (IQR) 4.0 (3.0, 4.0) 24-h urine collections/participant] and the mean 24-h sodium excretion was 168.2 ± 67.5 mmol/d (IQR 119.0, 210.4 mmol/d); thus, slightly higher than the national mean in the general US population (148 mmol/d) (32). Those with mean measured 24-h urine sodium excretion above the national mean were more likely to be younger and male, and to have diabetes (**Table 1**). They were also larger by both height and weight and BMI was higher. Furthermore, they had higher urine volume output, urine creatinine excretion, and estimated sodium excretion based on each of the 4 estimating equations. Importantly, spot urine sodium concentrations and urine sodium-to-creatinine ratios were similar between the groups with lower and higher measured 24-h urine sodium.

Correlation coefficients of different estimates of urine sodium excretion

The correlation coefficients between sodium estimates from each of the 4 equations and mean measured 24-h urine sodium excretion were weak to moderate, ranging between 0.31 and 0.49 (all $P < 0.001$; **Table 2**). We also tested the correlation of spot

TABLE 1
Participant characteristics stratified by mean sodium excretion in the US population[1]

	≤148 mmol Na/d (n = 53)	>148 mmol Na/d (n = 76)	P^2
Age, y	71 ± 11	64 ± 12	0.0004
Female	36 (68)	31 (41)	0.002
Black race	5 (9)	10 (13)	0.5
Diabetes	20 (38)	50 (66)	0.002
Medication use			
Diuretic	36 (68)	56 (75)	0.4
ACE-I	22 (42)	40 (53)	0.2
ARB	15 (28)	26 (35)	0.4
Height, cm	164 ± 8	171 ± 10	<0.0001
Weight, kg	80 ± 23	95 ± 22	0.0003
BMI, kg/m^2	30 ± 8	32 ± 7	0.05
Systolic blood pressure, mm Hg	129 ± 17	123 ± 17	0.04
Diastolic blood pressure, mm Hg	67 ± 10	68 ± 11	0.6
eGFR, mL · min^{-1} · 1.73 m^{-2}	33 ± 9	31 ± 8	0.2
Serum phosphate, mg/dL	4.0 ± 0.4	4.2 ± 0.5	0.04
24-h urine volume, mL/d	1601 ± 653	2358 ± 848	<0.0001
24-h urine sodium:creatinine ratio, mg	2.9 ± 1.1	3.5 ± 1.3	0.007
24-h creatinine excretion, mg/d	941.6 ± 337.1	1368.5 ± 427.9	<0.0001
Mean 24-h sodium excretion, mmol/d	108.9 ± 24.0	209.6 ± 56.1	<0.0001
24-h collections included in average 24-h, n	3.5 ± 0.8	3.6 ± 0.9	0.6
Spot urine sodium:creatinine ratio, mg	2.6 ± 1.9	2.7 ± 2.4	0.6
Spot urine sodium, mmol/L	71.6 ± 35.9	78.2 ± 30.9	0.3
Estimated 24-h urine sodium excretion, mmol/d			
Nerbass equation	112.3 ± 45.6	142.7 ± 42.1	0.0002
INTERSALT equation	122.1 ± 42.7	156.1 ± 44.9	<0.0001
Tanaka equation	148.5 ± 45.1	168.0 ± 52.8	0.03
Kawasaki equation	174.5 ± 67.9	210.3 ± 84.6	0.01

[1]Values are means ± SDs or n (%). Participant characteristics are stratified by mean measured 24-h sodium excretion less than or equal to, or greater than, the national mean sodium intake in the United States of 148 mmol/d (3400 mg/d). ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; INTERSALT, International Cooperative Study on Salt, Other Factors, and Blood Pressure.

[2]Assessed with t tests for continuous variables and chi-square tests for categorical variables.

TABLE 2
Correlations of mean measured 24-h urine sodium excretion and spot urine sodium estimating equations in patients with chronic kidney disease[1]

	Mean measured 24-h sodium excretion	Nerbass estimate	Tanaka estimate	Kawasaki estimate
Nerbass estimate	0.42			
Tanaka estimate	0.31	0.45		
Kawasaki estimate	0.34	0.44	0.98	
INTERSALT[2] estimate	0.49	0.70	0.50	0.57

[1] $n = 129$. Spearman correlation coefficients, $P < 0.001$.
[2] International Cooperative Study on Salt, Other Factors, and Blood Pressure.

urine sodium-to-creatinine ratio with a sodium-to-creatinine ratio in a measured 24-h urine collection done within 24 h of the spot specimen, and found a relatively weak correlation ($r = 0.30$, $P = 0.0005$).

Bias

Bias was assessed as the mean difference of estimated minus mean measured 24-h sodium excretion (**Table 3**). Of the 4 equations, the Tanaka equation demonstrated the least bias, with a mean difference of −8.2 mmol/d. Mean bias was substantially greater with the other 3 equations, with 2 in which the 24-h urine mean measured urine sodium was higher than the estimate (−38.1 mmol/d by Nerbass and −26.1 mmol/d by INTERSALT), and 1 in which 24-h urine mean measured urine sodium excretion was lower than the estimate (27.4 mmol/d by the Kawasaki equation).

Bland-Altman plots reveal systematic bias in the estimated values from the Nerbass, INTERSALT, and Tanaka equations, but not the Kawasaki equation (**Figure 2**). On average, the Nerbass, INTERSALT, and Tanaka equations underestimated sodium excretion when 24-h measured excretion was high.

Precision

Precision was assessed by evaluating the width of the 95% LoA of the mean difference (Table 3). All 4 equations demonstrated low precision with wide LoA. The INTERSALT equation demonstrated the best precision, yet the 95% LoA spanned 238.4 mmol/d.

Accuracy

Accuracy was defined as the P_{30} and as the absolute value of the percentage difference of mean measured 24-h sodium excretion (Table 3). Accuracy was low for all 4 equations. The INTERSALT equation demonstrated slightly greater accuracy than the others; however, only 57% of estimated values fell within 30% of 24-h urine-measured concentrations, and the mean absolute percentage difference was 30.3.

Rank order analysis

We categorized individuals into 4 quartiles on the basis of the mean measured 24-h urine sodium excretion and assessed the ability of the estimating questions to classify individuals into these quartiles appropriately. Performance was poor, with between 18% and 50% of observations appropriately classified (**Table 4**). We also evaluated whether spot urine sodium-to-creatinine ratios appropriately classified into quartiles on the basis of 24-h urine sodium-to-creatinine ratios obtained within 24 h of the spot urine collection, and observed that only 22–44% of measures were in the appropriate quartile (data not shown).

Sensitivity analyses

We investigated whether the performance of the estimating equations might be influenced by 24-h urine collection quality. In total, the 129 participants provided 454 24-h urine collections. We excluded collections from those for whom the measured creatinine excretion was >30% different from the mean creatinine excretion for that individual. This resulted in an exclusion of 23 collections (5%). One additional collection was excluded because the urine creatinine measurement was not available. Of the 129 participants, 123 had ≥2 24-h urine collections available with concordant creatinine excretion rates for use within the sensitivity analysis. All 129 had ≥1, so all were included in the sensitivity analysis. The bias, precision, and accuracy in the subset of 24-h urine collections thought to be of high quality was similar to those in the primary analysis for all 4 equations (**Supplemental Table 1**).

Results were also similar in persons with an eGFR <30 compared with ≥30 mL · min^{-1} · 1.73 m^{-2} (**Supplemental Table 2**) and in users compared with nonusers of diuretics (**Supplemental Table 3**).

TABLE 3
Performance of spot urine sodium–based equations for predicting mean 24-h urine sodium excretion in chronic kidney disease patients[1]

Equation	Difference,[2] mmol/d	Width of LoA, mmol/d	Absolute difference,[3] %	P_{30}, %
INTERSALT	−26.1 (−145.3, 93.1)	238.3	30.3 ± 23.7	57
Tanaka	−8.2 (−148.9, 132.5)	281.5	37.2 ± 36.6	56
Nerbass	−38.1 (−166.1, 89.9)	256.0	32.5 ± 26.6	54
Kawasaki	27.4 (−141.4, 196.2)	337.5	48.4 ± 54.4	50

[1] $n = 129$. INTERSALT, International Cooperative Study on Salt, Other Factors, and Blood Pressure; LoA, limits of agreement; P_{30}, percentage of estimated sodium excretion values within 30% of the measured 24-h sodium excretion.
[2] Estimated mean measured 24-h sodium excretion. Values are means; 95% LoA in parentheses. 95% LoA = mean ± 1.96 SDs.
[3] Absolute value of estimated minus mean measured 24-h sodium excretion. Values are means ± SDs.

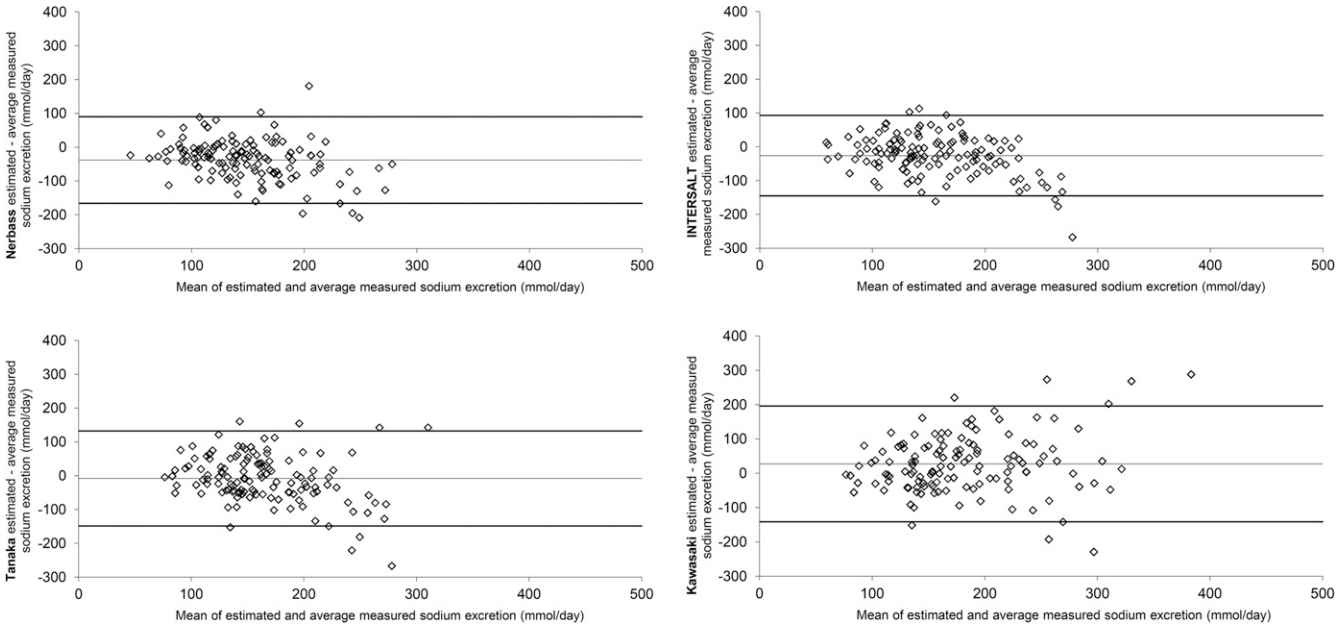

FIGURE 2 Bland-Altman plots depicting bias and precision of spot sodium–based estimating equations relative to mean 24-h urine sodium excretion. Solid lines represent the overall mean of the difference (estimated − measured 24-h sodium excretion); dashed lines represent 95% limits of agreement (mean ± 1.96 SDs); n = 129. INTERSALT, International Cooperative Study on Salt, Other Factors, and Blood Pressure.

We also evaluated whether performance was improved if we evaluated the 24-h urine collection that was obtained within 24 h of the spot urine sodium measurement. In all cases, bias, precision, and accuracy were similar or worse when compared by using the mean 24-h urine sodium excretion over the 9-mo study (data not shown).

DISCUSSION

In a population with moderate to severe CKD, we investigated the performance of 4 equations designed to predict dietary sodium intake from spot urine sodium measurements. We found that bias, precision, and accuracy were poor overall. Performance was sufficiently poor such that none of the estimating equations allowed for the appropriate classification of individuals into a given 24-h urine sodium quartile >50% of the time. Performance remained poor even in 24-h urine collection with high collection quality, irrespective of severity of CKD, and in users or nonusers of diuretics.

The INTERSALT equation (24), which we found to be the most accurate of the 4 equations, only successfully derived an estimate within 30% of 24-h measured sodium excretion 57% of the time and demonstrated substantial bias. The equation by Tanaka et al. (25) demonstrated the least bias, but suffered from poor precision, so its overall accuracy was slightly less than the INTERSALT equation. Only the equation by Nerbass et al. (28) was developed in a population with CKD, yet, in our study, it had the greatest bias, and precision and accuracy were as poor as the other 3. Furthermore, Bland-Altman plots revealed that the Tanaka, Nerbass, and INTERSALT equations all introduced systematic bias to the estimates, underestimating high sodium excretion. Other studies evaluating these equations in various populations identified similar systematic bias (34–38). Although we did not observe systematic bias with the Kawasaki equation, it grossly overestimated mean measured 24-h sodium excretion, a finding consistent with other studies (34, 37), and had the lowest overall accuracy. This may be because it was

TABLE 4
Percentage of participants appropriately classified into mean measured 24-h urine sodium excretion quartiles on the basis of spot urine sodium excretion equations[1]

	Q1	Q2	Q3	Q4
24-h sodium excretion, mmol/d	94.5 ± 19.2	138.3 ± 12.6	179.8 ± 15.6	260.1 ± 51.3
Equation				
Nerbass	47	31	30	44
INTERSALT	44	44	27	50
Tanaka	34	25	21	44
Kawasaki	38	31	18	44

[1]Values are means ± SDs or percentages. n = 129. Percentages represent the percentage of participants correctly categorized by estimated excretion from spot urine sodium into the quartile assigned by mean measured 24-h sodium excretion. Q1 represents the lowest 25% of measured 24-h sodium excretion and Q4 represents the highest 25% of measured 24-h sodium excretion. INTERSALT, International Cooperative Study on Salt, Other Factors, and Blood Pressure; Q, quartile.

developed in a Japanese population, in which the mean dietary sodium intake is much higher than that of the US population (27).

Despite the poor performance of these equations for individual patients with CKD, we considered whether the equations might allow appropriate rank ordering of dietary sodium intake to determine whether they may be useful in large epidemiologic studies. Our findings suggest that the equations do not reliably classify participants into high and low sodium intake categories. The best performing equation was only successful in categorizing 44–50% of individuals in each 24-h urine sodium excretion quartile.

To our knowledge, 2 prior studies have evaluated the Tanaka and Kawasaki equations in CKD populations; however, both of these studies were conducted in Japanese CKD populations in which dietary sodium intake is much higher (39, 40). Ogura et al. (39) evaluated the performance of the Tanaka equation in a CKD population and found its accuracy to be much higher than in our study, with a P_{30} of 70%. This discordance may be due to population differences in sodium intake and body composition, because the Japanese population has higher dietary sodium intake and lower body weight, on average (36). In addition, differences in body habitus may impact creatinine excretion and thus contribute to differences in equation performance across populations. The Nerbass equation was developed in the United Kingdom and the INTERSALT equation was developed in a population that included subjects from North America and Europe. Given population differences in sodium intake (27), lifestyle, and body composition, it perhaps is not surprising that the INTERSALT equation performed the best in terms of accuracy in our US CKD population. Performance may differ in other settings; this is an important question for future study.

This study has multiple strengths. It is the first study, to our knowledge, to externally validate the performance of the new CKD-specific Nerbass equation and compare its performance to that of the previously developed INTERSALT, Tanaka, and Kawasaki equations. Furthermore, to our knowledge, this is the first study to assess the performance of any of these equations in a population with CKD in the United States. On average, participants provided 3.5 24-h urine collections over 9 mo, providing a more reliable marker of usual dietary sodium intake than single measurements (18, 19). All data were collected in a controlled clinical trial from participants enrolled in a research study that did not focus on sodium intake. Given that the urine samples used were collected repeatedly over 9 mo with a high degree of care, the performance of the equations in our study might be considered a best-case scenario. Furthermore, eligibility criteria for the PNT required that participants not make any intentional changes in their diet for the duration of the study, minimizing the potential influence of sudden large changes in diet and sodium intake on sodium excretion. Lastly, we had the opportunity to assess the impact of 24-h urine collection accuracy, CKD severity, and diuretic use on equation performance. These variables did not influence the performance of the equations meaningfully.

Despite these and other strengths, the study also has important limitations. First, our interpretation of the INTERSALT equation is limited by our lack of spot urine potassium data, which is required for the INTERSALT equation. We imputed a concentration of 20 mmol/L for each participant. The influence of potassium measurement in the INTERSALT equation is small; assuming a range of 0–50 mmol K/L, potassium has the potential to affect INTERSALT estimates by $\leq$6.5 mmol Na/d for men and 4.5 mmol Na/d for women. Moreover, this imputation could have influenced bias only, and should not influence the precision, which was poor for the INTERSALT equation. Next, the Kawasaki equation was designed for use with second morning voids. Although all of our spot urine samples were collected in the morning, the protocol did not require all to be second morning urine voids, nor were all of the spot urine samples collected at the same time of day. Thus, by not specifically using second morning voids, we may have influenced the performance of the Kawasaki equation. Timed urine collections are cumbersome to obtain, and over- and undercollections are common in clinical practice. Our participants received detailed instructions and were closely monitored in this research study. Moreover, participants provided multiple 24-h urine collections over 9 mo, and we used the mean of these, which should render our results less likely to be influenced by inaccuracies in any individual collection and provide a better estimate of usual dietary intake. In addition, we conducted a sensitivity analysis with the use of the highest-quality timed collections and found similar results. Nonetheless, errors in collection accuracy still may have influenced the mean 24-h urine sodium excretion used as our gold standard for comparison. Finally, our sample size of 129 CKD participants is relatively small, and participants were recruited from a single center. Most individuals were Caucasian, and the range of eGFR was limited to 20–45 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}. Kidney disease may influence dietary preference and homeostatic regulation of sodium and fluid. Whether results are generalizable to other settings, including in persons in the general population or with heart failure or diabetes, is currently unknown.

The results of this study have important implications for the interpretation of prior and future studies that use spot urine sodium to estimate dietary sodium intake. The use of an imprecise estimate of sodium intake based on spot urine sodium is likely to bias any research question to the null; lack of association between estimates from spot urine sodium with important clinical outcomes may be the expected result of such inquiries, on the basis of the level of inaccuracy we observed here. Moreover, we observed systematic bias at a higher sodium intake with 3 equations. Thus, studies wherein extremes of sodium intake drive associations with outcomes particularly may be prone to bias.

In conclusion, available equations that estimate dietary sodium intake with the use of spot urine sodium measurements have substantial bias, poor precision, and poor accuracy when applied to persons with moderate to severe CKD. This study tempers the enthusiasm for the use of spot urine specimens in individual persons and in large epidemiologic research studies to assess dietary sodium consumption in CKD populations. For now, studies designed to estimate sodium intake in patients with CKD should rely on high-quality 24-h urine collections.

The authors' responsibilities were as follows—CAMA and JHI: designed the research; CED, DER, CAMA, and JHI: conducted the research; GS, MSP, GAB, and JHI: provided the essential materials; CED, DER, and JHI: performed the statistical analyses and had primary responsibility for the final content; CED: wrote the first draft of the manuscript; and all authors: provided critical feedback and revisions of the manuscript and read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

REFERENCES

1. 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.
2. Krikken JA, Laverman GD, Navis G. Benefits of dietary sodium restriction in the management of chronic kidney disease. Curr Opin Nephrol Hypertens 2009;18:531–8.
3. McMahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Johnson DW, Campbell KL. A randomized trial of dietary sodium restriction in CKD. J Am Soc Nephrol 2013;24:2096–103.
4. Campbell KL, Johnson DW, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Whitehead JP, Dimeski G, McMahon E. A randomized trial of sodium-restriction on kidney function, fluid volume and adipokines in CKD patients. BMC Nephrol 2014;15:57.
5. D'Elia L, Rossi G, Schiano di Cola M, Savino I, Galletti F, Strazzullo P. Meta-analysis of the effect of dietary sodium restriction with or without concomitant renin-angiotensin-aldosterone system-inhibiting treatment on albuminuria. Clin J Am Soc Nephrol 2015;10:1542–52.
6. Thomas MC, Moran J, Forsblom C, Harjutsalo V, Thorn L, Ahola A, Waden J, Tolonen N, Saraheimo M, Gordin D, et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. Diabetes Care 2011;34:861–6.
7. Tikellis C, Pickering RJ, Tsorotes D, Harjutsalo V, Thorn L, Ahola A, Wadén J, Tolonen N, Saraheimo M, Gordin D, et al. Association of dietary sodium intake with atherogenesis in experimental diabetes and with cardiovascular disease in patients with type 1 diabetes. Clin Sci 2013;124:617–26.
8. He J, Mills KT, Appel LJ, Yang W, Chen J, Lee BT, Rosas SE, Porter A, Makos G, Weir MR, et al. Urinary sodium and potassium excretion and CKD progression. J Am Soc Nephrol; 2016;27:1202–12.
9. Fan L, Tighiouart H, Levey AS, Beck GJ, Sarnak MJ. Urinary sodium excretion and kidney failure in nondiabetic chronic kidney disease. Kidney Int 2014;86:582–8.
10. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium intake, ACE inhibition, and progression to ESRD. J Am Soc Nephrol 2012;23:165–73.
11. McQuarrie EP, Traynor JP, Taylor AH, Freel EM, Fox JG, Jardine AG, Mark PB. Association between urinary sodium, creatinine, albumin, and long-term survival in chronic kidney disease. Hypertension 2014;64:111–7.
12. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1–150.
13. World Health Organization (WHO). Strategies to monitor and evaluate population sodium consumption and sources of sodium in the diet: report of a joint technical meeting convened by WHO and the Government of Canada. Geneva (Switzerland): WHO Press: World Health Organization; 2010. p. 4–42.
14. Leiba A, Vald A, Peleg E, Shamiss A, Grossman E. Does dietary recall adequately assess sodium, potassium, and calcium intake in hypertensive patients? Nutrition 2005;21:462–6.
15. Espeland MA. Statistical issues in analyzing 24-hour dietary recall and 24-hour urine collection data for sodium and potassium intakes. Am J Epidemiol 2001;153:996–1006.
16. McMahon EJ, Campbell KL, Mudge DW, Bauer JD. Achieving salt restriction in chronic kidney disease. Int J Nephrol 2012;2012:1–10.
17. Mercado CI, Cogswell ME, Valderrama AL, Wang C-Y, Loria CM, Moshfegh AJ, Rhodes DG, Carriquiry AL. Difference between 24-h diet recall and urine excretion for assessing population sodium and potassium intake in adults aged 18–39 y. Am J Clin Nutr 2015;101:376–86.
18. Lerchl K, Rakova N, Dahlmann A, Rauh M, Goller U, Basner M, Dinges DF, Beck L, Agureev A, Larina I, et al. Agreement between 24-hour salt ingestion and sodium excretion in a controlled environment. Hypertension 2015;66:850–7.
19. Liu K, Dyer AR, Cooper RS, Stamler R, Stamler J. Can overnight urine replace 24-hour urine collection to assess salt intake? Hypertension 1979;1:529–36.
20. Joosten MM, Gansevoort RT, Mukamal KJ, Lambers Heerspink HJ, Geleijnse JM, Feskens EJM, Navis G, Bakker SJL, PREVEND Study Group. Sodium excretion and risk of developing coronary heart disease. Circulation 2014;129:1121–8.
21. Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. Circulation 2014;129:981–9.
22. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr., Kronmal R, Liu K, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002; 156:871–81.
23. Ix JH, Biggs ML, Mukamal K, Djousse L, Siscovick D, Tracy R, Katz R, Delaney JA, Chaves P, Rifkin DE, et al. Urine collagen fragments and CKD progression—the Cardiovascular Health Study. J Am Soc Nephrol [Internet]. 2015 [cited 2015 Aug 31]. Available from: http://www.jasn.org/cgi/doi/10.1681/ASN.2014070696.
24. Brown IJ, Dyer AR, Chan Q, Cogswell ME, Ueshima H, Stamler J, Elliott P, INTERSALT Co-Operative Research Group. Estimating 24-hour urinary sodium excretion from casual urinary sodium concentrations in Western populations: the INTERSALT study. Am J Epidemiol 2013;177:1180–92.
25. Tanaka T, Okamura T, Miura K, Kadowaki T, Ueshima H, Nakagawa H, Hashimoto T. 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.
26. 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.
27. Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. Int J Epidemiol 2009;38:791–813.
28. Nerbass FB, Pecoits-Filho R, McIntyre NJ, McIntyre CW, Taal MW. Development of a formula for estimation of sodium intake from spot urine in people with chronic kidney disease. Nephron Clin Pract 2014;128:61–6.
29. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, Allison MA, Asplin J, Smits G, Hoofnagle AN, et al. Effects of phosphate binders in moderate CKD. J Am Soc Nephrol 2012;23:1407–15.
30. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.
31. Ix JH, Wassel CL, Stevens LA, Beck GJ, Froissart M, Navis G, Rodby R, Torres VE, Zhang YL, Greene T, et al. Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. Clin J Am Soc Nephrol 2011;6:184–91.
32. Centers for Disease Control and Prevention. Trends in the prevalence of excess dietary sodium intake—United States, 2003–2010. MMWR Morb Mortal Wkly Rep 2013;62:1021–5.
33. Bland JM, Altman DG. Comparing methods of measurement: why plotting difference against standard method is misleading. Lancet 1995;346:1085–7.
34. Rhee M-Y, Kim J-H, Shin S-J, Gu N, Nah D-Y, Hong K-S, Cho E-J, Sung K-C. Estimation of 24-hour urinary sodium excretion using spot urine samples. Nutrients 2014;6:2360–75.
35. Toft U, Cerqueira C, Andreasen AH, Thuesen BH, Laurberg P, Ovesen L, Perrild H, Jorgensen T. Estimating salt intake in a Caucasian population: can spot urine substitute 24-hour urine samples? Eur J Prev Cardiol 2014;21:1300–7.
36. Ji C, Miller MA, Venezia A, Strazzullo P, Cappuccio FP. Comparisons of spot vs 24-h urine samples for estimating population salt intake: validation study in two independent samples of adults in Britain and Italy. Nutr Metab Cardiovasc Dis 2014;24:140–7.
37. Kelly C, Geaney F, Fitzgerald AP, Browne GM, Perry IJ. Validation of diet and urinary excretion derived estimates of sodium excretion against 24-h urine excretion in a worksite sample. Nutr Metab Cardiovasc Dis; 2015;25:771–9.
38. McLean R, Williams S, Mann J. Monitoring population sodium intake using spot urine samples: validation in a New Zealand population. J Hum Hypertens 2014;28:657–62.
39. Ogura M, Kimura A, Takane K, Nakao M, Hamaguchi A, Terawaki H, Hosoya T. Estimation of salt intake from spot urine samples in patients with chronic kidney disease. BMC Nephrol 2012;13:36.
40. Imai E, Yasuda Y, Horio M, Shibata K, Kato S, Mizutani Y, Imai J, Hayashi M, Kamiya H, Oiso Y, et al. Validation of the equations for estimating daily sodium excretion from spot urine in patients with chronic kidney disease. Clin Exp Nephrol 2011;15:861–7.