A multiple 24-hour urine collection study indicates that kidney function decline is related to urinary sodium and potassium excretion in patients with chronic kidney disease.

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A multiple 24-hour urine collection study indicates that kidney function decline is related to urinary sodium and potassium excretion in patients with chronic kidney disease

**Aims:** We assessed kidney function decline for four years after baseline in relation to seven-time averaged 24-hour urinary sodium and potassium excretion (UNaV, UKV), their UNaV/UKV ratio, and their categorical combination in outpatients with chronic kidney disease.

**Study design:** A retrospective cohort study based on multiple 24-hour urine collections

7-time 24-hour urine collections within 2 years until the baseline
Baseline of each patient: date of the 7th 24-hour urine collection
4 years after the baseline

N = 240 with 7-time 24-hour urine collections
Main exposures:
- Average UNaV and UKV
- Their categorical combination of UNaV and UKV

Median follow-up [IQR]: 2.9 [1.4-4.0] years

**Primary outcomes:**
- Percentage changes in delta eGFR per year (%/year) based on repeatedly measured eGFR

**Primary results**
In linear mixed models, percentage changes in delta eGFR per year (%/year) were -3.26 (95% confidence interval: -5.85 to -0.60) and 5.20 (2.34 to 8.14), respectively, per 1SD increase in the average UNaV and UKV.

Additionally, percentage changes in delta eGFR per year (%/year) was -16.27 (-23.57 to -8.27) in the middle-to-high UNaV and low UKV group, compared with the low UNaV and middle-to-high UKV group.

**Conclusion**
Our study reinforces the observation of opposite associations between GFR decline and urinary excretion rates of sodium (positive association) and potassium (negative association), respectively. Whether changes in dietary sodium and potassium intake will slow GFR decline requires further study.
A multiple 24-hour urine collection study indicates that kidney function decline is related to urinary sodium and potassium excretion in patients with chronic kidney disease.

Running head: Sodium, potassium, and eGFR by multiple 24-hour urine collections

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Abstract
Multiple 24-hour urine collections are necessary to adequately assess sodium and potassium intake. Here, we assessed kidney function decline for four years after baseline in relation to seven-time averaged 24-hour urinary sodium and potassium excretion (UNaV, UKV), their UNaV/UKV ratio, and their categorical combination in outpatients with chronic kidney disease (CKD). This retrospective cohort study was based on 240 outpatients with baseline CKD stages 3-5, baseline age 20 years or more (median age 72.0 years), and a median follow-up (with interquartile range) of 2.9 (1.4–4.0) years. Outcome was the percentage change in annual slope of estimated glomerular filtration rate (delta eGFR per year). In linear mixed models, percentage changes in delta eGFR per year were -3.26% (95% confidence interval -5.85 to -0.60), +5.20% (2.34 to 8.14), and -5.20% (-7.64 to -2.69), respectively, per one standard deviation increase in the seven-time averaged UNaV and UKV, and their UNaV/UKV ratio. Additionally, percentage changes per year in delta eGFR per year were -16.27% (-23.57 to -8.27) in the middle-to-high UNaV and low UKV group, compared with the low UNaV and middle-to high UKV group. Thus, our study reinforces the observation of opposite associations between GFR decline and urinary excretion rates of sodium (positive) and potassium (negative), respectively. Whether changes in dietary sodium and potassium intake slow GFR decline still requires further study.

Keywords: urinary sodium excretion, urinary potassium excretion, dietary sodium intake, dietary potassium intake, chronic kidney disease
**Introduction**

Dietary restriction of sodium and potassium have historically been important in the prognosis of patients with chronic kidney disease (CKD) including end-stage kidney disease (ESKD) and premature deaths.\(^1,2\) However, meta-analyses and CKD guidelines have shown inconsistent results and no robust evidence for associations of dietary sodium and potassium intake with CKD incidence and progression.\(^2-7\) Some previous studies showed significant associations of higher urinary sodium excretion with CKD incidence and progression,\(^8-10\) though others showed none.\(^11-13\) Additionally, some studies showed that higher urinary potassium excretion decreased CKD incidence and progression\(^10-14\), while others showed that higher urinary potassium increased CKD progression\(^8\) and urinary potassium was not associated with kidney failure.\(^15\)

The previous inconsistent results can be due to methods vulnerable to measurement errors of urinary sodium and potassium excretion (i.e., food frequency questionnaires, spot urine collections, and single 24-hour urine collections).\(^16-20\) To decrease measurement errors, sodium/potassium ratio has been used.\(^21\) Higher sodium/potassium ratio was significantly associated with CKD incidence and progression, which could stratify these risks better than sodium and potassium alone.\(^9,22,23\)

Multiple 24-hour urine collections are necessary to estimate habitual dietary intakes of sodium and potassium,\(^18-20\) especially in relation to mortality, cardiovascular events, and ESKD.\(^24\) Long-term balance studies in which dietary intake of sodium and potassium was fixed in highly controlled environments have demonstrated that misclassification of sodium and potassium (i.e., differences between intake and excretion over 25 mmol/d) were, respectively, 51% and 34% by a single 24-hour urine collection, 25% and 19% by 3-time average values of three collections, and 8% and 13% by 7-time average values of seven collections.\(^18,19\) However, to investigate the association of sodium and potassium with CKD risks, most previous studies used single 24-hour urine collections, and very few studies used, at most, 2- or 3-time average values of UNaV and 24-hour urinary potassium excretion (UKV),\(^8,13\) which might be insufficient to estimate habitual UNaV and UKV.\(^18-20\)
The present study aimed to assess kidney function decline during 4 years after the baseline in relation to 7-time average UNaV and UKV, their UNaV/UKV ratio, and their categorical combination measured by 7-time 24-hour urine samples within 2 years until the baseline in CKD outpatients. Kidney function decline was assessed by annual changes in estimated glomerular filtration rate (eGFR) repeatedly measured during 4 years after the baseline.

**Methods**

**Study design and participants**

The present study used a retrospective cohort design based on outpatients with CKD in Daiko-Sunadabashi Clinic in Nagoya, Japan between September 2005 and April 2019. The present study design are summarized in Figure 1. As a treatment policy in this clinic, all CKD outpatients participated in 24-hour urine collections repeatedly. Additionally, all CKD outpatients received dietary guidance with the following target values regardless of CKD stage: salt intake < 6 g per day and protein intake < 0.8 g per body weight (kg) per day. The outpatients rarely received dietary guidance on potassium intake. If abnormalities in serum potassium levels were found, they were resolved with a prescription of anti-hyperkalemic agents such as polystyrene sulfonate. The baseline of each patient was defined as the date of the 7th 24-hour urine collection. Kidney function of each patient was followed up for 4 years (median follow-up [interquartile range [IQR]] = 2.9 [1.4–4.0] years) by multiple assessments of eGFR (median [IQR] of the number of eGFR assessments per patient = 24 [12–38] times).

The inclusion and exclusion criteria of the present analyses were as follows. First, sample quality of 24-hour urine collections was assured based on the comparison between measured urinary creatinine excretion rate (CER) and expected CER.\(^{25}\) Generally, 24-hour urine samples may be over- or under-collected by outpatients.\(^{26}\) As an index to check whether a 24-hour urine sample is correctly collected, historically, measured urinary CER has been compared to an individual’s expected CER.\(^{16,25}\) Thus, we used data of which measured...
urinary CER was between 70% and 130% of estimated CER by Horio’s equation (n = 758), using age, sex, body weight, and body mass index. Horio’s equation was developed in Japanese patients, by which estimated creatinine clearance rate (CCr) was highly correlated with measured CCr in the developed population (r = 0.882) and another Japanese population (r = 0.814). Second, we included patients the data of 7-time 24-hour urine samples collected from 2 years until the baseline (n = 319). Third, patients with baseline age ≥ 20 years, 7-time average eGFR < 60 mL/min/1.73 m² (i.e., CKD stage 3, 4, and 5), and follow-up eGFR assessment for at least 3 months, were included (n = 240). This study was approved by the Ethics Committee of Fujita Health University. The need for patient consent was waived due to the retrospective nature of the present study and the absence of personally identifiable data collected.

Assessment of eGFR

We assessed eGFR based on information from medical records and the following equation:

\[
eGFR (\text{mL/min/1.73 m}^2) = 194 \times \text{serum creatinine}^{-1.094} \times \text{Age}^{-0.287} \times 0.739 \ (\text{if female})
\]

This equation was developed and validated in Japan. The equation is regularly used in clinical settings in Japan, and recommended to assess eGFR by Evidence-based Clinical Practice Guideline for CKD in Japan.

24-hour urine collection, 7-time average UNaV and UKV

As a treatment policy, patients were provided detailed instructions to accurately collect 24-hour urine samples to bring to our clinic for medical treatment. During collection, a patient’s accumulated urine was stored in a vinyl chloride bag with a coolant in a dedicated heat-insulating container made of Styrofoam to prevent spoilage. These 24-hour urine collections were repeatedly performed in this method on all samples analyzed in this study. As results of the collections, urine volume, urine creatinine, UNaV, UKV, and urine protein were recorded.

Seven-time average UNaV (mEq/24-hour) and UKV (mEq/24-hour) were obtained by multiplying urine sodium and potassium concentration by urine volume from 7-time 24-
hour urine collections until the baseline (i.e., the 7th collection) and by calculating their arithmetic means. The median value (IQR) for the completion of collections for the 7-time urine samples per patient was 7.7 (6.2–10.1) months. Stability of multiple measurements of UNaVs and UKVs are summarized in Supplementary Methods.

**Clinical data**
From medical records, we derived information on age, sex, dates of the 24-hour urine collections, height, body weight, serum creatinine, systolic blood pressure (SBP), diastolic blood pressure (DBP), underlying diseases of CKD (diabetic nephropathy, chronic glomerulonephritis [CGN], nephrosclerosis, and others), urine protein per day (g/d), dietary protein intake per day corresponding to body weight (g/kg/d), medication use for hypertension and diabetes, and if or when renal replacement treatment (RRT) including death and dialysis initiation occurred. Body mass index (BMI) was obtained by weight (kg) divided by squared height (m²). Urine protein was calculated by urine protein concentration multiplied by urine volume. Dietary protein intake was obtained by the 24-hour urine samples and the Maroni formula.31

**Statistical analyses**
Baseline characteristics were summarized as medians (IQR) for continuous variables and N (%) for categorical variables. We used linear mixed models with random intercept and random slope of time for each patient to investigate the associations of 7-time average UNaV and UKV, their UNaV/UKV ratio, and their categorical combination with eGFR.32–34 The primary outcome was percentage change in eGFR annual slope (i.e., delta eGFR per year [%/year]) based on multiple eGFR modeled in linear mixed models. The secondary outcome was estimated marginal means (EMMs) of eGFR at the baseline, and 1, 2, 3, and 4 years after the baseline to make the results of the primary outcome easily interpretable, which was derived from the statistical models for the primary outcome.

In the linear mixed models, eGFR repeatedly measured were log-transformed and
modeled as a dependent variable. For independent variables of interest, 7-time average UNaV and UKV, and their UNaV/UKV ratio were modeled as continuous variables. The log-transformation allowed us to account for possible non-linear associations of the exposures and the outcome, maintain interpretability, as well as apply sensitivity analyses to the linear mixed models as described below. As an additional independent variable of interest, we modeled a combination of the lowest tertiles and the middle-to-high tertiles of the 7-time average UNaV and UKV. We included interaction terms between time and each independent variable of interest, of which exponentiated beta coefficients represented a ratio of geometric means of the eGFR annual slopes (i.e., 100% plus annual percentage change in delta eGFR) in relation to a one-unit increase in the three continuous independent variables, and in relation to categories in the combination of the 7-time average UNaV and UKV compared with the reference category.

These associations were adjusted for potential confounders in three models. Model 1 is an unadjusted model. Model 2 was adjusted for age at the baseline, sex, underlying diseases for CKD (i.e., chronic glomerulonephritis [CGN], diabetic nephropathy, nephrosclerosis, and others), and 7-time average urine protein and eGFR until the baseline. These covariates were background information of CKD patients. Model 3 was adjusted for Model 2 covariates, hypertension (defined by any use of antihypertensive drugs until the baseline, or 7-time average SBP ≥ 140 mmHg or DBP ≥ 90 mmHg until the baseline), use of diuretics until the baseline, medication use of diabetes until the baseline, and 7-time average dietary protein intake and BMI until the baseline. These covariates were established risk factors based on clinical experiments. Medication use for diabetes was indicated when a patient used this medication and his/her underlying disease for CKD was other than diabetic nephropathy to avoid multicollinearity between medication use for diabetes and diabetic nephropathy.

Significance tests were 2-sided, and the significance level for all analyses was p-value < 0.05. In R statistical software version 4.0.3, we used the “nlme” package for linear mixed models. Sensitivity analyses are described in Supplementary Methods.
Results

Characteristics of the present patients

We summarized the baseline characteristics of the participants by tertiles of 7-time average UNaV and UKV in Table 1. The median (IQR) values were 72.0 (63.0–79.0) years old for age, 24.0 (14.7–40.4) mL/min/1.73 m² for 7-time average eGFR, 124.6 (97.9–153.4) mEq/d for 7-time average UNaV corresponding to 7.3 (5.7–9.0) g/d of dietary salt intake, and 34.6 (26.5–45.1) mEq/d for 7-time average UKV corresponding to 1352 (1034–1762) mg/d.

Associations of the 7-time average UNaV and UKV, and their UNaV/UKV ratio with eGFR

We evaluated associations of 7-time average UNaV and UKV, and their UNaV/UKV ratio with eGFR by linear mixed models. From results of the linear mixed models, we calculated EMMs in eGFR (mL/min/1.73 m²) at each time point, as well as each value of mean, mean minus 1SD, and mean plus 1SD of the three exposures as shown in Figure 2, of which percentage changes per 1SD increases in the exposures are shown in Supplementary Table S1. These results corresponded to the secondary outcome.

For the primary outcome, multivariable-adjusted percentage change in delta eGFR per year (%/year) was -3.26 (95% CI: -5.85 to -0.60, p = 0.02 in Model 3) per 1SD increase in the 7-time average UNaV (corresponding to 44.4 mEq/d), meaning faster decline of eGFR was significantly associated with an increase in the 7-time average UNaV (Table 2). We also showed delta eGFR per year corresponding to continuous value points of the 7-time average UNaV (Figure 3A). For example, over the follow-up period, delta eGFR per year (%/year) was -11.66 (95% confidence interval [CI]: -14.91 to -8.28), -14.54 (-16.74 to -12.28), and -17.33 (-20.39 to -14.15), respectively, corresponding to the value points at mean minus 1SD, mean, and mean plus 1SD of the 7-time average UNaV.

Multivariable-adjusted percentage change in delta eGFR per year (%/year) was 5.20 (2.34 to 8.14, p < 0.001 in Model 3) per 1SD increase in the 7-time average UKV (corresponding to 13.2 mEq/d), meaning slower decline of eGFR was significantly associated
with an increase in the 7-time average UKV (Table 2). Additionally, we showed delta eGFR per year corresponding to continuous value points of the 7-time average UKV (Figure 3B). For example, delta eGFR per year (%/year) was -18.68 (95% CI: -21.73 to -15.52), -14.46 (-16.66 to -12.20), and -10.01 (-13.35 to -6.55), respectively, corresponding to the value points at mean minus 1SD, mean, and mean plus 1SD of the 7-time average UKV.

Multivariable-adjusted percentage changes in delta eGFR per year (%/year) was -5.20 (-7.64 to -2.69, p < 0.001 in Model 3) per 1SD increase in the UNaV/UKV ratio (corresponding to 1.59), meaning faster decline of eGFR was significantly associated with an increase in the UNaV/UKV ratio (Table 2). We also displayed delta eGFR per year corresponding to continuous value points of the UNaV/UKV ratio (Figure 3C). As an example, delta eGFR per year (%/year) was -9.76 (95% CI: -12.99 to -6.42), -14.45 (-16.63 to -12.22) and -18.90 (-21.85 to -15.85), respectively, corresponding to the value points at mean minus 1SD, mean, and mean plus 1SD of the UNaV/UKV ratio (Figure 3).

**Associations of categorical combination of the 7-time average UNaV and UKV with eGFR**

We evaluated whether the combination of the 7-time average UNaV and UKV was associated with delta eGFR by linear mixed models. From the linear mixed models, EMMs in eGFR (mL/min/1.73 m²) were calculated according to each time point and the categorical combination of the 7-time average UNaV and UKV as shown in Figure 4A, of which percentage changes are shown in Supplementary Table S2.

We observed that eGFR annually decreased by -5.54% (-11.38 to 0.68) in the reference group combining the lowest tertile of 7-time average UNaV and the middle-to-high tertiles of 7-time average UKV (Figure 4B). In a group combining the lowest tertile of 7-time average UNaV and that of 7-time average UKV, eGFR annually decreased by -17.14% (-22.23 to -11.72) in Figure 4B, in which multivariable-adjusted percentage changes in delta eGFR per year (%/year) were -12.28 (-19.83 to -4.02, p = 0.004 in Model 3) compared with the reference group (Table 3). Additionally, eGFR annually decreased by -14.06% (-17.11 to -10.89) in a group combining the middle-to-high tertiles of 7-time average UNaV and that of
7-time average UKV as shown in Figure 4, in which multivariable-adjusted percentage changes in delta eGFR per year (%/year) was -9.02 (-15.45 to -2.09, \( p = 0.01 \) in Model 3) compared with the reference group (Table 3). Furthermore, in a group combining the middle-to-high tertiles of 7-time average UNaV and the lowest tertile of 7-time average UKV, eGFR annually decreased by -20.91% (-25.91 to -15.57) as shown in Figure 4, in which multivariable-adjusted percentage changes in delta eGFR per year (%/year) was -16.27 (-23.57 to -8.27, \( p < 0.001 \) in Model 3) compared with the reference group (Table 3).

**Sensitivity analyses**

Similar results were obtained in all sensitivity analyses (Table 2 and Table 3), showing there were no serious problems related to differences in the baseline calendar year, use of 3-time average UNaV and UKV instead of the 7-time average UNaV and UKV, and differences in methods (i.e., using Ix’s equation instead of Horio’s equation) to check whether a 24-hour urine sample was correctly collected. Additionally, joint modeling showed no serious biases from possible informative dropout due to RRT or all-cause death (Table 2 and Table 3). Furthermore, the present results were not seriously biased in the point of view of possible measurement errors for the 7-time average UNaV and UKV, shown by simulation and extrapolation method (SIMEX) in Supplementary Figure S1. Detailed descriptive statistics are shown in Supplementary Table S3 and S4. Detailed results of model fitting and the joint modeling are shown in Supplementary Table S5, S6 and S7.

**Discussion**

In the present study, higher 7-time average UNaV and higher UNaV/UKV ratio were significantly associated with faster eGFR decline over time, as was lower 7-time average UKV. Additionally, faster eGFR decline was significantly observed in the group combining the middle-to-high tertiles of UNaV and the lowest tertile of UKV, while the group combining the lowest tertile of UNaV and the middle-to-high tertiles of UKV had slower decline in eGFR. Those associations were obtained even after adjusting for established
important covariables for CKD including age, sex, kidney function at baseline, urinary protein, underlying diseases for CKD, medication uses for hypertension and diabetes, and so on.

In the present study, faster decline in eGFR was observed in higher 7-time average UNaV and lower 7-time average UKV, which was supported by previous studies showing similar results.9-15,36 However, other previous studies showed no significant associations of urinary sodium excretion with kidney function.11-13 Additionally, higher urinary potassium increased CKD progression8 and urinary potassium was not associated with kidney failure.15 Those results were inconsistent to the present results, which can partially be due to imprecise measurement methods of UNaV and UKV. Most of the previous studies used spot urine collections and single 24-hour urine collections to assess UNaV and UKV.9,11,12,14,15 Very few studies used, at most, 2- or 3-time average UNaV and UKV by 2- or 3-time 24-hour urine collections.8,13 However, UNaV and UKV were reported to have large measurement errors when assessed not only by spot urine collections, but also by 1- to 3-time 24-hour urine collections.16-20 Additionally, a previous study reported that observed associations of sodium intake with long-term composite outcomes including those of mortality and cardiovascular events or of mortality and ESKD were different between when using a single UNaV and when using average values of multiple UNaV annually collected during a 1-year and 5-year follow-up.24 Thus, we averaged 7-time UNaV and UKV within 2 years to decrease measurement errors of UNaV and UKV. Note that misclassification of sodium and potassium (i.e., differences between intake and excretion over 25 mmol/d) were, respectively, 51% and 34% by a single 24-hour urine collection, and 25% and 19% by 3-time average values of 3 consecutive 24-hour urine collections have been demonstrated in long-term balance studies in which dietary intake of sodium and potassium was fixed in highly controlled environments.18,19 However, the measurement error was much improved (8% for UNaV and 13% for UKV) by 7-time average values of 7 consecutive 24-hour urine collections.18,19

Several randomized controlled trials (RCT) in CKD patients showed that restriction of sodium intake reduced blood pressure and albuminuria, but did not improve kidney
Sodium intake restriction seemed to be associated with eGFR decrease and serum creatinine increase in several RCTs; however, this was because restriction of sodium intake reduced glomerular hyperfiltration in the short-term study period. Additionally, most previous RCTs were limited to a short-term study period. Thus, these reductions in blood pressure, albuminuria, and glomerular hyperfiltration by restricting sodium intake can be maintained long-term, which can possibly maintain kidney function in CKD patients.

In the present study, faster eGFR decline was also observed in higher ratio of 7-time average UNaV to 7-time average UKV. Additionally, delta eGFR per year was significantly different among groups of the categorical combination of the 7-time average UNaV and UKV. The group combining the middle-to-high tertiles of UNaV and the lowest tertile of UKV had faster decline in eGFR. On the other hand, the group combining the lowest tertile of UNaV and the middle-to-high tertiles of UKV had slower decline in eGFR. These results were supported by studies showing that higher sodium/potassium ratio was associated with CKD incidence and progression. However, these previous studies only using the sodium/potassium ratio could not tell us whether low sodium intake or high potassium intake was better for maintaining eGFR. As new knowledge, the present study showed that both restricting sodium intake and avoiding excessive restriction of potassium intake could be important in maintaining eGFR in CKD patients.

Possible mechanisms of the associations of UNaV and UKV with kidney function can be as follows. UNaV reflects dietary sodium intake. High dietary sodium intake has been reported to induce hypertension, accelerated glomerular hyperfiltration, sympathetic activation, and increases of urinary protein, inflammatory cytokines, and oxidative stress resulting from increased extracellular fluid volume, which could promote nephrosclerosis. UKV also reflects dietary potassium intake. High dietary potassium intake has been reported to increase natriuresis, decrease adrenaline secretion, and lower blood pressure through vasodilation, which can possibly protect kidney function. Chronic potassium deficiency is known to damage tubules via increased renal ammonia production, which can impair renal function.
We recommend restriction of dietary sodium intake. In the present study, patients of the lowest tertile of 7-time average UNaV had slower decline in kidney function, in which the median (IQR) for dietary salt intake was 5.3 (4.7, 5.7) g/d. This was approximately equal to the quantity recommended by guidelines for CKD management in the US (dietary salt intake < 5 g/d) and Japan (dietary salt intake < 6 g/d). There is still no clear answer whether dietary potassium intake should be increased in CKD patients, even though maintaining a certain amount of UKV was reported to be protective of kidney function in CKD patients. This is because high dietary potassium intake in CKD patients is associated with hyperkalemia leading to severe arrhythmias. Additionally, the group with the middle and highest tertiles of UKV in this study was never the group with high potassium intake in non-CKD and CKD patients of other studies. In the present study, groups with the middle and highest tertiles of UKV, respectively, had median (IQR) UKV values of 34.6 (32.0, 37.4) mEq/d and 48.5 (44.6, 55.0) mEq/d (Table 1). Thus, the middle and highest tertiles of UKV in the present study were approximately equal to groups with restricted dietary intake of potassium in most of the previous studies investigating the association of potassium intake and kidney function prognosis. Note that we did not insist that 7-time 24-hour urine collections should be performed in clinical settings because it is difficult to collect them in clinical settings. In the present study, we used 7-time average UNaV and UKV to reduce measurement errors of UNaV and UKV for adequately evaluating the associations of UNaV and UKV with eGFR. In the sensitivity analyses, 3-time average UNaV and UKV were also significantly associated with delta eGFR per year (Table 2 and Table 3). Thus, we believe 3-time average UNaV and UKV is sufficient in clinical settings.

The present study had several limitations. First, this was an observational study; thus, this cannot verify causal effects of UNaV and UKV on kidney function decline. Second, this study was based on participants whose 7-time 24-hour urine samples were collected within 2 years until the baseline. This might increase selection bias; however, there were no significant differences in most variables except for baseline eGFR, urine protein, and UKV between CKD patients with 7-time average UNaV and UKV, and those without such
sufficient values. Compared with patients with 7-time average values of UNaV and UKV, patients without such sufficient values tended to have more advanced CKD, which might lead to low potassium intake and UKV (Supplementary Table S3). Third, we used data collected between 2006 and 2019. However, we could obtain very similar results to main results even after adjusting for the baseline calendar year in the statistical models (Table 2). Fourth, it might be possible that the present urine samples were not precise 24-hour samples (e.g., 23.5-hour or 24.5 hour urine sample). However, the present patients were provided detailed instructions to accurately collect 24-hour urine samples for medical treatment. Additionally, we excluded low quality 24-hour urine collections by only using 24-hour urine collections of which measured urinary CER was between 70% and 130% of estimated CER by Horio’s equation. Furthermore, averaging results of the 7-time 24-hour urine samples could ameliorate this possible limitation.

The present study had strengths. First, we used repeatedly measured 24-hour urine collections, which contributes to accurate estimation of dietary sodium and potassium intake. Second, we used 24-hour urine collections of which measured urinary CER was between 70% and 130% of estimated CER by Horio’s equation, which allowed us to use quality-assured 24-hour urine samples. This was important to avoid use of 24-hour urine samples over- or under-collected by outpatients.26

In conclusion, faster decline in eGFR was observed in high 7-time average UNaV and low 7-time average UKV. Our study reinforces the observation of opposite associations between GFR decline and urinary excretion rates of sodium (positive) and potassium (negative), respectively. Whether changes in dietary sodium and potassium intake will slow GFR decline requires further study.

Disclosures
S.O. and S.N. obtained funds for collaborative researches from H.U. Group Holdings, Inc. to conduct this study. The other authors declared no competing interests in relation to this study. H.U. Group Holdings Inc. had no role in study design, data, collection, data analysis, data
interpretation, or writing of the report.

**Supplementary Material**

**Supplementary Methods.** Stability of multiple measurements of UNaVs and UKVs

**Supplementary Methods.** Sensitivity analyses

**Supplementary Table S1.** Percentage changes in estimated marginal means of eGFR (mL/min/1.73 m²) at each time point with their 95% confidence intervals in relation to a 1SD increase in 7-time average UNaV, 7-time average UKV, and ratio of the 7-time average UNaV to UKV based on 7-time 24-hour urine collections until baseline in CKD patients (N = 240).

**Supplementary Table S2.** Percentage changes in estimated marginal means of eGFR (mL/min/1.73 m²) at each time point with their 95% confidence intervals by categorical combination of 7-time average UNaV and UKV based on 7-time 24-hour urine collections until baseline in CKD patients (n = 240).

**Supplementary Table S3.** Baseline characteristics of CKD patients with 7-time average 24-hour urine collections analyzed in the main analyses, and CKD patients with 1-to-6-time 24-hour urine collections not analyzed in the main analyses.

**Supplementary Table S4.** Characteristics of 24-hour urine collections among CKD patients who had both quality-assured 7-time average 24-hour urine collections and non-quality assured 24-hour urine collections until baseline (n = 121).

**Supplementary Table S5.** AIC and BIC according to models with and without log transformed eGFR, and polynomial functions of 7-time average UNaV and 7-time average UKV in CKD patients analyzed in the main analyses

**Supplementary Table S6.** Results of joint modeling for associations between 7-time average UNaV, 7-time average UKV, and ratio of UNaV to UKV based on 7-time 24-hour urine collections until baseline, and delta eGFR per year (%/year) and time-to-dropout due to RRT (n = 48) or death (n = 7) in CKD patients (N = 240).

**Supplementary Table S7.** Results of joint modeling for associations between categorical
combination of 7-time average UNaV and 7-time average UKV based on 7-time 24-hour urine collections until baseline, and delta eGFR per year (%/year) and time-to-dropout due to RRT (n = 48) or death (n = 7) in CKD patients (N = 240).

**Supplementary Figure S1.** Results of SIMEX sensitivity analyses for associations of 7-time average UNaV and 7-time average UKV to percentage changes in delta eGFR per year (%/year).

**Supplementary Figure S2.** Detailed patient flow diagram.
References


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**Acknowledgments**

We thank Issei Onji of Daiko-Sunadabashi Clinic for organizing the database of the present study and Kei Matsumaru for English proofreading. Additionally, we acknowledge Dr. Yukio Yuzawa and Dr. Naotake Tsuboi affiliated with Department of Nephrology, Fujita Health University School of Medicine for setting up a collaboration opportunity between Fujita Health University and NCVC.
**Figure legend**

**Figure 1.** Patient flow diagram and study design concept

**Legend:** Abbreviations: eGFR, estimated glomerular filtration rate; UNaV, 24-hour urinary sodium excretion; UKV, 24-hour urinary potassium excretion; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CKD, chronic kidney disease; CER, creatinine excretion rate.

**Figure 2.** EMMs in eGFR (mL/min/1.73 m² [95% CI]) corresponding to 7-time average UNaV, 7-time average UKV, and ratio of the 7-time average UNaV and UKV based on 7-time 24-hour urine collections a until baseline in CKD patients (n = 240)

**Legend:** EMMs were obtained from linear mixed models, Model 3 described in Table 2. Bar lines show 95% CI for the EMMs at each time point.

a 7-time average UNaV and 7-time average UKV were based on seven 24-hour urine collections within 2 years until the baseline.

**Abbreviations:** EMM, estimated marginal mean; eGFR, estimated glomerular filtration rate; CI, confidence interval; UNaV, 24-hour urinary sodium excretion; UKV, 24-hour urinary potassium excretion; CKD, chronic kidney disease; SD, standard deviation.

**Figure 3.** Percentage changes in eGFR annual slopes (i.e., delta eGFR per year [%/year]) with their 95% confidence intervals corresponding to 7-time average UNaV, 7-time average UKV, ratio of 7-time average UNaV to 7-time average UKV based on 7-time 24-hour urine collections a until baseline in CKD patients (n = 240)

**Legend:** Delta eGFR per year (%/year) was obtained from linear mixed models, Model 3 described in Table 2. Black lines show delta eGFR per year corresponding to value points of the exposures. Red lines show 95% confidence intervals for the delta eGFR per year.

a 7-time average UNaV and 7-time average UKV were based on seven 24-hour urine collections within 2 years until the baseline.

**Abbreviations:** eGFR, estimated glomerular filtration rate; UNaV, 24-hour urinary sodium excretion; UKV, 24-hour urinary potassium excretion; CI, confidence interval; UNaV, 24-hour urinary sodium excretion; UKV, 24-hour urinary potassium excretion; CKD, chronic kidney disease; SD, standard deviation.
excretion; UKV, 24-hour urinary potassium excretion; CKD, chronic kidney disease.

**Figure 4.** EMMs in eGFR (mL/min/1.73 m²) and percentage changes in eGFR annual slopes (i.e., delta eGFR per year [%/year]) with their 95% confidence intervals corresponding to categorical combinations\(^a\) of 7-time average UNaV and UKV\(^b\) in CKD patients (n = 240)

**Legend:** EMMs (A) and delta eGFR per year (B) were obtained from linear mixed models; Model 3 described in Table 3. In Figure 4A, bar lines show 95% CI for the EMMs at each time point in each category. In Figure 4B, bar lines show 95% CI for the delta eGFR per year (%/year) in each category.

\(^a\) The threshold between the lowest, and middle and highest tertiles of the 7-time average values corresponded to 107.0 mEq/d for UNaV and 29.1 mEq/d for UKV.

\(^b\) 7-time average UNaV and UKV were based on seven 24-hour urine collections within 2 years until the baseline.

**Abbreviations:** EMM, estimated marginal mean; eGFR, estimated glomerular filtration rate; CI, confidence interval; UNaV, 24-hour urinary sodium excretion; UKV, 24-hour urinary potassium excretion; CKD, chronic kidney disease.
Table 1. Baseline characteristics of present participants by 7-time average UNaV and UKV\(\text{a}\) based on 7-time 24-hour urine collections until baseline (N = 240)

<table>
<thead>
<tr>
<th>Tertiles</th>
<th>7-time average UNaV (mEq/d) based on 7-time 24-hour urine collections until baseline</th>
<th>7-time average UKV (mEq/d) based on 7-time 24-hour urine collections until baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (&lt; 107.0)</td>
<td>Middle (107.0 – 138.0)</td>
</tr>
<tr>
<td>N</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years old</td>
<td>72.0 (66.0, 80.0)</td>
<td>74.0 (65.0, 81.5)</td>
</tr>
<tr>
<td>UNaV, mEq/d</td>
<td>90.8 (81.1, 97.5)</td>
<td>123.2 (117.0, 131.5)</td>
</tr>
<tr>
<td>UKV, mEq/d</td>
<td>28.8 (23.0, 40.3)</td>
<td>34.3 (28.2, 43.3)</td>
</tr>
<tr>
<td>Ratio of UNaV to UKV</td>
<td>2.7 (2.2, 3.9)</td>
<td>3.7 (2.9, 4.4)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m(^2)</td>
<td>22.4 (16.2, 36.8)</td>
<td>24.8 (15.9, 44.8)</td>
</tr>
<tr>
<td>Ccr, mL/min/1.73m(^2)</td>
<td>32.1 (22.5, 49.7)</td>
<td>33.2 (22.7, 58.4)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>2.0 (1.4, 3.2)</td>
<td>2.1 (1.2, 2.9)</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>21.4 (19.9, 23.0)</td>
<td>22.5 (20.9, 24.3)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>129.0 (126.0, 134.8)</td>
<td>130.8 (126.7, 136.7)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>74.0 (71.6, 77.1)</td>
<td>74.6 (71.9, 78.4)</td>
</tr>
<tr>
<td>Urine protein, g/d</td>
<td>0.3 (0.1, 0.9)</td>
<td>0.4 (0.1, 1.0)</td>
</tr>
<tr>
<td>Dietary protein intake, g/kg/d</td>
<td>0.8 (0.7, 0.9)</td>
<td>0.9 (0.8, 0.9)</td>
</tr>
<tr>
<td><strong>No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (53.2)</td>
<td>54 (68.4)</td>
</tr>
<tr>
<td>CKD stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>27 (34.2)</td>
<td>32 (40.5)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>34 (43.0)</td>
<td>29 (36.7)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>18 (22.8)</td>
<td>18 (22.8)</td>
</tr>
<tr>
<td>Underlying disease of CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGN</td>
<td>24 (30.4)</td>
<td>16 (20.3)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>14 (17.7)</td>
<td>23 (29.1)</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>20 (25.3)</td>
<td>29 (36.7)</td>
</tr>
<tr>
<td>Others</td>
<td>21 (26.6)</td>
<td>11 (13.9)</td>
</tr>
<tr>
<td>Hypertension(b)</td>
<td>58 (73.4)</td>
<td>60 (75.9)</td>
</tr>
<tr>
<td>Use of hypertension medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any uses</td>
<td>58 (73.4)</td>
<td>57 (72.2)</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>47 (59.5)</td>
<td>41 (51.9)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>26 (32.9)</td>
<td>36 (45.6)</td>
</tr>
<tr>
<td>Ca channel blocker</td>
<td>20 (25.3)</td>
<td>20 (25.3)</td>
</tr>
<tr>
<td>Others</td>
<td>18 (22.8)</td>
<td>19 (24.1)</td>
</tr>
<tr>
<td>Use of diabetes medication</td>
<td>12 (15.2)</td>
<td>14 (17.7)</td>
</tr>
</tbody>
</table>
Abbreviations: IQR, interquartile range; UNaV, 24-hour urinary sodium excretion; UKV, 24-hour urinary potassium excretion; eGFR, estimated glomerular filtration rate; Ccr, creatinine clearance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; CGN, Chronic glomerulonephritis; ACE, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.

a Baseline characteristics were 7-time average values of when seven 24-hour urine collections were performed for two years until the baseline (i.e., the 7th collection), except for age, which was determined when the seventh urine sample was collected.

b Hypertension was defined by any use of antihypertensive drugs until the baseline, or 7-time average SBP ≥ 140 mmHg or DBP ≥ 90 mmHg until the baseline.
<table>
<thead>
<tr>
<th>Models</th>
<th>7-time average UNaV</th>
<th>7-time average UKV</th>
<th>Ratio of the UNaV to the UKV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (unadjusted model)</td>
<td>-3.30 (-5.87 to -0.66)</td>
<td>5.13 (2.30 to 8.04)</td>
<td>-5.20 (-7.65 to -2.69)</td>
</tr>
<tr>
<td>Model 2c</td>
<td>-3.27 (-5.86 to -0.61)</td>
<td>5.17 (2.31 to 8.12)</td>
<td>-5.20 (-7.65 to -2.69)</td>
</tr>
<tr>
<td>Model 3d</td>
<td>-3.26 (-5.85 to -0.60)</td>
<td>5.20 (2.34 to 8.14)</td>
<td>-5.20 (-7.64 to -2.69)</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3 with additional adjustment for baseline calendar year</td>
<td>-3.27 (-5.86 to -0.61)</td>
<td>5.20 (2.34 to 8.14)</td>
<td>-5.20 (-7.65 to -2.70)</td>
</tr>
<tr>
<td>Model 3 when using joint modeling to consider time-to-dropout due to RRT (n = 48) or death (n = 7)</td>
<td>-3.29 (-5.44 to -1.08)</td>
<td>5.28 (2.85 to 7.77)</td>
<td>-5.26 (-7.09 to -3.40)</td>
</tr>
<tr>
<td>Model 3 when using Ix’s equation to check quality of 24-hour urine collections</td>
<td>-2.95 (-5.55 to -0.27)</td>
<td>5.57 (2.67 to 8.56)</td>
<td>-5.03 (-7.48 to -2.52)</td>
</tr>
<tr>
<td>Model 3 using 3-time average UNaV, UKV, and ratio of UNaV to UKV</td>
<td>-3.14 (-5.69 to -0.51)</td>
<td>6.00 (3.16 to 8.93)</td>
<td>-5.64 (-8.03 to -3.19)</td>
</tr>
</tbody>
</table>

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation; UNaV, 24-hour urinary sodium excretion; UKV, 24-hour urinary potassium excretion; CKD, chronic kidney disease; RRT, renal replacement treatment including dialysis and renal transplant; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

a Percentage changes in delta eGFR per year were obtained from linear mixed models.

b 1SD of UNaV, UKV, and ratio of the UNaV to the UKV corresponded to 44.4 mEq/d, 13.2 mEq/d, and 1.59 when conducting main analyses (n = 240), 48.4 mEq/d, 13.6 mEq/d, and 1.78 when using 3-time average UNaV, UKV, and ratio of UNaV to UKV (n = 240), and 48.3 mEq/d, 13.3 mEq/d, and 1.57 when using Ix’s equation (n = 249).

c Model 2 was adjusted for age at baseline, sex, underlying diseases for CKD, and 7-time average urine protein and eGFR until baseline.

d Model 3 was adjusted for Model 2 covariates, hypertension (defined by any use of antihypertensive drugs until baseline, or 7-time average SBP ≥ 140 mmHg or DBP ≥ 90 mmHg until baseline), use of diuretics until baseline, medication use of diabetes until baseline, and 7-time average dietary protein intake and BMI until baseline, of which results are also shown in Figure 3.
Table 3. Percentage changes in eGFR annual slopes (i.e., delta eGFR per year [%/year]) with their 95% confidence intervals by categorical combination of 7-time average UNaV and 7-time average UKV based on 7-time 24-hour urine collections until baseline in CKD patients (n = 240)

<table>
<thead>
<tr>
<th>7-time average UNaV (mEq/d)</th>
<th>Low (&lt; 107)</th>
<th>Middle-to-high (≥ 29.2)</th>
<th>Low (&lt; 107)</th>
<th>Middle-to-high (≥ 29.2)</th>
<th>Low (&lt; 107)</th>
<th>Middle-to-high (≥ 107)</th>
<th>Low (&lt; 107)</th>
<th>Middle-to-high (≥ 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N = 38</td>
<td>N = 41</td>
<td>N = 123</td>
<td>N = 38</td>
<td>N = 41</td>
<td>N = 123</td>
<td>N = 38</td>
<td>N = 123</td>
</tr>
<tr>
<td>Model 1 (unadjusted model)</td>
<td>0 (Ref.)</td>
<td>-12.46 (-20.01 to -4.2)</td>
<td>-9.52 (-15.94 to -2.6)</td>
<td>-16.75 (-24.03 to -8.76)</td>
<td>0 (Ref.)</td>
<td>-12.31 (-19.87 to -4.04)</td>
<td>-9.06 (-15.51 to -2.12)</td>
<td>-16.28 (-23.6 to -8.26)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0 (Ref.)</td>
<td>-12.31 (-19.87 to -4.04)</td>
<td>-9.06 (-15.51 to -2.12)</td>
<td>-16.28 (-23.6 to -8.26)</td>
<td>0 (Ref.)</td>
<td>-12.28 (-19.83 to -4.02)</td>
<td>-9.02 (-15.45 to -2.09)</td>
<td>-16.27 (-23.57 to -8.27)</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3 with additional adjustment for baseline calendar year</td>
<td>0 (Ref.)</td>
<td>-12.22 (-19.77 to -3.96)</td>
<td>-9.00 (-15.44 to -2.08)</td>
<td>-16.27 (-23.57 to -8.26)</td>
<td>0 (Ref.)</td>
<td>-12.39 (-18.84 to -5.43)</td>
<td>-9.07 (-14.82 to -2.94)</td>
<td>-16.34 (-22.53 to -9.65)</td>
</tr>
<tr>
<td>Model 3 when using joint modeling to consider time-to-dropout due to RRT (n = 48) or death (n = 7)</td>
<td>0 (Ref.)</td>
<td>-13.00 (-20.39 to -5.43)</td>
<td>-8.94 (-15.36 to -2.04)</td>
<td>-17.55 (-24.74 to -9.66)</td>
<td>0 (Ref.)</td>
<td>-13.83 (-21.3 to -5.65)</td>
<td>-7.51 (-13.86 to -0.69)</td>
<td>-15.82 (-22.88 to -8.10)</td>
</tr>
<tr>
<td>Model 3 when using Ix’s equation to check quality of 24-hour urine collections</td>
<td>0 (Ref.)</td>
<td>-12.82 (-20.01 to -4.2)</td>
<td>-9.52 (-15.94 to -2.6)</td>
<td>-16.75 (-24.03 to -8.76)</td>
<td>0 (Ref.)</td>
<td>-12.31 (-19.87 to -4.04)</td>
<td>-9.06 (-15.51 to -2.12)</td>
<td>-16.28 (-23.6 to -8.26)</td>
</tr>
<tr>
<td>Model 3 using 3-time average UNaV, UKV, and the ratio of UNaV to UKV</td>
<td>0 (Ref.)</td>
<td>-12.29 (-19.83 to -4.02)</td>
<td>-9.02 (-15.45 to -2.09)</td>
<td>-16.27 (-23.57 to -8.27)</td>
<td>0 (Ref.)</td>
<td>-12.39 (-18.84 to -5.43)</td>
<td>-9.07 (-14.82 to -2.94)</td>
<td>-16.34 (-22.53 to -9.65)</td>
</tr>
</tbody>
</table>

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation; UNaV, 24-hour urinary sodium excretion; UKV, 24-hour urinary potassium excretion; CKD, chronic kidney disease; RRT, renal replacement treatment including dialysis and renal transplant; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

a Percentage changes in delta eGFR per year were obtained from linear mixed models.

b Low, and middle-to-high categories corresponded to the lowest, and middle and highest tertiles of the 7-time average UNaV and UKV. Thresholds between low, and middle-to-high categories were 107.0 mEq/d and 28.4 mEq/d, respectively, for the 3-time average UNaV and UKV (n = 240). Thresholds between low, and middle-to-high categories were 111.0 mEq/d and 31.0 mEq/d, respectively, for the 7-time average UNaV and UKV when using Ix’s equation (n = 249).

c Model 2 was adjusted for age at baseline, sex, underlying diseases for CKD, and 7-time average urine protein and eGFR until baseline.

d Model 3 was adjusted for Model 2 covariates, hypertension (defined by any use of antihypertensive drugs until baseline, or 7-time average SBP ≥ 140 mmHg or DBP ≥ 90 mmHg until baseline), use of diuretics until baseline, medication use of diabetes until baseline, and 7-time average dietary protein intake and BMI until baseline, of which results are also shown in Figure 4 B.
7-time 24-hour urine collections within 2 years until the baseline

Baseline of each patient: date of the 7th 24-hour urine collection

N = 240 with 7-time 24-hour urine collections within 2 years until the baseline (including the baseline)

Main exposures:
- 7-time average UNaV
- 7-time average UKV
- Ratio of the 7-time average UNaV to the 7-time average UKV
- Categorical combination between the 7-time average UNaV and the 7-time average UKV

Baseline data:
- Age at baseline
- 7-time average values (e.g., urine protein, eGFR, SBP, DBP, BMI, etc)

N = 240 with median follow-up [interquartile range] = 2.9 [1.4-4.0] years
- eGFR was repeatedly measured

Primary outcome:
- eGFR annual slope (i.e., delta eGFR per year) modeled by linear mixed models

Secondary outcome:
- Estimated marginal means of eGFR at the baseline, 1, 2, 3, and 4 years after the baseline modeled by linear mixed models.

Figure 1. Patient flow diagram and study design concept
Figure 2. EMMs in eGFR (mL/min/1.73 m² [95% CI]) corresponding to 7-time average UNaV, 7-time average UKV, and ratio of 7-time average UNaV and 7-time average UKV based on 7-time 24-hour urine collections until baseline in CKD patients (n = 240)
Figure 3. Percentage changes in eGFR annual slopes (i.e., delta eGFR per year [%/year]) with their 95% confidence intervals corresponding to 7-time average UNaV, 7-time average UKV, ratio of 7-time average UNaV to 7-time average UKV based on 7-time 24-hour urine collections\textsuperscript{a} until baseline in CKD patients (n = 240)
Figure 4. EMMs in eGFR (mL/min/1.73 m$^2$) and percentage changes in eGFR annual slopes (i.e., delta eGFR per year [%/year]) with their 95% confidence intervals corresponding to categorical combination of 7-time average UNaV and UKV in CKD patients (n = 240)