Formulas to Estimate Dietary Sodium Intake From Spot Urine Alter Sodium-Mortality Relationship

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Abstract—To study the effect of formulas on the estimation of dietary sodium intake (sodium intake) and its association with mortality, we analyzed the TOHP (Trials of Hypertension Prevention) follow-up data. Sodium intake was assessed by measured 24-hour urinary sodium excretion and estimations from sodium concentration using the Kawasaki, Tanaka, and INTERSALT (International Cooperative Study on Salt, Other Factors, and Blood Pressure) formulas. We used both the average of 3 to 7 urinary measurements during the trial period and the first measurement at the beginning of each trial. Additionally, we kept sodium concentration constant to test whether the formulas were independently associated with mortality. We included 2974 individuals aged 30 to 54 years with prehypertension, not assigned to sodium intervention. During a median 24-year follow-up, 272 deaths occurred. The average measured sodium intake was 3766±1290 mg/d. All estimated values, including those with constant sodium concentration, were systematically biased with overestimation at lower levels and underestimation at higher levels. There was a significant linear association between the average measured sodium intake (ie, gold standard method) and mortality. This relationship was altered by using the estimated sodium intakes. There appeared to be a J- or U-shaped relationship for the average estimated sodium by all formulas. Despite variations in the sodium-mortality relationship among various formulas, a common pattern was that all estimated values including those with constant sodium appeared to be inversely related to mortality at lower levels of sodium intake. These results demonstrate that inaccurate estimates of sodium cannot be used in association studies, particularly as the formulas per se seem to be related to mortality independent of sodium. **(*Hypertension*. 2019;74:572-580. DOI: 10.1161/HYPERTENSIONAHA.119.13117.)** ● **Online Data Supplement**

Key Words: cohort studies ■ follow-up studies ■ humans ■ mortality ■ sodium, dietary

There is a causal, linear relationship between sodium intake and blood pressure (BP)[1–4] and a continuous relationship between BP and cardiovascular disease mortality.[5,6] Several lines of evidence have shown that a lower sodium intake is associated with a reduced risk of cardiovascular disease events and mortality.[7–10] However, a few recent cohort studies have reported a J-shaped relationship, that is, both lower and higher sodium intake were associated with an increased risk.[11–13] These studies have several methodological problems, one of which is the biased estimate of individuals' usual sodium intake from spot urine using a formula.[14–17] An analysis of the TOHP (Trials of Hypertension Prevention) follow-up data demonstrated that use of an estimated sodium intake based on urinary sodium (UNa) concentration by the Kawasaki formula changed the direct linear relationship between sodium intake and mortality seen when sodium was measured by the gold standard multiple nonconsecutive 24-hour urine collections.[7,8,18]

A number of other formulas, for example, Tanaka[19] and INTERSALT,[20] have also been used to estimate sodium intake from spot urine. All these formulas include age, weight, height, and urinary creatinine concentration, although the equations vary across formulas. For example, some formulas have sex-specific equations[20,21] and others also include urinary potassium concentration.[20] These variables are associated with sodium intake and also strongly related to death and, therefore, may confound the relationship between the estimated sodium intake and mortality. To investigate the impact of the formulas on the estimation of sodium intake and its association with mortality, we performed a secondary analysis of the TOHP follow-up data.

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Methods

Anonymized data and materials from the TOHP trial periods have been made publicly available at https://biolincc.nhlbi.nih.gov/studies/tohp/, and researchers can apply to use the trial data. The methods of the original TOHP and the subsequent follow-up study for mortality have been reported in detail elsewhere.[8,22–24] The number of participants included/excluded was the same as that in our previous analysis.[18] In brief, our current study included 1844 individuals with high-normal BP in TOHP I[23] and 1167 individuals with prehypertension and a body mass index of 110% to 165% of desirable body weight in TOHP II.[24] Among these participants, 37 took part in both phases, and, therefore, 2974 unique individuals (age, 30–54 years at baseline) were included. We excluded individuals who were randomized to sodium reduction group during the trial period. Three to seven 24-hour urine collections were made during the trials, which lasted for 18 months for TOHP I and 3 to 4 years for TOHP II.

The trial period constitutes the baseline exposure period for subsequent follow-up. Post-trial follow-up was conducted for mortality after each trial had been completed. A search of the National Death Index was performed, accruing death information through December 2013.

The primary outcome in this analysis is all-cause mortality in relation to sodium intake estimated by various methods. We also examine the accuracy of the different estimates of sodium intake both at population and individual level.

Sodium intake was assessed by 2 methods: (1) measured by 24-hour UNa excretion and (2) estimated from UNa concentration using formulas. For each method, we estimated the values based on both the average of 3 to 7 urinary measurements during the trial period and the first urinary measurement at the beginning of each trial. The average measured sodium intake is the best characterized measure of individuals' usual sodium intake and therefore considered as the gold standard method.

We used 3 formulas, that is, Kawasaki,[21] Tanaka,[19] and INTERSALT,[20] all of which have been commonly used for estimating sodium intake from spot urine. The calculations of sodium intake, that is, 24-hour UNa, are described below.

Kawasaki formula[21]:

$$\text{24-hour UNa (mg/d)} = 23 \times \left(16.3 \times \text{XNa}^{0.5}\right),$$

where XNa=(spot Na [mmol/L]/spot creatinine [mg/dL]×10) ×(Pr24hCr [mg/d]).

$$\text{Pr24hCr (mg/d) for men} = \left(-12.63 \times \text{age [y]}\right) + \left(15.12 \times \text{weight [kg]}\right) + \left(7.39 \times \text{height [cm]}\right) - 79.9.$$

$$\text{Pr24hCr (mg/d) for women} = \left(-4.72 \times \text{age [y]}\right) + \left(8.58 \times \text{weight [kg]}\right) + \left(5.09 \times \text{height [cm]}\right) - 74.5.$$

Tanaka formula[19]:

$$\text{24-hour UNa (mg/d)} = 23 \times \left(21.98 \times \text{XNa}^{0.392}\right),$$

where XNa=(spot Na [mmol/L]/spot creatinine [mg/dL]×10) ×(Pr24hCr [mg/d]).

$$\text{Pr24hCr (mg/d)} = \left(-2.04 \times \text{age [y]}\right) + \left(14.89 \times \text{weight [kg]}\right) + \left(16.14 \times \text{height [cm]}\right) - 2244.45.$$

INTERSALT formula[20]:

$$\text{Men: 24-hour UNa (mg/d)} = 23 \times \{25.46 + [0.46 \times \text{spot Na (mmol/L)}] - [2.75 \times \text{spot creatinine (mmol/L)}] - [0.13 \times \text{spot K (mmol/L)}] + [4.10 \times \text{BMI (kg/m}^2)] + [0.26 \times \text{age (y)}]\}$$

$$\text{Women: 24-hour UNa (mg/d)} = 23 \times \{5.07 + [0.34 \times \text{spot Na (mmol/L)}] [2.16 \times \text{spot creatinine (mmol/L)}] [0.09 \times \text{spot K (mmol/L)}] + [2.39 \times \text{BMI (kg/m}^2)] + [2.35 \times \text{age (y)}] [0.03 \times \text{age}^2\text{(y)}]\}$$

Spot urine was not collected in TOHP. We used 24-hour UNa concentration instead of spot UNa concentration in the above formulas, that is, spot UNa, spot creatinine, and spot K refer to sodium, creatinine, and potassium concentration of 24-hour urine, respectively. Pr24hCr indicates predicted 24-hour urinary creatinine excretion.

In additional analyses, we used a constant sodium concentration in the formulas, to test whether the formulas per se were associated with mortality independent of sodium. The constant for men and women was the mean UNa concentration of their respective group.

Statistical Analysis

Mean bias was calculated as the difference between the estimated 24-hour UNa excretion and the measured value. Paired *t* tests were performed to test whether the mean bias was statistically significant. Bland-Altman plots were used to compare agreement of the estimated sodium intakes with the measured values. To examine whether the trend of the bias was statistically significant and to quantify the magnitude of the bias in relation to sodium level, we calculated the predicted differences (ie, bias) from the regression of the differences between the estimated and the measured sodium over their average and then performed the regression of the absolute value of residuals from this model on the average of the estimated and the measured sodium.[25]

In addition to the analyses with sodium concentration kept constant in the formulas, we performed further analyses to examine whether other variables in the formulas were influencing the association of estimated sodium intake with mortality. We calculated the predicted sodium concentration from regression on average sodium concentration of the three to seven 24-hour urine collections during the trial period with age, sex, height, and body weight at baseline as covariates. We then used the predicted sodium concentration to estimate sodium intake with the formulas. The results were the same as those when sodium concentration was kept constant (data not shown).

The measured sodium intake was grouped into categories of <2300, 2300 to <3600, 3600 to <4800, and ≥4800 mg/d, where 2300 mg/d represents the currently recommended upper level for adults in the United States[26] and 3600 mg/d represents the median sodium intake in the US population aged 31 to 50 years.[27] For the estimated sodium intake, because of overestimation or underestimation by different formulas, they were grouped into categories of <3600, 3600 to <4800, 4800 to <6000, and ≥6000 mg/d for the Kawasaki formula and <3600, 3600 to <4800, and ≥4800 mg/d for the Tanaka and INTERSALT formulas.

Baseline characteristics were reported as percentages or means and were tested for trend over sodium categories using χ^2 statistics or regression analysis. Cox regression analysis was performed to examine the association between sodium intake and mortality. Separate analyses were performed for sodium intake as a continuous variable and in categories. The Cox regression models were stratified by study phase, and all models were adjusted for clinic, age, sex, race/ethnicity, other treatment assignments, education, baseline weight, alcohol use and amount, smoking, exercise, and family history of cardiovascular disease. Penalized splines with 4 *df* were fit to examine linearity of effect in models adjusting for the same factors. Both these and the Bland-Altman plots were fit using R. All other analyses were conducted using SAS, version 9.3 (SAS, Cary, NC).

Results

Among the 2974 participants included in the analysis, 68% were men, 16% were black, and the mean age at baseline was 43 years. The mean number of 24-hour urine collections during the trial periods was 4.4 in TOHP I and 3.5 in TOHP II.

Bias of the Estimated Sodium Intake

The means and distributions of sodium intake (ie, 24-hour UNa excretion) estimated by various methods are shown in Figure S1 in the online-only Data Supplement. Compared with the measured 24-hour UNa, all estimated values (both the average and the first estimates) had smaller variance. The overall mean

(±SD) measured 24-hour UNa from three to seven 24-hour urine collections (ie, gold standard) during the trial periods was 3766±1290 mg/d (9.42±3.23 g/d salt). Compared with the average measured 24-hour UNa, the mean bias for the average estimated sodium (ie, difference between the average estimated and the average measured sodium) ranged from −78 (95% CI, −113 to −42) to 1299 mg/d (1269–1329), with the INTERSALT formula being the least biased and the Kawasaki formula being the most biased. The mean bias for the first estimated sodium (ie, difference between the first estimated and the average measured sodium) was −74 (95% CI, −112 to −36), 75 (34–115), and 1264 mg/d (95% CI, 1223–1304) for the INTERSALT, Tanaka, and Kawasaki formulas, respectively (Table S1).

The mean first measured 24-hour UNa was 3941±1812 mg (9.85±4.53 g/d salt). In comparison with the average measured value, the first measured 24-hour UNa overestimated the intake by 159 mg/d (95% CI, 109–210) and had a wider variability.

Comparing the first estimated 24-hour UNa excretions with the first measured ones, the mean bias was −95 (95% CI, −149 to −41), −240 (95% CI, −295 to −185), and 1088 mg/d (95% CI, 1042–1134) with the Tanaka, INTERSALT, and Kawasaki formulas, respectively (Table S1).

The Bland-Altman plots showed poor agreement between the measured and the estimated 24-hour UNa by all formulas for both the average and the first estimated values (Figure 1). Compared with the average measured (gold standard), all estimates were systematically biased with overestimation at lower levels and underestimation at higher levels (Figure 1). The limits of agreement were wider for the first estimated sodium by the Kawasaki formula (Figure 1). For the comparison between the first estimated and the first measured 24-hour UNa, there was a similar pattern for all formulas (Figure 1).

When sodium concentration was kept constant, the estimated 24-hour UNa showed a similar systematic bias, that is, overestimation at lower levels and underestimation at higher levels, for all formulas and for both the average (ie, average estimated versus average measured sodium) and the first estimates (ie, first estimated versus first measured sodium; Figure S2). For the Kawasaki formulas, limits of agreement were wider, and the variability of the bias increased with increasing sodium level (Figure S2).

The regression analyses in which the slopes indicate the changes in bias for a 1-mg/d increase in the average of estimated and measured 24-hour UNa showed that the trend of the bias was significant for all estimates by all formulas (Figure 1; Figure S2). The slope was less extreme for the Kawasaki formula compared with all others.

Association With Mortality

Baseline characteristics by categories of the average measured 24-hour UNa are shown in Table S2. During the post-trial follow-up, 272 deaths occurred, 189 among TOHP I participants and 83 among TOHP II participants (Table 1). Median follow-up time was 23.9 years for TOHP I and 18.8 years for TOHP II.

Figure 2 shows the spline plots of different average estimates of sodium intake and mortality. The average measured sodium appeared to show a positive linear association with mortality within the range of 1200 to 9000 mg/d (3.00–22.50 g/d salt; Figure 2A). Compared with sodium intake of 3600 to <4800 mg/d (9.00–12.00 g/d salt), the hazard ratios for sodium levels of 2300 to <3600 (5.75–9.00 g/d salt) and <2300 mg/d (5.75 g/d salt) were 0.94 and 0.73, respectively, but the trend across categories did not reach statistical significance (Table 1). When sodium was entered as a continuous variable, a 1000-mg/d higher sodium level was associated with a 12% increase in mortality (P=0.032; Table 1).

For the average estimated sodium intakes by the formulas, because of the overestimation at lower levels and underestimation at higher levels, their distributions were shifted toward the mean values as shown by the rug marks on x axis of the spline plots (Figure 2B through 2D). There appeared to be a J- or U-shaped relationship between the average estimated sodium intake and mortality for all formulas, although the test for deviation from linearity was not significant. Instead, the trend analysis was statistically significant for linearity for the Kawasaki and Tanaka formulas, but the sample size was small at tails as shown by the wide 95% CIs (Figure 2; Table 2).

When sodium concentration was kept constant, the average estimated sodium intakes by the Kawasaki and Tanaka formulas appeared to be inversely associated with mortality at a level of <4000 mg/d (10 g/d salt; Figure 3) and significantly so for the Kawasaki formula (Table 2). For sodium level of ≥4000 mg/d, the spline was flat. For the INTERSALT formula, the average estimated sodium with constant sodium concentration showed a U-shaped association with mortality (Figure 3).

The first measured 24-hour UNa showed no association with mortality, likely because of the lack of precision in the measurement (Figure S3A). For the first estimated sodium, at lower levels, the spline plots were either flat or slightly flip up, and at higher sodium levels, a higher sodium appeared to be associated with an increased risk, particularly for the Kawasaki and Tanaka formulas (Figure S3B and S3D). Statistical tests were not significant for either linear or nonlinear splines. When sodium concentration was kept constant, the first estimated values appeared to show an inverse association, that is, a lower sodium intake being associated with an increased risk, at lower sodium levels (Figure 3). At higher sodium levels, the lines were either flat (INTERSALT) or inversely related to mortality (Kawasaki and Tanaka). Tests were not significant for either linear or nonlinear relationship.

Discussion

Our analysis showed that 24-hour UNa excretions estimated from sodium concentration using the 3 commonly used formulas (Kawasaki, Tanaka, and INTERSALT) all are systematically biased with overestimation at lower levels and underestimation at higher levels of sodium intake. Furthermore, when sodium concentration was kept constant, the estimated values showed a similar systematic bias for all formulas. These results suggest that other variables in the formulas, independent of sodium, are contributing to the biased estimates. This is further evident by the findings that all estimated 24-hour UNa excretions altered the linear relationship with mortality observed in the TOHP follow-up study. A

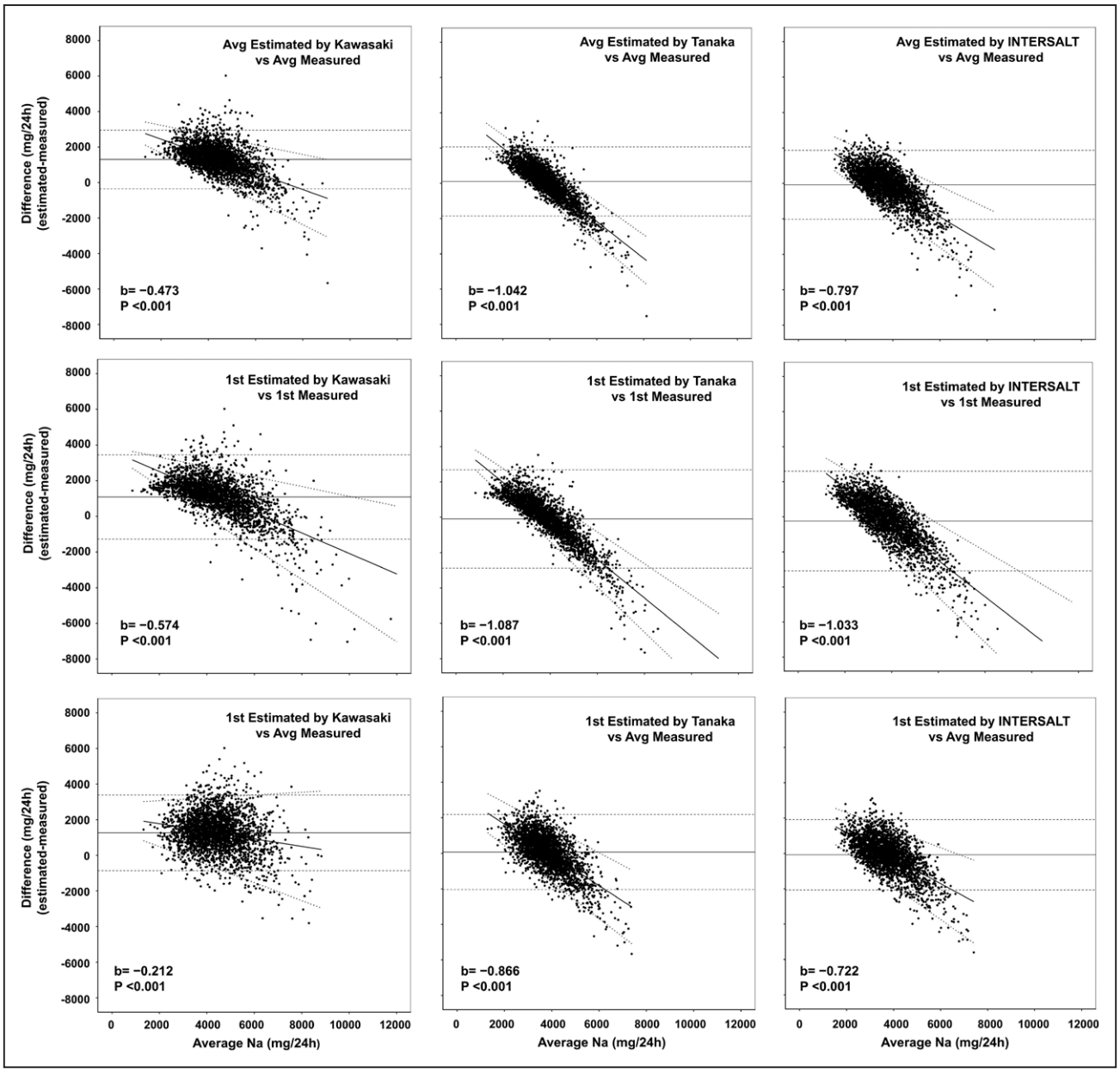

Figure 1. Bland-Altman plot comparing estimated 24-h urinary sodium excretion with measured values during the trial periods. Avg indicates average; Na, 24-h urinary sodium excretion; and INTERSALT, International Cooperative Study on Salt, Other Factors, and Blood Pressure.

common pattern of the alterations by all formulas including those with a constant sodium concentration is that, at lower levels of sodium intake, all estimated 24-hour UNa excretions appeared to be inversely related to mortality. Taken together, our results suggest that variables used in the formulas, other than sodium, could at least partially explain the increased risk of mortality with a lower sodium intake reported in some cohort studies. This is not surprising, given that other variables in the formulas (eg, age, sex, body weight, and creatinine concentration) are known to be associated with mortality.[28,29]

Over the past 30 years, numerous formulas have been developed among various populations in an attempt to estimate population sodium intake from spot urine because of the obvious advantage of collecting spot urine over 24-hour urine in terms of burden to the participants, costs, and challenges in implementation. However, these formulas have been inappropriately used to estimate an individual's usual sodium intake and its association with health outcome.[11–13] The most commonly used formulas are Kawasaki, Tanaka, and INTERSALT. Our findings of a similar systematic bias by all these 3 formulas are in agreement with a number of studies from various countries including the United Kingdom,[14] United States,[17] Portugal,[15] New Zealand,[30] Italy,[14] India,[31] and China.[32,33]

Our study also showed that, at the population level, there was a significant bias in estimating mean sodium intake. The magnitude and direction of the mean bias varied between formulas, and the Kawasaki was the most biased, overestimating mean sodium intake by 1299 mg/d (3.2 g/d salt). The population level bias found in our study is also in keeping with several other studies[15,31] but in contrast with the study by Mente et al[34] who reported that the Kawasaki formula produced

Table 1. Total Mortality in the Trials of Hypertension Prevention Cohorts Post-Trial Follow-Up by Categories of Measured 24-h UNa Excretion Among Individuals Not in a Sodium Reduction Intervention

Variable	Measured Sodium Excretion (mg/24 h)				*P* Trend	Hazard Ratios per 1000 mg/24 h	*P* Value
	<2300	2300–<3600	3600–<4800	≥4800			
Average measured 24-h UNa							
Deaths/total (%)	23/312 (7.4)	105/1182 (8.9)	93/979 (9.5)	51/538 (9.5)			
Hazard ratios (95% CI)	0.73 (0.45–1.20)	0.94 (0.70–1.26)	1 (reference)	1.09 (0.76–1.55)	0.204	1.12 (1.01–1.25)	0.032
First measured 24-h UNa							
Deaths/total (%)	44/440 (10.0)	71/811 (8.8)	57/693 (8.2)	68/716 (9.5)			
Hazard ratios (95% CI)	1.23 (0.81–1.86)	1.15 (0.80–1.64)	1 (reference)	1.20 (0.84–1.73)	0.850	0.99 (0.91–1.06)	0.703

From Cox proportional hazards regression models stratified by trial phase and adjusted for age, sex, race/ethnicity, clinic, treatment assignment, education status, baseline weight, alcohol use, smoking, exercise, and family history of cardiovascular disease. UNa indicates urinary sodium.

the least bias at the group level compared with Tanaka and INTERSALT in a validation study involving 540 participants from 11 countries. The discrepancy between study findings could be attributable to various factors, for example, difference in the timing of spot urine collection, study population, and the levels of their sodium intake, as well as quality of the studies, particularly the inclusion of a large proportion of incomplete 24-hour urine samples (≈70%) in Mente study.[35,36] Both the Kawasaki and Tanaka formulas were developed in a Japanese population with a high sodium intake, and the Kawasaki formula used second morning fasting urine samples.[19,21] However, using an identical protocol as that for the development of the Kawasaki formula, a study in a Chinese population who also had a high sodium intake showed that the Kawasaki formula was unreliable, underestimating mean population sodium intake by 740 mg/d (1.9 g/d salt).[32]

An accurate measurement of an individual's sodium intake is vital for epidemiological studies relating sodium intake to health outcome.[37] Twenty-four–hour UNa excretion is considered the gold standard method for assessing sodium intake. Despite this, 1 single 24-hour urine cannot be used to estimate an individual's usual intake because of the large day-to-day variations in sodium intake. To get a reasonably reliable estimate for an individual, a minimum of three 24-hour urine collections are needed.[38–40] TOHP collected three to seven 24-hour urines during a period of 18 months to 4 years and demonstrated a direct linear relationship between sodium intake and mortality. However, replacing the accurately

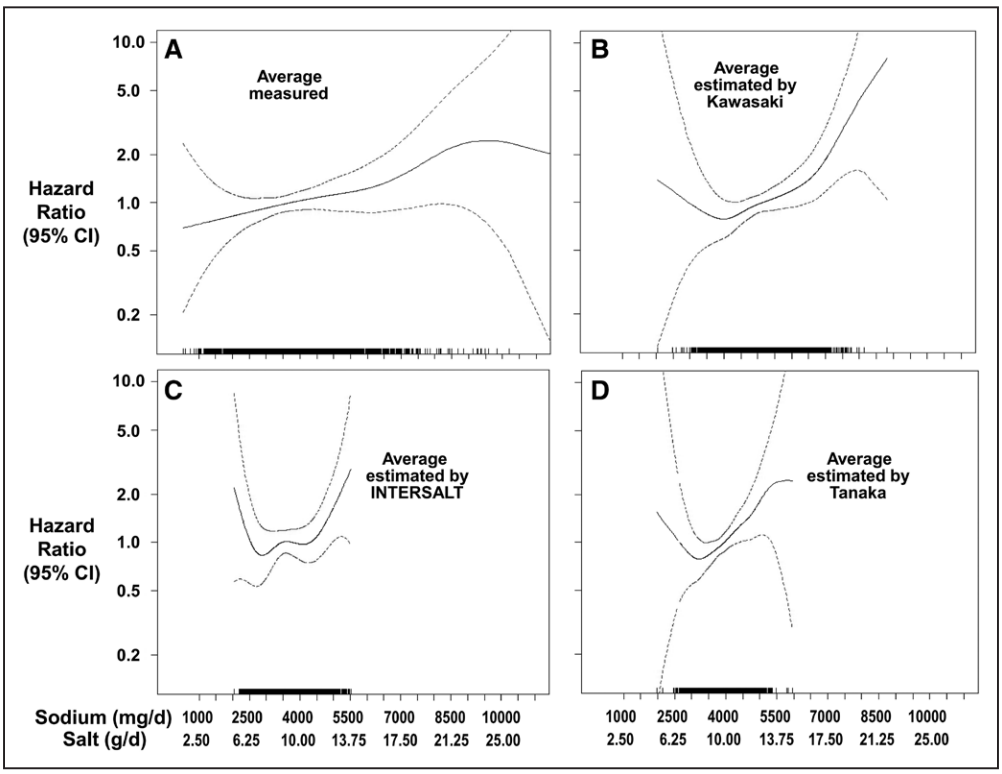

Figure 2. Spline plots for the association between average estimates of 24-h urinary sodium excretion and all-cause mortality adjusted for age, sex, race/ethnicity, clinic, treatment assignment, education status, baseline weight, alcohol use, smoking, exercise, and family history of cardiovascular disease. Rug plot indicates distribution of sodium excretion. **A**: *P* (linear)=0.029; *P* (nonlinear)=0.87. **B**: *P* (linear)=0.006; *P* (nonlinear)=0.26. **C**: *P* (linear)=0.13; *P* (nonlinear)=0.083. **D**: *P* (linear)=0.010; *P* (nonlinear)=0.56. INTERSALT indicates International Cooperative Study on Salt, Other Factors, and Blood Pressure.

Table 2. Total Mortality in the Trials of Hypertension Prevention Cohorts Post-Trial Follow-Up by Categories of Estimated 24-h UNa Excretion Using the Kawasaki, Tanaka, and INTERSALT Formulas Among Individuals Not in a Sodium Reduction Intervention

Variable	Estimated Sodium Excretion (mg/24 h)				*P* Trend	Hazard Ratios per 1000 mg/24 h	*P* Value
	<3600	3600–<4800	4800–<6000	≥6000			
Estimated with Kawasaki formula							
Average estimated 24-h UNa							
Deaths/total (%)	8/89 (9.0)	85/1100 (7.7)	132/1418 (9.3)	47/403 (11.7)			
Hazard ratios (95% CI)	1.26 (0.60–2.65)	1 (reference)	1.39 (1.01–1.92)	1.83 (1.17–2.85)	0.015	1.28 (1.06–1.55)	0.010
Average estimated 24-h UNa with constant sodium concentration							
Deaths/total (%)	16/137 (11.7)	73/972 (7.5)	120/1216 (9.9)	63/685 (9.2)			
Hazard ratios (95% CI)	1.97 (1.11–3.51)	1 (reference)	1.18 (0.86–1.60)	1.06 (0.74–1.53)	0.640	1.01 (0.90–1.14)	0.820
First estimated 24-h UNa							
Deaths/total (%)	19/229 (8.3)	77/903 (8.5)	104/1130 (9.2)	46/478 (9.6)			
Hazard ratios (95% CI)	0.89 (0.53–1.48)	1 (reference)	1.03 (0.75–1.41)	1.13 (0.75–1.70)	0.422	1.09 (0.95–1.25)	0.227
First estimated 24-h UNa with constant sodium concentration							
Deaths/total (%)	20/225 (8.9)	76/1013 (7.5)	98/904 (10.8)	53/614 (8.6)			
Hazard ratios (95% CI)	1.52 (0.89–2.58)	1 (reference)	1.44 (1.06–1.97)	1.08 (0.75–1.56)	0.932	0.98 (0.88–1.08)	0.671
	<3600	3600–<4800	≥4800				
Estimated with Tanaka formula							
Average estimated 24-h UNa							
Deaths/total (%)	64/810 (7.9)	192/2097 (9.2)	16/103 (15.5)				
Hazard ratios (95% CI)	0.78 (0.57–1.07)	1 (reference)	2.05 (1.18–3.55)		0.015	1.50 (1.10–2.06)	0.011
Average estimated 24-h UNa with constant sodium concentration							
Deaths/total (%)	70/861 (8.1)	164/1803 (9.1)	38/346 (11.0)				
Hazard ratios (95% CI)	0.99 (0.74–1.34)	1 (reference)	1.07 (0.74–1.53)		0.792	1.03 (0.84–1.25)	0.805
First estimated 24-h UNa							
Deaths/total (%)	73/903 (8.1)	150/1661 (9.0)	23/176 (13.1)				
Hazard ratios (95% CI)	0.86 (0.64–1.16)	1 (reference)	1.67 (1.05–2.65)		0.074	1.14 (0.91–1.44)	0.254
First estimated 24-h UNa with constant sodium concentration							
Deaths/total (%)	79/1062 (7.4)	137/1352 (10.1)	31/342 (9.1)				
Hazard ratios (95% CI)	0.76 (0.57–1.02)	1 (reference)	0.82 (0.55–1.23)		0.455	0.97 (0.82–1.15)	0.710
	<3600	3600–<4800	≥4800				
Estimated with INTERSALT (International Cooperative Study on Salt, Other Factors, and Blood Pressure) formula							
Average estimated 24-h UNa							
Deaths/total (%)	112/1367 (8.2)	141/1527 (9.2)	19/116 (16.4)				
Hazard ratios (95% CI)	0.94 (0.64–1.37)	1 (reference)	1.84 (1.09–3.10)		0.333	1.29 (0.91–1.82)	0.161
Average estimated 24-h UNa with constant sodium concentration							
Deaths/total (%)	103/1366 (7.5)	163/1605 (10.2)	6/39 (15.4)				
Hazard ratios (95% CI)	0.82 (0.54–1.23)	1 (reference)	1.61 (0.68–3.79)		0.435	1.11 (0.73–1.71)	0.621
First estimated 24-h UNa							
Deaths/total (%)	107/1244 (8.6)	119/1329 (9.0)	20/167 (12.0)				
Hazard ratios (95% CI)	1.15 (0.80–1.65)	1 (reference)	1.20 (0.72–1.99)		0.876	1.07 (0.80–1.43)	0.642
First estimated 24-h UNa with constant sodium concentration							
Deaths/total (%)	105/1328 (7.9)	137/1387 (9.9)	5/41 (12.2)				
Hazard ratios (95% CI)	1.05 (0.72–1.51)	1 (reference)	1.41 (0.56–3.58)		0.844	1.00 (0.69–1.45)	0.996

From Cox proportional hazards regression models stratified by trial phase and adjusted for age, sex, race/ethnicity, clinic, treatment assignment, education status, baseline weight, alcohol use, smoking, exercise, and family history of cardiovascular disease. UNa indicates urinary sodium.

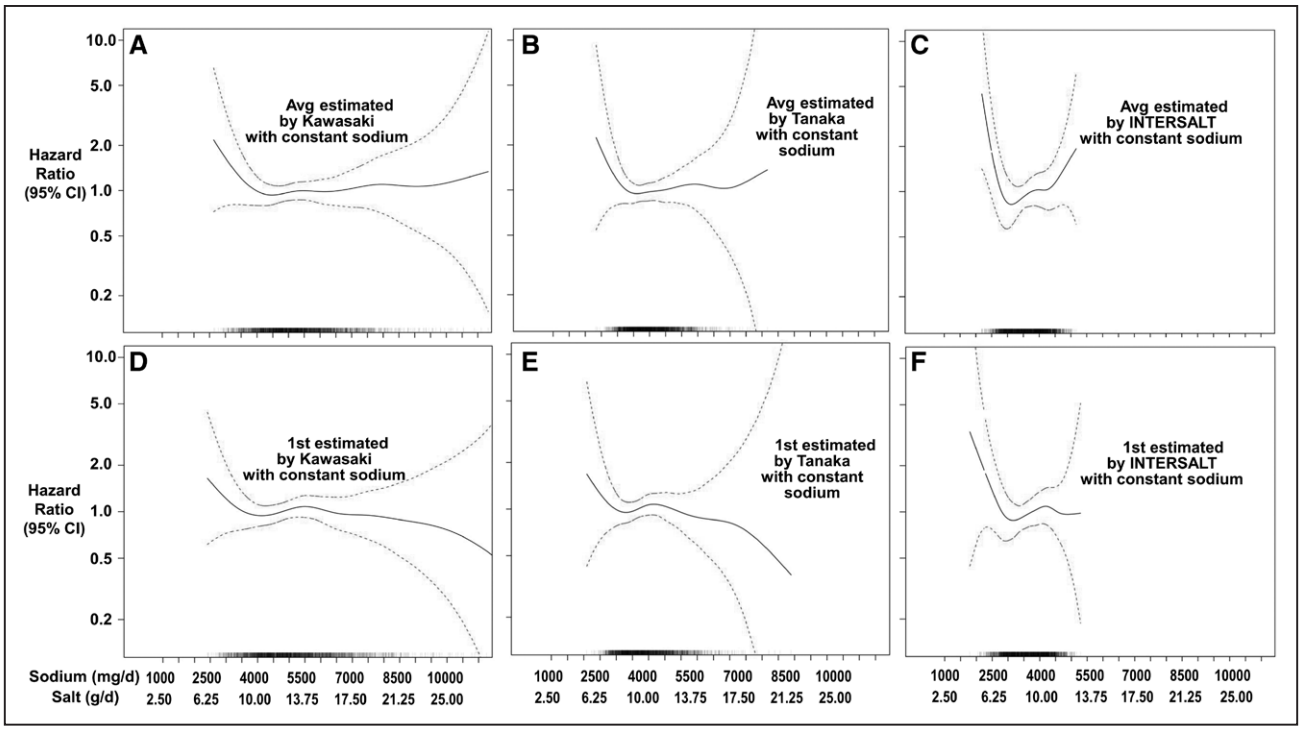

Figure 3. Spline plots for the association between estimated 24-h urinary sodium excretion with constant sodium concentration and all-cause mortality adjusted for age, sex, race/ethnicity, clinic, treatment assignment, education status, baseline weight, alcohol use, smoking, exercise, and family history of cardiovascular disease. **A**: *P* (linear)=0.83; *P* (nonlinear)=0.42. **B**: *P* (linear)=0.82; *P* (nonlinear)=0.64. **C**: *P* (linear)=0.69; *P* (nonlinear)=0.0048. **D**: *P* (linear)=0.70; *P* (nonlinear)=0.41. **E**: *P* (linear)=0.73; *P* (nonlinear)=0.64. **F**: *P* (linear)=0.93; *P* (nonlinear)=0.26. Avg indicates average; and INTERSALT indicates International Cooperative Study on Salt, Other Factors, and Blood Pressure.

measured sodium intake with those estimated from sodium concentration using the formulas changed this linear relationship. The average estimated sodium intakes appeared to show a J- or U-shaped relationship with mortality for all 3 formulas. These findings indicate that the biased estimation of sodium intake from spot urine by the formulas could explain much of the paradoxical J-shaped association reported in some of the cohort studies.[12]

By using a constant sodium concentration, our analysis further confirmed that other variables in the formulas (eg, age, sex, body weight, and creatinine concentration) independently biased the estimations of sodium intake and altered the linear association between sodium intake and mortality. It is well known that age is the major risk factor for chronic diseases and mortality. There is also a variation in sodium intake between different age groups, and a reduction in sodium intake has a greater effect on BP in the elderly compared with young people.[1] Both sodium intake and mortality rates are higher in men compared with women.[41] A higher body weight (overweight/obesity) increases the risk of type II diabetes mellitus and death.[28] In obese individuals, BP is more sensitive to the changes in sodium intake.[42] Twenty-four–hour urinary creatinine excretion is a marker of muscle mass—an indicator of fitness, which is also associated with sodium intake and mortality.[29] Therefore, the use of creatinine concentration in the formulas may further confound the estimated sodium intake, as well as the associated risk.

The strength of our analysis includes the use of data on dietary sodium intake based on measurements of multiple nonconsecutive 24-hour urines to minimize the potential for systematic bias and random error in sodium intake and the careful assessment and a priori exclusion of people at risk of cardiovascular disease to minimize the potential for reverse causality. Our analysis also has a number of limitations. First, spot urine was not collected in TOHP, and we used sodium concentration from 24-hour urine instead. However, a key assumption in using spot urine to estimate sodium intake is that the ratio of spot UNa-to-creatinine concentration is equivalent to that in 24-hour urine.[21] Indeed, in our analysis, the overestimation and underestimation of sodium intake based on the Kawasaki formula with 24-hour urine[18] is similar to that found in studies with fasting morning spot urine.[34] Second, the sample size was small with limited statistical power to test the relationship between sodium intake and mortality at the highest and lowest sodium levels. This could be one of the reasons for the statistically nonsignificant result for deviation from linearity, but significant linear association, when the curve appeared J shaped. Third, no urine collection was made during follow-up, and baseline sodium measurement does not reflect long-term intake. This is likely to have resulted in an underestimation of the strength of the association between sodium intake and mortality, as demonstrated by a recent study with use of long-term multiyear 24-hour urine collections.[43]

Perspectives

By comparing various estimates of sodium intake with the gold standard method of careful collections of multiple nonconsecutive 24-hour urines during a period of 18 months to 4

years, our analysis demonstrates that none of the 3 commonly used formulas can be used to estimate individuals' sodium intake accurately. It is thus inappropriate to associate unreliable and biased estimations of sodium intake with mortality, particularly because the formulas per se seem to be related to death, independent of sodium intake. Paradoxical J-shaped findings reported in some cohort studies,[12,44] which use biased estimates of sodium intake from formulas with UNa concentration, should not be used to refute the totality of evidence for the beneficial effects of population-wide reduction in sodium intake.[26,45]

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Novelty and Significance

What Is New?

- To our knowledge, our study is the first to have compared estimations of sodium intake by 3 commonly used formulas to accurately measured sodium intake by multiple nonconsecutive 24-hour urine collections in relation to mortality.
- All estimated sodium intakes were systematically biased and altered the sodium-mortality relationship.
- An additional analysis keeping sodium concentration constant further confirmed the independent role of the formulas per se on the biased estimation of sodium intake and its association with deaths.

What Is Relevant?

- Some cohort studies using spot urine to estimate sodium intake by formulas reported a J-shaped association with mortality, with both lower and higher sodium intake being related to an increased risk. This caused controversy, casting doubt on the current public health recommendations of sodium reduction.
- Our study demonstrates that the paradoxical J-shaped findings are, at least partially, attributable to biased estimation of sodium intake using the formulas.

Summary

Accurately measured sodium intake through multiple nonconsecutive 24-hour urine collections showed a positive linear relationship with mortality down to a sodium level of 1200 mg/d (3 g/d salt). Inaccurate estimations of sodium intake from spot urine by formulas altered this relationship. It is, therefore, vital to accurately assess an individual's sodium intake in studies of health outcomes.