ORIGINAL RESEARCH

CURRENT DEVELOPMENTS IN NUTRITION

Nutritional Epidemiology and Public Health

Estimating 24-Hour Urinary Excretion of Sodium and Potassium Is More Reliable from 24-Hour Urine Than Spot Urine Sample in a Feeding Study of US Older Postmenopausal Women

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ABSTRACT

Background: Assessing estimated sodium (Na) and potassium (K) intakes derived from 24-h urinary excretions compared with a spot urine sample, if comparable, could reduce participant burden in epidemiologic and clinical studies.

Objectives: In a 2-week controlled-feeding study, Na and K excretions from a 24-h urine collection were compared with a first-void spot urine sample, applying established algorithms and enhanced models to estimate 24-h excretion. Actual and estimated 24-h excretions were evaluated relative to mean daily Na and K intakes in the feeding study.

Methods: A total of 153 older postmenopausal women ages 75.4 ± 3.5 y participated in a 2-wk controlled-feeding study with a 4-d repeating menu cycle based on their usual intake (ClinicalTrials.gov Identifier: NCT00000611). Of the 150 participants who provided both a first-void spot urine sample and a 24-h urine collection on the penultimate study day, statistical methods included Pearson correlations for Na and K between intake, 24-h collections, and the 24-h estimated excretions using 4 established algorithms: enhanced biomarker models by regressing ln-transformed intakes on ln-transformed 24-h excretions or ln-transformed 24-h estimated excretions plus participant characteristics and sensitivity analyses for factors potentially influencing Na or K excretion (e.g., possible kidney disease estimated glomerular filtration rate <60 mL/min/1.73 m^2).

Results: Pearson correlation coefficients between Na and K intakes and actual 24-h excretions were 0.57 and 0.38–0.44 for estimated 24-h excretions, depending on electrolyte and algorithm used. Enhanced biomarker model cross-validated R^2 (CVR^2) for 24-h excretions were 38.5% (Na), 40.2% (K), and 42.0% (Na/K). After excluding participants with possible kidney disease, the CVR^2 values were 43.2% (Na), 40.2% (K), and 38.1% (Na/K).

Conclusions: Twenty-four-hour urine excretion measurement performs better than estimated 24-h excretion from a spot urine as a biomarker for Na and K intake among a sample of primarily White postmenopausal women. *Curr Dev Nutr* 2021;5:nzab125.

Keywords: controlled-feeding study, postmenopausal women, biomarker, sodium, potassium, 24-hour urine, spot urine

Manuscript received June 25, 2021. Initial review completed September 17, 2021. Revision accepted September 29, 2021. Published online October 12, 2021.
The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, 75N92021D00005, and HHSN271201600004C; National Cancer Institute (NCI) grants R01 CA119171; and in part through the NIH/NCI Cancer Center Support grant P30 CA015704.
Author disclosures: The authors report no conflicts of interest.
Supplemental Tables 1–9 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/cdn/.

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Abbreviations used: ACE, angiotensin converting enzyme; CT, clinical trial; CVR^2, cross-validated R^2; eGFR, estimated glomerular filtration rate; Ein, energy intake derived from doubly labeled water; Fred Hutch, Fred Hutchinson Cancer Research Center; HNL, Human Nutrition Lab; INTERSALT, International Study of Electrolyte Excretion and Blood Pressure; LASSO, least absolute shrinkage and selection operator; NDS-R, Nutrition Data System for Research software; NPAAS-FS, Nutrition and Physical Activity Assessment Study–Feeding Study; NSAID, nonsteroidal anti-inflammatory drug; NSES, neighborhood socioeconomic status; OS, observational study; PURE, Prospective Urban and Rural Epidemiology; RD, registered dietitian; WHI, Women's Health Initiative; 4DFR, 4-d food record.

Introduction

Global (1) and US national (2) health and dietary guidelines call for dietary sodium (Na) reduction together with shifts to correct the underconsumption of potassium (K) (2). Accurate assessment of intakes is necessary when providing dietary modification guidance to individuals, families, and communities. However, assessment of population sodium and potassium intakes is limited by dependence upon self-reported dietary assessment and sodium intake is especially poorly quantified (3, 4). Urinary measures of both sodium and potassium are recovery biomarkers (3, 5), where the biomarker is a good quantitative estimate of intake and an improvement over self-report.

The gold standard for estimating daily dietary Na and K intakes is multiple 24-h urine collections (6), but participant and economic burdens imposed by even a single 24-h urine collection often preclude its use in large population studies (4). Previous studies have explored the use of spot compared with a 24-h urine collection, with inconsistent results. The spot urine is subject to diurnal variation (7), but the practicality of this approach continues to foster algorithm development for estimating 24-h Na and K excretion, including those by Kawasaki et al. (8, 9), Tanaka et al. (10), and International Study of Electrolyte Excretion and Blood Pressure (INTERSALT) for Na only (11). Recently, Mente and colleagues (12) evaluated these algorithms for use in the Prospective Urban and Rural Epidemiology (PURE) Study, an international cohort of men and women that investigated Na and K intakes and cardiovascular disease (13). The PURE study selected the Kawasaki algorithm to estimate 24-h urinary excretion from a midmorning spot urine sample. The Kawasaki algorithm was also recommended (12) for use in large studies when estimating 24-h Na or K excretion from a spot urine sample.

Demonstrating highly correlated excretion concentrations of Na and K derived from spot urine compared with those of 24-h urine would offer a methodologic advantage in clinical research trials. However, direct comparisons of the 2 methods in the context of a controlled-feeding study with known intakes are rare (14). The purpose of this study was to *1*) evaluate a measured 24-h urine collection and 4 algorithms [Kawasaki et al. (8, 9), Tanaka et al. (10), INTERSALT for Na only (11), and Mann et al. (7) for estimating 24-h excretion (7)] of Na and K from a first-void spot urine sample and *2*) develop enhanced algorithms by adding participant characteristics to the measured and estimated 24-h urine excretions of Na and K. Algorithms were evaluated against the consumed diets from a 2-wk controlled-feeding study of 153 postmenopausal women (15) within the Women's Health Initiative (WHI) (16).

Methods

Women's Health Initiative

The WHI (NCT00000611) enrolled 161,808 postmenopausal women across the United States from 1993 to 1998 into 1 or more of 4 clinical trials (CTs) or an observational study (OS) at 1 of 40 clinical sites in the United States (16). In 2005, when CT follow-up ended (17–23), the WHI offered participants from the CTs and the OS the opportunity to consent to a mailed follow-up phase, which remains ongoing.

The WHI Nutrition and Physical Activity Assessment Feeding Study

WHI older postmenopausal participants living in metropolitan Seattle who had participated previously in the WHI Seattle Clinical Center ($n = 153$) completed a 2-wk controlled-feeding study between 2011 and 2013 at the Fred Hutchinson Cancer Research Center (Fred Hutch; Seattle, WA) in the Prevention Center Shared Resource Human Nutrition Lab (HNL). Each participant had her own unique set of 4-d rotating menus based on her usual intake of self-selected foods and beverages as documented on pre-study 4-d food records (4DFRs) (15). Eligibility included being an active participant in the WHI who had been enrolled in the Dietary Modification Comparison (nonintervention) group, Hormone Therapy trials, or the OS; up to 80 y of age at time of recruitment; living in the Seattle, WA, area; being free of medical conditions that could interfere with usual care during the clinical phases of the protocol, such as diabetes or urinary incontinence; being weight stable (within 15 pounds over the past 4 wk to meet doubly labeled water protocol requirements); and willing to complete all protocol activities that necessitated at-home tasks as well as coming to the Fred Hutch before and several times during the study (15) (see **Figure 1** for the participant flow).

Participants consumed weighed and measured meals at the HNL 2–3 times/wk for a single meal, with all remaining meals packaged for home consumption. The study protocol asked that participants eat only the foods provided or allowed by the study for the 2-wk duration. Participants kept detailed records of consumed foods, including off-protocol foods, and returned all uneaten foods to the HNL for weigh-backs and documentation by the project's registered dietitian (RD). Alcohol was allowed and, if consumed, was obtained by the participant and documented. Salt (50 g) was weighed and placed into a saltshaker for each participant to consume as desired. Participants returned the saltshaker with the remaining salt to each HNL visit for documentation. The RD used the 4DFR to plan the 4-d rotating menus for the 2-wk planned diet controlled-feeding study period, entering each participant's documented consumed intake into the Nutrition Data System for Research software (NDS-R; Nutrition Coordinating Center, version 2010; University of Minnesota).

Body-weight measurement occurred at each HNL visit. Body-weight loss triggered modest diet adjustments to maintain weight close to clinic visit 1 body weight. Participants continued their usual medications, both prescription and over-the-counter, and usual dietary supplements. Participants brought their medications and dietary supplements to the HNL for documentation and therapeutic class matching (medications) and nutrient analysis (NDS-R dietary supplement module).

On the first and last days of the 2-wk feeding study period, participants attended clinic visits to complete the protocols, which included doubly labeled water biomarker assessment for estimated energy expenditure, fasting blood draws, measurement of height at visit 1 and weight at visits 1 and 2, indirect calorimetry, and completion of questionnaires on lifestyle habits (recreational physical activity, smoking, and alcohol intake). The biomarker-estimated energy intake (Ein) from doubly labeled water was computed by accounting for weight change during the 2-wk feeding period. Body weight in grams per day was multiplied by 2 kcal/g to estimate the change in body energy stores and then Ein was calculated as total energy expenditure (by doubly labeled water) plus change in body energy stores (24).

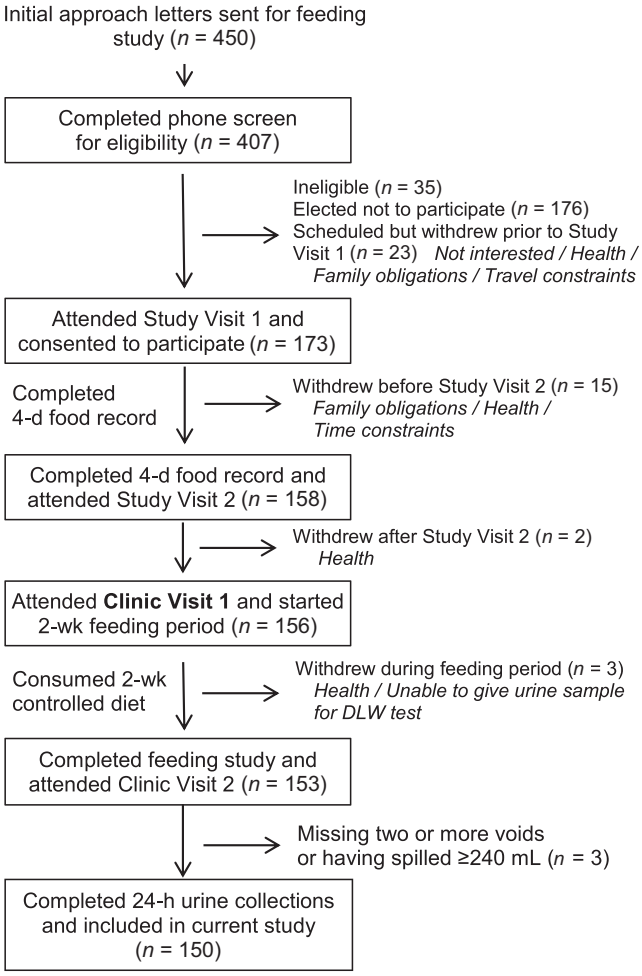

FIGURE 1 Flow diagram of participant eligibility and final inclusion.

Urine and blood collection and assays

Participants received a kit and instructions for collecting a first-void spot urine sample immediately preceding the 24-h urine on the penultimate study day with the clock for the 24-h urine starting after collecting the spot urine sample. The spot urine was collected up to 120 mL, with the remainder flushed away. The containers included boric acid as a preservative. All collections were refrigerated away from food or stored in coolers with ice packs until brought to the Prevention Center for processing. Urine collections were thoroughly mixed and, for the 24-h urine, weighed, before being placed into aliquots for −80°C freezer storage. To convert the 24-h urine collections from weight to volume, a density equality with 1 g equaling 1 mL was applied. Samples were shipped on dry ice to the laboratories for analysis of Na, K, and creatinine. Sodium and K were analyzed by selective ion electrode (25). Creatinine from the spot urine sample and 24-h urine collection, as an adjustment factor for the spot urine sample Na and K concentrations, was assayed by spectrophotometric detection of a colored creatinine-picrate complex (26). For the algorithms evaluated for the PURE study, we estimated urine creatinine according to the methods described by Mente et al. (12).

Fasting blood collection occurred at the final clinic visit (15). Serum aliquots were stored at −80°C until being assayed. Serum creatinine was assessed through targeted serum metabolite profiling, leading to a calculated estimated glomerular filtration rate (eGFR) (27). An eGFR <60 mL/min/1.73 m^2, suggestive of possible kidney disease (28), was used in statistical sensitivity analyses.

Ethics

The procedures were in accordance with the ethical standards of and approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and all participants signed informed consent in accordance with the Helsinki Declaration of 1975 as revised in 1983. The WHI consent and Nutrition and Physical Activity Assessment Study–Feeding Study (NPAAS-FS) consent allowed for use of biological samples and data. Participants' parking for and cab fares to the Fred Hutchinson Cancer Research Center Prevention Center Human Nutrition Lab were paid by the study. Participants received $300 compensation for completing the study. Data were anonymized during creation of the analytic datasets. The WHI Clinical Coordinating Center Principal Investigator and database unit manager are responsible for data security.

Ancillary study principal investigators sign data and materials transfer agreements and the lead author and collaborators for papers sign data use agreements. eGFR was computed for the statistical analyses conducted for this paper, which was after completion of the NPAAS-FS. The identification of possible kidney disease from eGFR occurred after the feeding study was completed and participants were not notified of the results.

Statistical analysis

Statistical analyses included participant-related data from both the WHI and the NPAAS-FS studies. Participant age, race, ethnicity, and educational level were obtained from the WHI database. Daily intakes of Na and K, height, weight, BMI (kg/m^2), biomarker measures, urine and serum creatinine, season, recreational physical activity for computation of metabolic equivalent task-h/wk (METs), smoking status, medications, eGFR, and biospecimen data were obtained from the NPAAS-FS.

The primary goal was to investigate whether 24-h urinary excretions of Na and K estimated by 4 algorithms based on a spot urine sample performed as well as measured 24-h urine excretions. The secondary goal was to determine whether modeling the spot urine sample together with participant characteristics would enhance the variance explained, thus improving the 24-h estimations. Application of the formula by Mann et al. (7) divided the spot urine sample electrolyte by spot urine sample creatinine multiplied by 24-h urinary excretion of creatinine to compute the estimated 24-h urinary electrolyte excretion. The Kawasaki, Tanaka, and INTERSALT algorithms were applied in the same manner as for the PURE study (12).

Pearson correlations were examined between the ln-transformed daily mean of the 14-d consumed intakes of Na, K, and Na/K and the respective urinary excretions (ln-transformed) from the 24-h urine collection and from the estimated 24-h urinary excretion from the spot urine sample. Pearson correlations were examined additionally between the 24-h urine collection and the estimated 24-h urinary excretion based on the spot urine sample.

Next, the aim was to investigate whether the estimated Na and K intakes could be improved through linear regression analyses that included participant characteristics. Biomarker evaluation equations were calculated by regressing the ln-transformed mean daily intakes from the 2-wk consumed diets, on the ln-transformed actual 24-h urine excretion measurements and the estimated 24-h urine excretion plus participant-related characteristics selected by the model. These variables included age, race, ethnicity, education, BMI, recreational physical activity, season, diuretic medications (nonspecified indication), smoking status, and biomarker-estimated energy intake from doubly labeled water accounting for weight change during the 2-wk feeding period (Ein). Mean daily Na and K from the 2-wk 4-d repeating cycle consumed diet served as the referent of highly controlled usual intake (29). Diuretics taken by the NPAAS-FS participants included loop diuretics, thiazide and thiazide-like diuretics, and diuretic combinations and these were included in the main model due to their known effects on Na and K excretion (29). Variable selection for the biomarker equations was conducted using least absolute shrinkage and selection operator (LASSO) regression analysis (30) and the model was then refit using the selected variables. The predictive performance of the models was assessed by 10-fold cross-validation with 10,000 repetitions (31) to compute a cross-validated R^2 (CVR^2). A CVR^2 $\geq$36% was selected as a benchmark for being an acceptable biomarker based on urinary recovery biomarkers of energy and protein as described by Lampe et al. (15).

Sensitivity analyses were conducted on the main models by excluding participants (n = 16) with potential kidney disease as estimated by eGFR <60 mL/min/1.73 m^2. In addition, sensitivity analyses included alternative participant characteristics in the regression models. The first involved the additions of nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates into the participant characteristics. The second added anti-hypertension–related medications in addition to diuretics that may influence Na and K excretion, including angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, B-blockers, and calcium channel blockers. The third excluded participants with 24-h urine <800 mL as being a lower volume than expected (32). The fourth averaged the consumed diets and the 24-h urine collection before regressing on the predicted 24-h urine and participant characteristics, acknowledging that nutrient estimates from consumed diets may be noisy due to variations in nutrients in foods consumed relative to those used to populate databases. For example, variations in nutrients may be due to food preparation, growing conditions, and food ripeness, as well as noise in urine collections relative to diurnal variations and consumption to excretion time. Each of the additional sensitivity analyses was further assessed after excluding participants with an eGFR <60 mL/min/1.73 m^2. Finally, correlations were examined of both the actual and estimated Na and K excretions using the past day of intake as well as the past 4 d.

Results

Three of the 153 (2%) participants returned incomplete 24-h urine collections based on self-reporting $\geq$2 missed collections or having spilled $\geq$240 mL and were excluded from analysis, leaving n = 150 participants in the analytic sample. Participants primarily self-identified as non-Hispanic White, college educated or higher, with a mean age of 75 y at the time of the feeding study. Nearly half of participants were taking at least 1 antihypertension-related medication, including diuretics, ACE inhibitors, angiotensin II receptor agonists, calcium channel blockers, and B-blockers. Over half of participants were overweight or obese (BMI $\geq$25); participants unintentionally lost a mean of 0.78 kg of body weight during the 2-wk feeding study period. The mean Na and K intakes during the 2-wk feeding study were 2508 and 3111 mg/d, respectively. Sixteen (11%) participants had an eGFR <60 mL/min/1.73 m^2 (**Table 1**).

The mean 24-h urine volume was 2107 $\pm$ 902 mL (range: 429–5605 mL), with a mean Na excretion of 2172 $\pm$ 842 mg (range: 513–5576 mg). The spot urine, Kawasaki, and Tanaka 24-h Na excretion estimates were higher than the measured 24-h excretion, whereas the INTERSALT estimate was lower than the measured excretion. The mean 24-h urine K excretion was 2442 $\pm$ 803 mg. The spot urine, Kawaski, and Tanaka 24-h K excretion estimates were lower than the measured 24-h K excretion (**Table 2**).

The Pearson correlations between consumed dietary Na, K, and Na/K and their 24-h urine biomarkers, ranged from 0.57 to 0.60, while those from the estimated 24-h urine biomarkers ranged from 0.38 to 0.45. The percentage of variation explained (R^2) was 32.6–35.9% for

TABLE 1 Baseline demographic and lifestyle characteristics of the 150 postmenopausal women who participated in the NPAAS-FS and provided complete urine collections[1]

Characteristics	Mean ± SD or *n* (%)
Age, y	75.4 ± 3.54
Race/ethnicity	
American Indian or Alaskan Native	1 (0.7)
Asian or Pacific Islander	1 (0.7)
Black or African American	3 (2)
Hispanic	2 (1.3)
White	143 (95)
Education	
High school/General Educational Development diploma	10 (7)
Schooling after high school	58 (39)
College degree or higher	81 (54)
Missing	1 (<1)
Current smoker	3 (2)
Medications	
Anti-hypertension-associated medication[2]	66 (44)
Diuretics	24
Beta blockers	30
Calcium channel blockers	23
Antihypertensives	38
Salicylates	50 (33)
NSAIDs	9 (6)
BMI, kg/m^2	26.4 ± 4.19
BMI <25	60 (4)
25 ≤ BMI < 30	57 (38)
BMI ≥ 30	33 (22)
Recreational physical activity, MET-h/wk	15.9 ± 14.4
Consumed diet intake (2-wk daily mean)	
Energy intake, kcal	1921 ± 292
Carbohydrate, % of energy	45.3 ± 6.9
Protein, % of energy	16.6 ± 3
Fat, % of energy	37.9 ± 5.9
Sodium, mg/d	2508 ± 676
Potassium, mg/d	3111 ± 632
Ein, kcal/d	2107 ± 902
Weight change during the 2-wk feeding study, kg	−0.8 ± 0.8
24-h urine volume, mL	2107 ± 902
eGFR < 60 mL/min/1.73 m^2	16 (11)

[1]ACE, angiotensin converting enzyme; eGFR, estimated glomerular filtration rate; Ein, energy intake derived from doubly labeled water; MET-h, metabolic equivalent task-hour; NPAAS-FS, Nutrition and Physical Activity Assessment Feeding Study; NSAID, nonsteroidal anti-inflammatory drug.
[2]Anti-hypertension–associated medications taken by NPAAS-FS participants included diuretics (loop diuretics, thiazide and thiazide-like diuretics, and diuretic combinations), beta blockers, calcium channel blockers, and antihypertensives (ACE inhibitors, angiotensin II receptor antagonists, and anti-adrenergics). Counts are not mutually exclusive as participants may be taking >1 medication (n = 31 taking 1, n = 23 taking 2, n = 10 taking 3, and n = 2 taking 4 anti-hypertension–associated medications; nonspecified indications).

the actual 24-h urine and 14.1–20.2% for the estimated 24-h urines (**Table 3**). The correlations between actual 24-h urine Na and estimated 24-h urine Na were 0.46 when using the Mann algorithm (0.46) and were 0.31, 0.33, and 0.36 when using the Kawasaki, Tanaka, or INTERSALT algorithms, respectively (**Supplemental Table 1**). For K, the correlations between actual and estimated 24-h urine excretions were 0.61 using the Mann algorithm and 0.36 and 0.37 when using the Kawasaki or Tanaka algorithms, respectively (Supplemental Table 1).

Table 4 provides results for the models for enhanced biomarker estimation. In each model, the biomarker (Na, K, or Na/K) contributed the most to the CVR^2 followed by Ein and often BMI, whereas contributions to the variance explained by other characteristics varied. Performance by the estimated 24-h urinary excretion of Na, K, and each ratio from the algorithms using spot urine samples yielded CVR^2 <36%. By excluding participants with potential kidney disease (eGFR <60 mL/min/1.73 m^2) for the enhanced methods in the main models, the estimated 24-h urine Na predictive performance improved compared with the main model. The estimated 24-h urinary excretion of Na (from a creatinine-adjusted spot urine sample) resulted in a CVR^2 of 36.5% (compared with a CVR^2 of 30.4% in the main model) (**Table 5**). For K, the predictive performance after removing participants with possible kidney disease remained about the same for measured 24-h urine and estimated 24-h urine excretion, which resulted in lower predictive performances for the Na/K ratios. The predictive performance of measured 24-h excretions of Na, K, and Na/K surpassed those of estimated 24-h excretions with or without excluding participants with possible kidney disease. Covariates presented in Tables 4 and 5 were selected using the LASSO procedure, based on a tuning parameter that maximizes the R^2 in 10-fold cross-validation. In this sense, these terms can be considered important contributors to overall R^2.

Sensitivity analyses adding NSAIDs and salicylates or additional antihypertensives or excluding participants with low urine volumes for the enhanced methods did not alter interpretations relative to the main models (**Supplemental Tables 2–7**). When regressing the change in daily consumed K and the 24-h urine K on the estimated 24-h K, a CVR^2 of 38.6% was achieved, which mainly was attributed to the large correlation (r = 0.61) between the 24-h urine K and the estimated 24-h K (**Supplemental Tables 8** and **9**). Sensitivity analyses based on the 1 d and a mean of 4 d of intake before urine collection for Pearson's correlations and algorithm assessed both actual and estimated urinary excretions of Na and K intake. Results were unchanged from using the mean 14 d of intake (data not shown).

Discussion

In this feeding study of 150 postmenopausal women, Na and K urinary excretions from the 24-h urine collection resulted in substantially higher correlations with the consumed and quantified intakes of Na, K, and Na/K than correlations for any of the estimated 24-h urine values derived from a spot urine sample. Results were similar for the correlations between the measured 24-h urine electrolytes and the estimated 24-h electrolyte values, further suggesting that, for postmenopausal women, spot urine algorithms are inadequate substitutes for a measured 24-h urine assessment of Na and K intake. Despite the overall weaker correlations of urinary estimated Na and K with dietary intakes, relations were strengthened by regression models specific to our feeding study that included participant characteristics.

Several studies have more recently reported results using the Kawasaki, Tanaka, INTERSALT, and other spot urine algorithms in a variety of populations. In an Iranian study of 79 adults, Mohammadifard et al. (33) reported that the Tanaka algorithm Na estimate was not significantly different from the study 24-h urine Na, although 2 newly proposed algorithms including self-assessment of discretionary salt and

TABLE 2 Measured and estimated 24-h urine sodium, potassium, and creatinine excretion from the 2-wk controlled-feeding study among the 150 postmenopausal women who participated in the NPAAS-FS and provided complete urine collections[1]

	Volume (1 g = 1 mL), mL	Sodium, mg	Potassium, mg	Creatinine
24-h, measured	2107 ± 902	2172 ± 842	2442 ± 803	868 ± 186
24-h estimated[2] from first void spot urine (5)	NA	2437 ± 1372	1818 ± 772	NA
Kawasaki, estimated 24-h (8, 9)	NA	4004 ± 1099	2014 ± 415	984 ± 119
Tanaka, estimated 24-h (10)	NA	3511 ± 782	1778 ± 340	1239 ± 231
INTERSALT, estimated 24-h (11)	NA	1895 ± 359	NA	NA

[1]Values are means ± SDs. INTERSALT, International Study of Electrolyte Excretion and Blood Pressure; NA, not applicable; NPAAS-FS, Nutrition and Physical Activity Assessment Feeding Study.
[2]All estimations were computed using first-void spot urine collected immediately preceding the 24 h on the penultimate day of the 2-wk controlled-feeding study.

participant characteristics of BMI, sex, age, and physical activity were less biased than the Tanaka algorithm. Two large studies, one in France (34) and one in the Shandong province of China (35), ruled out the Kawasaki, Tanaka, and INTERSALT algorithms for estimating individual Na intake, while not ruling out their use for group estimation. Allen et al. (36) concluded that, for the Multi-Ethnic Study of Atherosclerosis (MESA) and the Coronary Artery Risk Development in Young Adults (CARDIA), biases from the Tanaka, Kawasaki, INTERSALT, and Mage algorithms over- or underestimated sodium excretion across sex and race or ethnicity subgroups. Three studies found underestimation of Na at higher levels and overestimation at lower levels (37), resulting in altered associations of Na with blood pressure (38) and mortality (39). Estimated 24-h urinary Na was associated with a J-shaped curve for blood pressure and mortality, whereas measured 24-h urinary sodium was linearly associated with mortality. A policy statement from the World Hypertension League issued in 2019 cautions against the use of spot urines and urges rigorous study of spot urines based on systematic review of Na–disease association studies published November 2018–August 2019 (40).

Adding more detailed participant characteristics enhanced biomarker evaluation methods when regressing accurately assessed intakes on estimated 24-h urine excretions from a spot urine sample: for example, average daily energy intake derived from doubly labeled water, BMI, diuretic medications. Forty-four percent of participants reported taking antihypertensive medication during the NPAAS-FS from 2011 to 2013, which is consistent with antihypertensive medication use reported on WHI medical history updates. Inclusion of antihypertensive medication use in the enhanced models did contribute to model performance. The fall season contributed to the CVR^2 of Na, whereas for K, winter season and not diuretic medication contributed to the CVR^2. Accurate assessment of dietary intake supports the use of a controlled-feeding study design within a population subset (4).

In addition to general participant characteristics, several factors pertinent to older populations or statistical considerations were considered when assessing Na, K, and Na/K urinary excretion through sensitivity analyses. For example, including or excluding from analysis participants with potential kidney disease, medication use that may affect Na excretion, low 24-h urine volume output, as well as averaging the daily consumed intake and 24-h excretions to reduce potentional statistical noise. By excluding participants with possible kidney disease, algorithm performance improved among the postmenopausal women in our

TABLE 3 Pearson correlations (*r*) of average daily consumed dietary intakes of sodium, potassium, and sodium/potassium from the 2-wk controlled-feeding study, NPAAS-FS, with urinary biomarker excretions of sodium, potassium, and sodium/potassium[1]

Dietary intakes	Urinary biomarker	*r*
Sodium intake (mg)	24-h sodium (mg/d)	0.57
	Estimated[2] 24-h sodium from spot urine (mg) (5)	0.38
	Kawasaki, estimated sodium from spot urine (mg) (8, 9)	0.40
	Tanaka, estimated sodium from spot urine (mg) (10)	0.42
	INTERSALT, estimated sodium from spot urine (mg) (11)	0.45
Potassium intake (mg)	24-h potassium (mg)	0.57
	Estimated 24-h potassium from spot urine (mg) (5)	0.39
	Kawasaki, estimated potassium from spot urine (mg) (8, 9)	0.39
	Tanaka, estimated potassium from spot urine (mg) (10)	0.44
Sodium/potassium intake	24-h sodium/potassium	0.60
	Estimated 24-h from spot sodium/potassium (5)	0.38
	Kawasaki, estimated sodium/potassium from spot urine (8, 9)	0.38
	Tanaka, estimated sodium/potassium from spot urine (10)	0.38

[1]*n* = 150 postmenopausal women who participated in the NPAAS-FS and provided complete urine collections. INTERSALT, International Study of Electrolyte Excretion and Blood Pressure; NPAAS-FS, Nutrition and Physical Activity Assessment Feeding Study.
[2]All estimations were computed using first-void spot urine collected immediately preceding the 24 h on the penultimate day of the 2-wk controlled-feeding study.

TABLE 4 Enhanced biomarker evaluation methods regressing electrolyte consumed intakes on ln-transformed estimated 24-h urine electrolytes plus participant and study characteristics in the NPAAS-FS[1]

Variable	$\beta \pm$ SE	R^2	CVR[2]
Sodium intake (mg/d) on 24-h urinary sodium (mg)			
Intercept	7.787 ± 0.024	NA	
Biomarker	0.306 ± 0.04	32.38	
Age	0.008 ± 0.005	0.88	
BMI	0.009 ± 0.004	5.53	
Recreational physical activity	–0.001 ± 0.001	0.17	
Fall season	–0.056 ± 0.044	0.56	
Winter season	0.028 ± 0.044	0.79	
Race/ethnicity (non-White)	0.133 ± 0.078	0.99	
Ein	0.39 ± 0.121	4.46	
Diuretic medication[2]	0.08 ± 0.047	1.13	
Overall	NA	46.89	38.45
Sodium intake (mg/d) on estimated 24-h sodium (mg) from spot urine			
Intercept	7.756 ± 0.022	NA	
Biomarker	0.167 ± 0.033	14.24	
BMI	0.01 ± 0.004	7.98	
Winter season	0.053 ± 0.044	1.41	
Race/ethnicity (non-White)	0.257 ± 0.083	3.74	
Ein	0.491 ± 0.119	8.06	
Diuretic medication	0.116 ± 0.05	2.43	
Overall	NA	37.86	30.42
Potassium intake (mg/d) on 24-h potassium (mg) from spot urine			
Intercept	8.031 ± 0.013	NA	
Biomarker	0.288 ± 0.04	34.05	
Race/ethnicity (non-White)	–0.184 ± 0.058	3.95	
Ein	0.415 ± 0.086	8.82	
Overall	NA	46.82	40.17
Potassium intake (mg/d) on estimated 24-h potassium (mg) from spot urine			
Intercept	8.033 ± 0.02	NA	
Biomarker	0.131 ± 0.035	15.71	
Recreational physical activity	0.001 ± 0.001	1.2	
Schooling after high school	0.033 ± 0.029	1.05	
Fall season	–0.063 ± 0.036	0.12	
Race/ethnicity (non-White)	–0.206 ± 0.065	4.58	
Ein	0.528 ± 0.095	14.36	
Overall	NA	37.01	29.61
Sodium/potassium intake on 24-h sodium/potassium			
Intercept	–0.263 ± 0.021	NA	
Biomarker	0.424 ± 0.047	35.91	
BMI	0.005 ± 0.005	1.87	
Recreational physical activity	–0.002 ± 0.001	1.32	
Race/ethnicity (non-White)	0.291 ± 0.088	3.6	
Diuretic medication	0.138 ± 0.053	2.63	
Overall	NA	45.33	42.01
Sodium/potassium intake on estimated 24-h sodium/potassium from spot urine			
Intercept	–0.27 ± 0.024	NA	
Biomarker	0.219 ± 0.04	14.35	
BMI	0.007 ± 0.005	2.5	
Recreational physical activity	–0.001 ± 0.002	0.84	
Race/ethnicity (non-White)	0.445 ± 0.1	9.08	
Diuretic medication	0.123 ± 0.06	2.09	
Overall	NA	28.86	25.06

[1] $n = 150$ postmenopausal women who participated in the NPAAS-FS and provided complete urine collections. CVR[2], cross-validated R^2; Ein, energy intake derived from doubly labeled water; NA, not applicable; NPAAS-FS, Nutrition and Physical Activity Assessment Feeding Study.
[2] Diuretic medications taken by NPAAS-FS participants included loop diuretics, thiazide and thiazide-like diuretics, and diuretic combinations.

TABLE 5 Enhanced biomarker evaluation methods by regressing electrolyte consumed intakes on ln-transformed estimated 24-h urine electrolytes plus participant and study characteristics in the NPAAS-FS, excluding 16 participants with eGFR <60[1]

Variable	$\beta \pm$ SE	R^2	CVR[2]
Sodium intake (mg/d) on 24-h urinary sodium (mg)			
Intercept	7.759 ± 0.02	NA	
Biomarker	0.312 ± 0.04	39.12	
BMI	0.01 ± 0.004	5.44	
Recreational physical activity	–0.001 ± 0.001	0.34	
Winter season	0.084 ± 0.041	2.58	
Race/ethnicity (non-White)	0.107 ± 0.085	0.44	
Ein	0.342 ± 0.113	3.87	
Diuretic medication[2]	0.047 ± 0.05	0.36	
Overall	NA	52.16	43.18
Sodium intake (mg/d) on estimated 24-h sodium (mg) from spot urine			
Intercept	7.741 ± 0.026	NA	
Biomarker	0.175 ± 0.033	18.1	
BMI	0.01 ± 0.005	9.87	
Smoker, current	–0.121 ± 0.121	0.08	
Recreational physical activity	0 ± 0.001	0.08	
Schooling after high school	0.038 ± 0.038	1.42	
Winter season	0.085 ± 0.044	2.96	
Race/ethnicity (non-White)	0.221 ± 0.095	2.18	
Ein	0.517 ± 0.118	9.76	
Diuretic medication[2]	0.089 ± 0.056	1.15	
Overall	NA	45.6	36.5
Potassium intake (mg/d) on 24-h potassium (mg) from spot urine			
Intercept	8.024 ± 0.014	NA	
Biomarker	0.322 ± 0.044	35.32	
Ein	0.427 ± 0.09	9.82	
Overall	NA	45.14	40.21
Potassium intake (mg/d) on estimated 24-h potassium (mg) from spot urine			
Intercept	8.052 ± 0.017	NA	
Biomarker	0.139 ± 0.038	15.15	
Fall season	–0.078 ± 0.037	0.47	
Race/ethnicity (non-White)	–0.171 ± 0.078	2.5	
Ein	0.549 ± 0.099	16.26	
Overall	NA	34.38	28.15
Sodium/potassium intake on 24-h sodium/potassium			
Intercept	–0.266 ± 0.021	NA	
Biomarker	0.434 ± 0.05	36.87	
BMI	0.005 ± 0.005	1.83	
Recreational physical activity	–0.002 ± 0.001	1.59	
Race/ethnicity (non-White)	0.221 ± 0.1	1.86	
Diuretic medication	0.101 ± 0.058	1.36	
Overall	NA	43.51	38.09
Sodium/potassium intake on estimated 24-h sodium/potassium from spot urine			
Intercept	–0.285 ± 0.026	NA	
Biomarker	0.217 ± 0.042	14.42	
BMI	0.008 ± 0.005	3.73	
Recreational physical activity	–0.001 ± 0.002	1.23	
Winter season	0.076 ± 0.053	0.63	
Race/ethnicity (non-White)	0.404 ± 0.115	6.69	
Diuretic medication	0.08 ± 0.066	0.83	
Overall	NA	27.54	20.75

[1] $n = 134$ postmenopausal women who participated in the NPAAS-FS and provided complete urine collections excluding 16 participants with eGFR <60. CVR[2], cross-validated R^2; eGFR, estimated glomerular filtration rate; Ein, energy intake derived from doubly labeled water; NA, not applicable; NPAAS-FS, Nutrition and Physical Activity Assessment Feeding Study.
[2] Diuretic medications taken by NPAAS-FS participants included loop diuretics, thiazide and thiazide-like diuretics, and diuretic combinations.

feeding study, particularly for Na where this exclusion resulted in estimated 24-h excretion meeting our group's standard of explaining at least 36% of the variation from the consumed diet intake. Averaging the daily consumed intake with 24-h excretion to reduce statistical noise improved model performance for the estimated 24-h excretion of K. These 2 improvements reinforce the importance of considering participant characteristics.

Interest exists in using the Na/K ratio for making dietary recommendations related to reducing cardiovascular disease factor risks, such as blood pressure (41, 42). A lower ratio reflects both decreasing Na intake and increasing K intake. In our NPAAS-FS as well as the Kawasaki and Tanaka algorithms, correlations with the feeding study change in consumed daily dietary intakes for the spot urine sample were lower than with the 24-h urine collection. Further, our NPAAS-FS enhanced methods incorporating study subject characteristics did not result in acceptable biomarker performance for the spot urine sample, whereas the 24-h urine collection did meet our group's criterion for use as a biomarker.

Participant burden is a consideration in choosing to use single or multiple 24-h urine collections, as is timing of spot urine collections. Multiple 24-h urine collections are considered the gold standard for estimating Na and K intake, particularly for individual intake prediction, due to diurnal variation in excretion, environmental fluctuations including sweat loss, and other noted variations in intake (6, 43, 44). A single 24-h urinary excretion, even under controlled conditions (45, 46), may underestimate daily intakes due to a rhythmicity longer than 24 h (47). Further, for dietary assessment instrument validation, multiple 24-h urine collections are pertinent. For example, in the European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk cohort, two 24-h collections were obtained 3 times during 9 mo (48). Nonetheless, a single 24-h urine collection has been used for estimating group rather than individual sodium and potassium intakes (49–51). When using a single 24-h urine collection for group estimation, recommendations include collections representing different days of the week and seasons (6, 52). Our feeding study with 153 participants ($n = 150$ with urinary Na and K measures), although not a population study, was intended to estimate Na and K excretions during the 2-wk study period but not to assess daily variations. Participant collections varied by day of the week and season. For our purposes, a single 24-h urine collection was adequate. The timing of spot urine sample collections when used for estimating 24-h urinary excretion has been studied and summarized (6, 53). There is not a clear "best" time under all circumstances scientifically or practically for either Na (54) or K (55), which suggests that documenting the time of collection may be most salient.

Our study has a number of strengths, most notably its design as a controlled-feeding study. More studies of this type are needed (4, 56). The study supported participants' attendance at clinic visits by providing transportation as needed, and telephone and in-person response to questions about the study procedures. The feeding study was funded by the NIH and underwent rigorous scientific review. The prepared diets were individualized to mimic each participant's unique food intake, which offered study-wide nutrient variety within a controlled manner and permitted use of the measured intake as the standard for estimating 24-h Na, K, and Na/K from spot urine.

The study also had limitations. Recruitment involved WHI participants from the Seattle WHI clinical center, who were primarily White and educated, although neighborhood socioeconomic status (NSES; combining elements of education, household organization, and indicators of household employment and income) was similar to the NSES diversity within the WHI (57). The choice of the Seattle location supported access to the Fred Hutch Human Nutrition Lab in Seattle, WA, a rigorously maintained facility under scientific and administrative institutional oversight, a strength that supported study implementation. Information was collected on medication, but not on the timing of administration, which for antihypertensive medications could influence the first-void spot urine volumes and electrolyte quantity. Because clinic visits were long (5 h for the first clinic visit and 2 h for the second visit) and involved specified meal-replacement beverages during the protocol, participants with diabetes were excluded. A larger study sample with greater race and ethnicity diversity, multiple 24-h urine collection, and a subsample repeat some months later would have been ideal, but was cost and burden prohibitive.

In conclusion, our results suggest that a 24-h urine collection remains preferential to estimating 24-h urinary excretion from a spot urine sample. Future directions may include additional details relevant to Na and K excretion, such as environmental conditions, health and social determinants of health, and collaborative study initiatives that support combining data from feeding studies with diverse participant characteristics.

Acknowledgments

The WHI Investigator Short List: *Program Office*: (National Heart, Lung, and Blood Institute, Bethesda, MD) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller; *Clinical Coordinating Center*: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg; *Investigators and Academic Centers*: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner; *Women's Health Initiative Memory Study*: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland.

The authors' responsibilities were as follows—LFT, MLN, JWL, YH, and RLP: designed the research; LFT, MLN, JWL, and RLP: conducted the research; YH: analyzed the data; LFT: wrote the manuscript; and all authors: reviewed, critically evaluated, and read and approved the final manuscript.

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