The Urine-to-Plasma Urea Concentration Ratio is associated with eGFR and eGFR decline over time in a population cohort

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source: https://doi.org/10.48350/184240 | downloaded: 7.8.2023

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ABSTRACT

Background.

Evaluation of renal function and of factors associated with its decline are important public health issues. Besides markers of glomerular function (e.g., GFR), those of tubular functions are rarely evaluated. Urea, the most abundant urinary solute, is markedly concentrated in urine when compared to plasma. We explored the urine-to-plasma ratio of urea concentrateions (U/P-urea-ratio) as a marker of tubular functions.

Methods.

We evaluated the relationship of the U/P-urea-ratio with eGFR at baseline in 1043 participants (48±17y) from the SKIPOGH population-based cohort, using mixed regression. In 898 participants, we assessed the relation between U/P-urea-ratio and renal function decline between two study waves 3 years apart. We studied U/P ratios for osmolarity, Na, K, uric acid for comparison.

Results.

In a transversal study at baseline, eGFR was positively associated with U/P-urea-ratio (β_{scaled}=0.08, 95%CI[0.04;0.13]) but not with the U/P ratio of osmolarity. Considering separately participants with renal function > or ≤ 90 ml/minx1.73m^2, this association was observed only in those with reduced renal function. In the longitudinal study, eGFR declined at a mean rate of 1.2 ml/min per year. A significant association was observed between baseline U/P-urea-ratio and eGFR decline (β_{scaled}=0.08, 95%CI[0.01;0.15]). A lower baseline U/P-urea-ratio was associated with a greater eGFR decline.

Conclusion.

This study provides evidence that the U/P-urea-ratio is an early marker of kidney function decline in the general adult population. Urea is easy to measure with well-standardized techniques and at low cost. Thus, the U/P-urea-ratio could become an easily available tubular marker for evaluating renal function decline.

Keywords: chronic kidney disease, potassium, tubular marker, uric acid, urine concentration

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KEY LEARNING POINTS

What was known:

- Evaluation of factors associated with impaired renal function and its decline over time are important public health issues.
- Most markers of CKD progression studied presently (e.g., eGFR, urinary albumin excretion) are related to glomerular functions.
- Markers of tubular functions are not commonly evaluated despite their association with cardiovascular and all-cause mortality as well as rapid eGFR decline.

This study adds:

- This study proposes a novel marker that is based on the ability of the kidney to concentrate urea (the most abundant urinary solute) in the urine with respect to its concentration in plasma: the urine-to-plasma urea concentration ratio (U/P urea ratio). The U/P urea ratio is not representative of glomerular functions. It reflects transport functions that occur along the renal tubule and collecting duct.
- The present epidemiology study concerns a general population cohort. In cross-sectional analyses, the study shows that the U/P urea ratio is strongly and positively associated with eGFR after multiple adjustments including copeptin, blood pressure, 24h urinary albumin and urea excretions. This relationship is specific to urea because it is not observed with the ratios of the two other main urinary solutes, sodium and potassium.
- In longitudinal analyses, the U/P urea ratio at baseline was significantly associated with the eGFR decline over a 3-year interval after appropriate adjustments. The lower the initial U/P urea ratio, the larger the eGFR decline, even after multiple adjustments including copeptin, blood pressure, 24h urinary albumin and urea excretions.

Potential impact:

- The U/P urea ratio adds an important marker for evaluating kidney disease and its progression, a marker of tubular functions, thus broadening the tools presently used that mostly address glomerular functions.
- This marker brings useful information not only in people who are already known to have a chronic kidney disease but also even in a general population.
- This marker is widely accessible at low cost because urea is easily measured in routine laboratories.

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INTRODUCTION

Evaluation of renal function and factors associated with its decline are important public health issues given the high prevalence of silent chronic kidney disease (CKD) in the general population. Renal function is mainly evaluated by glomerular markers such as plasma creatinine or cystatine C concentrations to estimate the glomerular filtration rate (eGFR), and by the urinary albumin excretion rate (UAE) or albumin over creatinine ratio (ACR). Markers of tubular functions are not commonly evaluated in current clinical practice despite their association with cardiovascular and all-cause mortality [1, 2] as well as rapid eGFR decline [3].

The kidney's ability to concentrate urine is an important function that allows excreting our daily load of urinary solutes with a significant water economy. Urea is the most abundant solute in the urine and is known to have a crucial role in the overall ability to concentrate urine. But not often mentioned is the fact that most of the concentrating activity of the kidney is devoted to the concentration of urea itself [4].

The plasma concentration of urea is kept at a relatively low level (3 to 8 mmol/L). Thus, urea must be markedly concentrated in the urine in order to excrete the daily load (300 - 900 mmol) in the usual urine volume of 1-3 liters per day [5]. The most appropriate way to evaluate the kidney's ability to concentrate urea is to consider the concentration of urea in urine relative to that in plasma, thus the urine-to-plasma ratio of urea concentrations (U/P urea ratio). This ratio is more informative than urine urea concentration alone because of the relatively large variations in plasma urea concentration, in contrast to that of tightly regulated electrolytes, such as plasma Na, K or Cl.

In the last two years, longitudinal studies in two independent cohorts of ADPKD patients [6] and patients with all forms of CKD [7] showed that the U/P urea ratio at baseline was significantly associated with the slope of eGFR decline over a follow-up of 4 and 7 years, respectively. However, the potential of the U/P urea ratio to predict GFR decline in a population-based cohort is largely unknown. Therefore, we studied the U/P urea ratio in a Swiss multicentric population cohort (SKIPOGH) [8]. The first aim of our study was to evaluate the relationship between the U/P ratio of urea and that of osmolarity and of other individual solutes with eGFR, cross-sectionally at baseline. The second aim was to examine, in a longitudinal approach, whether baseline U/P urea ratio was predictive of the renal function decline between two measurements performed at 3-year interval.

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MATERIALS AND METHODS

Study population

We used data from the Swiss Kidney Project on Genes in Hypertension (SKIPOGH), a family- and population-based cohort investigating the genetic and environmental determinants of renal function and blood pressure in the Swiss population. Briefly, SKIPOGH is a multicenter, longitudinal study with participants recruited in the city of Lausanne and the cantons of Geneva and Bern [9, 10]. Study inclusion criteria were: 1. written informed consent; 2. at least 18 years of age; 3. European ancestry; 4. at least one other first-degree family member willing to participate to the study. More details on the recruitment process are summarized elsewhere [11-13]. The first SKIPOGH wave took place between 2009 and 2013 (baseline visit: SKIPOGH 1), whereas the second wave began in 2012 and ended in 2016 (follow-up visit: SKIPOGH 2). SKIPOGH 1 included 1129 participants coming from 275 nuclear families, while SKIPOGH 2 included 1034 participants from 270 families, with 87% of participants (N=984) participating to both study waves. At both waves, study participants had blood sampling in the morning after an overnight fast and provided a 24h urine collection, starting at the day of the medical visit. They also completed a detailed heath questionnaire inquiring about their medical history, medication intake, lifestyle factors, and socioeconomic circumstances [14].

Urine and plasma solutes

We used 24h urine and plasma solutes as the main predictor variables, including urea, sodium, potassium, uric acid, and creatinine concentrations. Urine and plasma concentrations were measured according to standard laboratory procedures at the central laboratories of Lausanne, Geneva, and Bern University hospitals. Plasma and 24h urine osmolarity was computed according to Khajuria's equation [15, 16], respectively. Plasma copeptin was assessed using a commercially available automated fluorescent sandwich immunoassay (BRAHMS Copeptin proAVP KRYPTORTM, Thermo Fisher Scientific, Breman, Germany) with a detection limit of 0.9 pmol/l. The functional assay sensitivity, defined as the concentration with an interassay coefficient of variation of <20%, was 2 pmol/l [17]. The 24h excretions of total osmoles and of each solute were calculated (osmolarity or each solute's concentration multiplied by 24h urine volume). We subsequently calculated a 24h urine-to-plasma concentration ratio for all solutes (U/P) by dividing 24h urine concentrations by plasma concentrations.

Estimated Glomerular Filtration Rate

Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) based on serum creatinine concentration, sex,

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and age, and expressed as eGFR-EPI in ml/min per 1.73m^2 [18]. In parallel, we considered non-indexed eGFR values (see discussion) by dividing eGFR-EPI by 1.73m^2 and multiplying by each participant's actual body surface area (BSA) [19].

Covariates

We used covariates that are systematically accounted for in analyses of SKIPOGH data including age, sex, recruitment center, and familial structure (random-effect covariable). In addition, we adjusted for physiologically relevant covariates including body mass index (BMI), systolic and diastolic blood pressure, and urinary albumin excretion. Several self-reported variables were also included as covariates because of their known relationship with kidney disease. These included smoking status (current smoking vs. never/former smoking), self-reported kidney disease (*"Has a doctor ever told you that you have a disease of your kidneys?"* – Yes/No), and diabetes status (*"Has a doctor ever told you that you have diabetes?"* – Yes/No), or by self-reporting use of insulin or other oral anti-diabetic drug, or by having ≥ 7 mmol/L of blood glucose at clinical visit in fasting conditions. Finally, copeptin (a validated marker for vasopressin [20]) was added as a covariate because of the major role played by vasopressin in urinary urea concentration.

Statistical analyses

We applied mixed linear regression models to investigate cross-sectional associations between urine-to-plasma concentration ratios (predictor variables) and eGFR (response variable) at SKIPOGH 1. For the longitudinal analyses, we investigated the associations between multiple U/P ratios at SKIPOGH 1 as the main predictors, and the change in eGFR between the two waves (Δ eGFR) as the main response variable, defined as the arithmetic difference in eGFR between SKIPOGH 2 and SKIPOGH 1, and representing kidney function decline between the two study waves. Because of missing data for at least one of the variables, 1043 (out of 1129) participants were studied in the cross-sectional analyses, and 898 (out of 1034) in the longitudinal analyses.

To allow a meaningful comparison between U/P concentration ratios of different solutes and eGFR estimates, we scaled and centered all predictor and response variables to the mean (μ=0, σ=1). We adjusted all regression models using aforementioned fixed- and random-effect covariates, whereas associations involving Δ eGFR were additionally adjusted for the time difference between SKIPOGH 2 and SKIPOGH 1 visits. For associations and graphs involving U/P urea, we used both untransformed and $\log_{10}$-transformed data, because of the non-normal distribution of U/P urea. Linear regression model assumptions (homoscedasticity, normality of

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residuals, linearity) were tested at implementation of each linear model (cross-sectional and longitudinal analyses).

We carried out all statistical analyses using the R statistical software and relevant CRAN and Bioconductor packages (R Foundation for Statistical Computing, Vienna, Austria). The significance thresholds were set at $P < 0.05$.

Stratification of associations by eGFR-EPI

Considering that even modest renal dysfunction may have a confounding effect on the associations addressed in this study, we repeated the main regression models after stratifying the associations at an eGFR-EPI of 90 ml/min x 1.73m^2. This threshold was chosen based on a previously established classification indicating that eGFR-EPI $\geq$ 90 ml/min x 1.73m^2 corresponds to normal renal function with no CKD ("NORM-participants"), whereas lower values (eGFR-EPI < 90 ml/min x 1.73m2) indicate some decline in renal function ("LOW-participants") [21].

RESULTS

1. Cross-sectional analyses in SKIPOGH 1 in all participants

The baseline characteristics of the 1043 SKIPOGH-1 participants are presented in **Table 1**. eGFR was 7.3% higher than eGFR-EPI because, on the average, the BSA exceeded the reference of 1.73m^2. We observed that 43.1% of the participants had a normal BMI (20-25 kg/m^2); 11.3% were underweight, 32.5% overweight, and 13.1% obese (>30 kg/m^2). The urinary excretion of urea represented 47% of that of all solutes, whereas Na and K excretions represented only 18% and 8%, respectively. The U/P urea ratio (51±23) was much higher than that of other solutes or of osmolarity, except for that of creatinine (**Table 1**). Noteworthy, sodium was less concentrated in urine than in plasma, as is most often the case, although not often realized (see also Table 2 in [22]). **Figure 1A** shows the distribution of urine urea concentration and urine osmolarity and **Figure 1B** the distribution of the U/P urea ratio among all participants.

The associations between the U/P urea ratio and several demographic and physiological variables were evaluated in a regression model. The results are shown in **Table 2**. The U/P urea ratio was significantly and negatively associated with age (P<0.001) and UAE (P=0.006), and positively associated with study centers, plasma copeptin concentration and eGFR (in ml/min) (P<0.001 for all three). It was marginally positively associated with 24h urinary urea excretion (P= 0.63). **Figure 1C** shows the unadjusted linear relationship between the U/P urea ratio and the 24h

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urea excretion (assumed to be proportional to dietary protein intake). It shows that the link between these two variables is relatively weak: the U/P urea ratio was only 19% higher for a two-fold higher 24h urea excretion.

We then analyzed the associations between several U/P ratios and eGFR or eGFR-EPI in linear regression models, using scaled and centered predictors and outcomes (μ=0, σ=1). Results are shown in **Table 3** (for complete regression output, please see Supplemental data, sheet S1). The two outcome eGFR variables were positively and strongly associated with U/P urea ratio (eGFR: β_{scaled} = 0.08, p<0.001, eGFR-EPI: β_{scaled} = 0.09, p<0.001) and much less intensely with the U/P uric acid ratio. The two eGFR variables were not associated with the U/P ratios of sodium, potassium or osmolarity. In line with these findings, we observed a positive and significant relationship between individual eGFR values and $\log_{10}$-transformed U/P urea ratio, as shown in **Figure 2** (unadjusted regression model).

2. Cross-sectional analyses in SKIPOGH 1 participants stratified by eGFR-EPI

According to the KDIGO classification [21], 34% of the SKIPOGH participants (N=361) had an eGFR-EPI below 90 ml/min per 1.73m^2. **Table 4** shows the comparison between two subgroups of participants stratified according to their "CKD" status defined by this threshold (Supplemental data, sheets S2-S3). Those with a reduced renal function ("LOW-participants") had a mean eGFR of 82 ml/min vs 113 ml/min for those with normal kidney function ("NORM-participants"). LOW-participants were significantly older, heavier, were more frequently diabetic, and had a slightly higher plasma osmolarity than NORM-participants. The plasma concentrations of urea, Na, K, uric acid and creatinine in LOW-participants were higher than in NORM-participants and plasma copeptin was also modestly higher. LOW-participants had similar 24h urine volume and osmolarity than NORM-participants. However, they excreted about 10% less of all solutes except for potassium excretion that did not differ between the two subgroups. The U/P ratios for urea, Na, uric acid and creatinine were significantly lower in LOW-participants than in NORM-participants (and almost significantly lower for osmolarity). Of note, the U/P ratio was lower by 24% for urea, by only 7% for sodium, and was exactly the same in both subgroups for potassium.

Figure 3 illustrates the distribution of U/P urea and U/P osmolarity for the two subgroups. For urea, the distribution curve of LOW-participants is shifted to lower values than those of NORM-participants. In contrast, for the U/P ratio of whole urine osmolarity there is almost no difference between the two subgroups. The associations between other U/P ratios and eGFR or eGFR-EPI

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were studied separately in these two subgroups of participants with normal or reduced kidney function. Results of the linear regression models are shown in **Table 5**. In LOW-participants, U/P urea was strongly and positively associated with both eGFR and eGFR-EPI (eGFR: β_{scaled} = 0.24, eGFR-EPI: β_{scaled} = 0.22, *P*<0<001 for both), and with U/P uric acid (eGFR: β_{scaled} = 0.18, eGFR-EPI: β_{scaled} = 0.20, *P*<0<001) for both). In contrast, in NORM-participants, eGFR, but not eGFR-EPI, was negatively associated with the U/P potassium (eGFR: β_{scaled} = -0.05, P=0.034), and almost significantly and negatively with the U/P sodium (P=0.057). No association was observed with the U/P urea ratio.

3. Longitudinal analyses: change observed between SKIPOGH 1 and SKIPOGH 2

During a second wave, at a mean interval of 36.3 ± 4.7 months, 898 participants underwent another visit with the same protocol. The change in eGFR (Δ eGFR) between the two waves was evaluated. The mean eGFRs at SKIPOGH 1 and SKIPOGH 2 were 101.9 ± 22.1 and 98.3 ± 22.1 ml/min, respectively. The mean change for all participants over three years was -3.8 ± 9.8 ml/min (one sample t-test: *t* (df=897) = -3.8*, P* <0.001).

However, **Figure 4** shows that eGFR went down in some participants ("Decreasing", N = 611) and went up in others ("Increasing", N = 287). Obviously, with only two GFR estimates based on plasma creatinine, at a relatively short time difference, and in participants the majority of whom had a normal renal function, differences between the two values may occur at random, and the meaning of positive or negative changes may not reflect real changes in eGFR. However, if this were the case, the number of positive and negative values for Δ eGFR should be equally distributed (about 50% in each direction). Actually, 68 % of the participants exhibited a decline in eGFR and 32% a rise (one sample proportions test: χ^2 (1) = 116.2, *P* < 0.001) (**Figure 5**). Moreover, the mean eGFR at SKIPOGH 1 for "Increasing" participants was significantly lower than that for "Decreasing" participants. This suggests that their GFR estimate at SKIPOGH 1 was slightly underestimated compared to that of "Decreasing" participants. As a whole, the decline of 3.8 ml/min in the whole cohort reflects a real, although modest degradation of renal function between the two waves of 1.2 ml/min per year.

The associations between the U/P ratios and eGFR difference between SKIPOGH 2 and SKIPOGH 1 are shown in **Table 6** (Supplemental data, sheet S4). Overall, an association was observed between the baseline U/P urea ratio and eGFR difference (Δ eGFR: β_{scaled} = 0.08, *P*=0.036). These findings indicate that individuals with a lower U/P urea ratio at baseline displayed a greater decline in eGFR than individuals with a higher U/P urea ratio at baseline. This is illustrated in **Figure 6**, depicting a modelization of these association results. There was a

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borderline positive association between the U/P potassium ratio and Δ eGFR in the whole sample (β_{scaled} = 0.07, *P*=0.068).

Upon stratifying the analyses according to the eGFR-EPI threshold defined above, we observed significant associations only in LOW-participants (Table 7) (Supplemental data, sheets S5-S6). Both U/P urea and U/P potassium were positively associated with Δ eGFR (U/P urea: β_{scaled} = 0.18, *P*=0.016), and U/P potassium: β_{scaled} = 0.15, *P*=0.026).

DISCUSSION

In the present study, we examined whether the tubular handling of urea, evaluated by the U/P urea concentration ratio, might be an early marker of further renal function decline in a population-based cohort. First, in the cross-sectional analysis, we observed that the U/P urea ratio, but not the ratio for osmolarity, was strongly and positively associated with eGFR. This relationship was specific to urea because it was not observed with the ratios of the two other main urinary solutes, sodium and potassium. Second, in a 3-year longitudinal analysis we observed that the eGFR decline was inversely associated with the baseline U/P urea ratio. The lower the initial U/P urea ratio, the larger the eGFR decline, even after multiple adjustments including (among others) copeptin, blood pressure, 24h urinary albumin and urea excretions.

Several decades ago, this U/P urea ratio had been proposed to identify different forms of acute tubular injury [23] or oliguria [24]. It had also been shown to predict the response to the selective V2 receptor antagonist tolvaptan in patients with congestive heart failure [25]. A few studies have described a "urea-selective" urine concentrating defect in mice models with either deletion of a facilitated urea transporter or a mutation in Na-K-2Cl [26, 27]. This defect is characterized by a significant reduction in the U/P urea ratio without a distinct fall in urine osmolarity, or by a more severe decline in this urea ratio than in the overall urine concentration.

An important function of the kidney is to concentrate solutes in the urine for the sake of water economy. The usual way to assess this concentrating process is to measure urine osmolality (in mosm/kg H_2O) or to calculate an estimated urine osmolarity (in mosm/L) [28]. Yet, these variables do not take into account the fact that all solutes are not equally concentrated in the urine. Urea is the most abundant urinary solute and one of the most concentrated. This concentration depends on the accumulation of urea in the deep inner medullary interstitium delivered through vasopressin-activated facilitated urea transporters UT-A1 and UT-A3 expressed exclusively in the terminal portion of the inner medullary collecting ducts [29]. Moreover, an energy-dependent urea

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secretion in the proximal straight tubule contributes to raise urine urea concentration while lowering plasma urea concentration, thus increasing further the U/P urea ratio [30]. The high concentration of urea in the deep inner medulla, in turn, plays a significant role in the concentration of other solutes in the urine because it creates a strong driving force for water reabsorption though AQP2.

Cross-sectional analyses

This study reveals that the baseline U/P urea ratio was strongly and positively associated with eGFR. No such relationship was observed with the ratio for osmolarity, sodium or potassium, but a positive association was also observed with the U/P ratio of uric acid, another nitrogenous endproduct, although of much weaker statistical significance. Strong positive correlations of U/P urea and GFR have already been observed in previous studies, but the U/P ratios of osmolarity or other electrolytes had not been evaluated [5, 31-33].

In LOW-participants (eGFR-EPI <90 ml/min per 1.73m^2), both eGFR and eGFR-EPI were positively associated with U/P urea and with U/P uric acid, whereas no association was observed in participants with normal renal function. Interestingly, in LOW-participants, the U/P urea ratio was significantly reduced, while the U/P osmolarity ratio was within the normal range. The whole distribution curve of U/P urea in LOW-participants was shifted down compared to that of NORM-participants. This suggests that early CKD exhibits a "urea-specific" urinary concentrating defect, as already observed in patients with ADPKD [6, 34] and in some animal models [26, 27]. This shows that the U/P urea ratio is not a "marker of urine concentration" (as assumed in [6]) because it declines significantly when urine osmolarity (or its U/P ratio) is still within a normal range. The decline in the kidney's ability to concentrate urea appears earlier than the decline in overall urine concentration. The U/P urea ratio is thus an earlier and more sensitive marker of kidney dysfunction.

Longitudinal analyses

The suggestion by Bankir and Bichet that a decline in the U/P urea ratio could be an early marker of progression of kidney dysfunction in ADPKD [34] was confirmed when Heida et al showed that the rate of eGFR decline in ADPKD patients, during a mean follow up of 7 years, was strongly associated with the baseline U/P urea ratio, independently of usually evaluated biomarkers [6]. In this disease, the medullary architecture is disrupted by cysts which markedly compromise urea accumulation in the inner medulla. Shortly later, the study of Liu et al showed that a similar association is also found in patients with CKD of other etiologies [7]. Participants

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within the lowest quintile of U/P urea ratio at baseline had a significantly greater eGFR decline than those in the highest quintile. Interestingly, this association was restricted to patients with a baseline eGFR > 30 ml/min per 1.73m^2. In advanced CKD, the accumulation of urea in the inner medulla is compromised by the diminished responsiveness of the collecting duct to vasopressin [35]. The ability to concentrate urea in the urine is abolished and the U/P urea ratio reaches its minimum value with limited inter-individual variability [7].

In the present study, the average eGFR decline was inversely associated with the baseline U/P urea ratio. In other words, the lower the initial U/P urea ratio, the larger the eGFR decline, even after multiple adjustments including copeptin, blood pressure, 24h urinary albumin and urea excretions. This association, observed in the entire study sample, was driven by LOW-participants and was not observed in those with normal renal function. The U/P potassium ratio was also associated with the decline in eGFR in LOW-participants only. Actually, previous observations suggest that urea and potassium concentrations in the urine are associated [36].

About eGFR indexation

The way to express eGFR deserves a special comment. The indexation of eGFR on 1.73 m^2 of BSA may be justified when comparing different independent studies performed in different countries, investigating different ethnic groups. It may also be justified for establishing thresholds defining different CKD stages that are widely recognized [37]. However, it is not justified within a given study, performed with a well-defined homogenous protocol. This indexation blunts the inter-individual diversity and thus reduces the strength of some statistical relationships. It may result in failure to reveal significant differences. This is the case for the associations of eGFR with U/P potassium in NORM participants and for U/P osmolality in LOW-participants. The associations are significant with eGFR in ml/min, but not with eGFR in ml/min per 1.73m^2 (**Table 5**). A few recent studies already questioned this indexation [38, 39] because it introduces a bias in obese patients as excess weight leads to a higher BSA, and results in an underestimation of eGFR [40]. In the present study, mean BSA was higher than 1.73m^2, and 46% of the participants were overweight or obese. To our knowledge, no study has ever shown that GFR (or eGFR) is related to BSA. GFR is known to vary with protein intake and urine concentration [5], not with BSA. In ADPKD, the total kidney volume (TKV) is usually indexed on the height of the patients. In that case, this indexation is justified because kidney length (and thus most likely kidney volume) has been shown to be positively and linearly related to body height in the general adult population, over a large range of body heights [41].

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Strength and limitations

This study has several strengths and some limitations. It identifies a simple early marker of renal dysfunction in the general adult population of European descent in Switzerland, without prior selection of participants according to any health characteristics. It includes a detailed phenotype description and exhibits a large range of protein intake (an important determinant of GFR), as shown by the wide range of 24h urinary urea excretion. Further, urine data was based on a 24h collection, not on a spot urine sample. This is important as all urinary solutes do not display the same circadian pattern of excretion. Thus, a morning urine sample or a random sample during the day may not accurately reflect the proportion of the different solutes. Urine was collected in usual life conditions, thus representing everyday kidney function, not after a water deprivation test or dDAVP administration. Finally, the present study allowed comparing U/P urea and U/P osmolarity ratios. The limitations of this study include the fact that it deals with a relatively low number of participants of European descent. Further studies should address people of other ethnic origins. Urine osmolality was not measured; instead, an estimated urine osmolarity was calculated, based on a previously validated formula. Another limitation is that the decline of kidney function over time was based on only two measurements collected over a 3-year interval on average.

CONCLUSION

The present research extends to the general adult population the relationships reported previously in patients with overt kidney diseases [6, 7]. It suggests, for the first time, that the U/P urea ratio may be used widely as a marker of very early renal dysfunction (eGFR <90ml/min x 1.73m^2). However, this urea ratio may no longer be a valid marker in advanced CKD (eGFR <30 ml/min per 1.73m^2) [7].

In conclusion, the present study provides evidence that the U/P urea ratio is a marker of an early decline in renal function. It is more sensitive than the decline in urine osmolarity or the U/P ratio of osmolarity. Unlike other markers, this U/P urea ratio is not based on glomerular functions but reflects transport functions that occur along the renal tubule and collecting duct. This broadens our panel of markers available for evaluating renal function in epidemiological studies. Finally, and importantly, urea is easy to measure in routine facilities, with well-standardized techniques and at a low cost. Thus, the U/P urea ratio has the potential to become a widely used marker for evaluating the risk of renal function decline, even in its earliest phase.

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FUNDING

The SKIPOGH study was funded by grants from the Swiss National Science Foundation (FN 33CM30-124087/ 140331) and by intramural support of Lausanne, Geneva, and Bern University Hospitals.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

ETHICS STATEMENT

The SKIPOGH study was approved by relevant local or national ethics committees and all procedures performed in these studies were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants gave written informed consent. This work does not contain any studies with animals performed by any of the authors.

ACKNOWLEDGEMENTS

We want to thank the study nurses involved in the study and the recruitment: Marie-Odile Levy, Guler Gök Sogüt, Ulla Spüchbach, Dominique Siminski. We also thank Sandrine Estoppey-Younes for her help in the logistic and database management. We also want to thank Ragnar Palsson (Division of Nephrology, Massachusetts General Hospital, Boston, MA, USA) for valuable suggestions during the preparation of the manuscript.

AUTHORS' CONTRIBUTIONS

Lise BANKIR, Dusan PETROVIC and Murielle BOCHUD: conceived the study.

Dusan PETROVIC and Lise BANKIR: did the analyses, interpreted the data and wrote the manuscript.

Murielle BOCHUD, Menno PRUIJM and Belén PONTE interpreted the data and revised the manuscript.

Yassine BOUATOU, Daniel ACKERMANN, Bruno VOGT: data collection

Tanguy CORRE, Jean-Pierre GHOBRIL: data management, data quality control

All authors revised and approved the manuscript.

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DATA AVAILABILITY STATEMENT

"SKIPOGH data is not public, but may be made available upon a formal request submitted to the SKIPOGH steering board. For further details about the study design and the phenotypes available in SKIPOGH, please see https://www.maelstrom-research.org/study/skipogh."

SUPPLEMENTARY MATERIAL

See ndt online.

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Figure 1

Petrovic et al. U/P urea ratio and eGFR decline.....

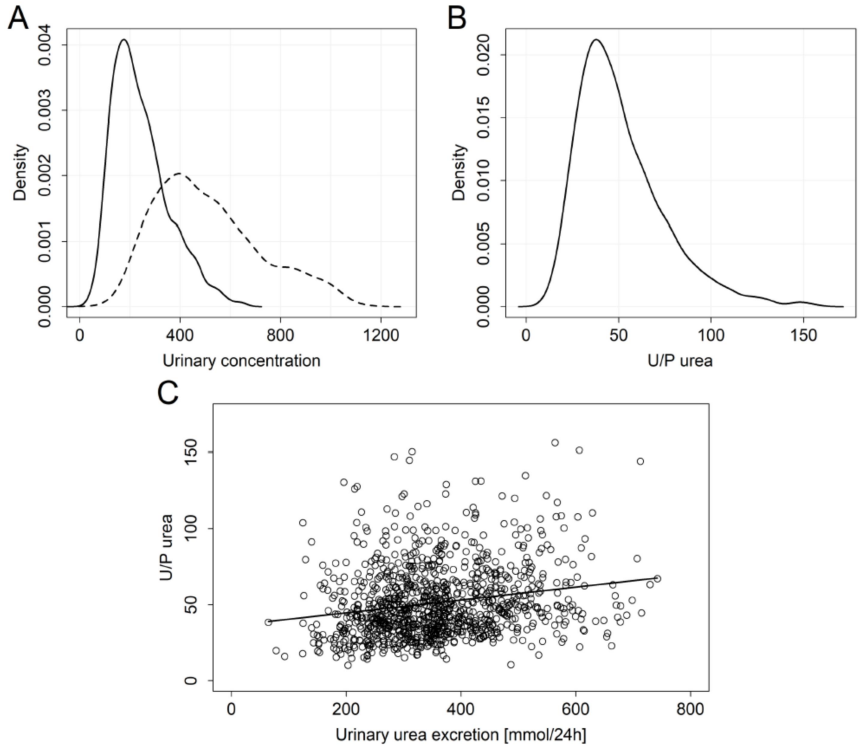

Figure 1. A: Kernel density distribution of urinary concentration of urea (solid line) and osmolarity (dotted line). **B**: Kernel density distribution of the U/P urea concentration ratio. **C**: Relationship between U/P urea and 24h urea excretion. **D**: Relationship between U/P urea and 24h urine volume (original units). Linear regression model in C: U/P urea = (24h urea excretion × 0.04) + 36.10, $P < 0.001$. Logarithmic regression fit in D: Log_{10} (U/P urea) = (24h urine volume × -1.62×10^{-4}) + 1.94, $P < 0.001$.

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Figure 2

Petrovic et al. U/P urea ratio and eGFR decline.....

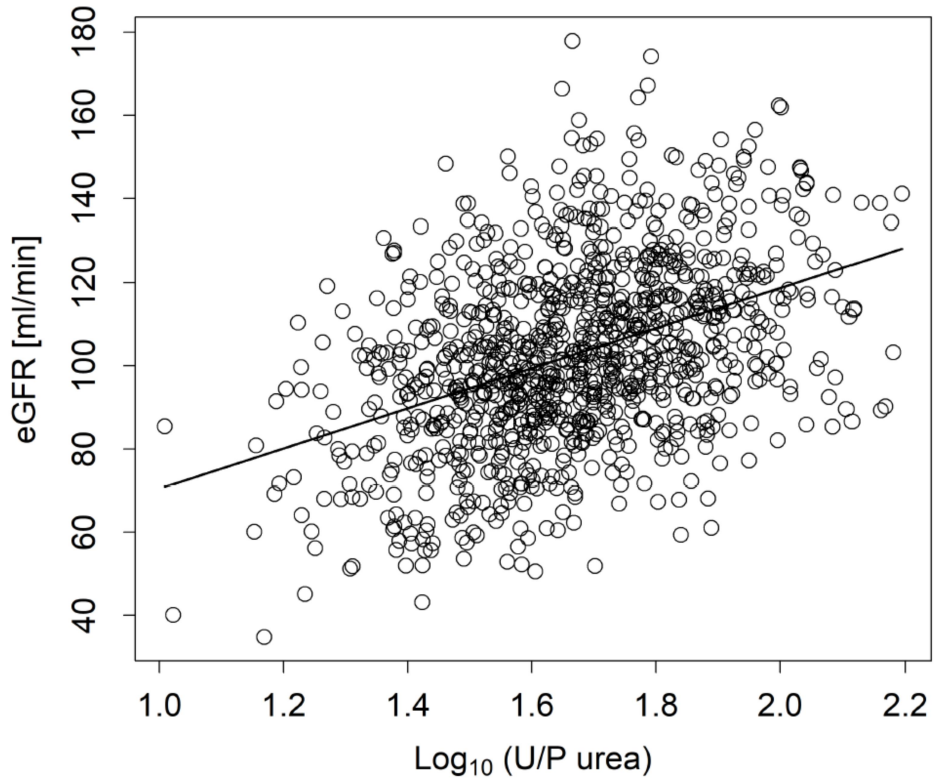

Figure 2. Association between Log_{10} (U/P urea) and eGFR. Linear regression: eGFR = (Log_{10} (U/P urea) × 48.24) + 22.20, $P < 0.001$. Note: the three very low values of Log_{10} (U/P urea) (below 1.1) correspond to two male participants with low eGFR-EPI (< 40 ml/min × 1.73m^2) and one female participant with normal eGFR-EPI (96 ml/min × 1.73m^2) but low 24h urea excretion (203 mmol/24h).

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Figure 3 *Petrovic et al. U/P urea ratio and eGFR decline.....*

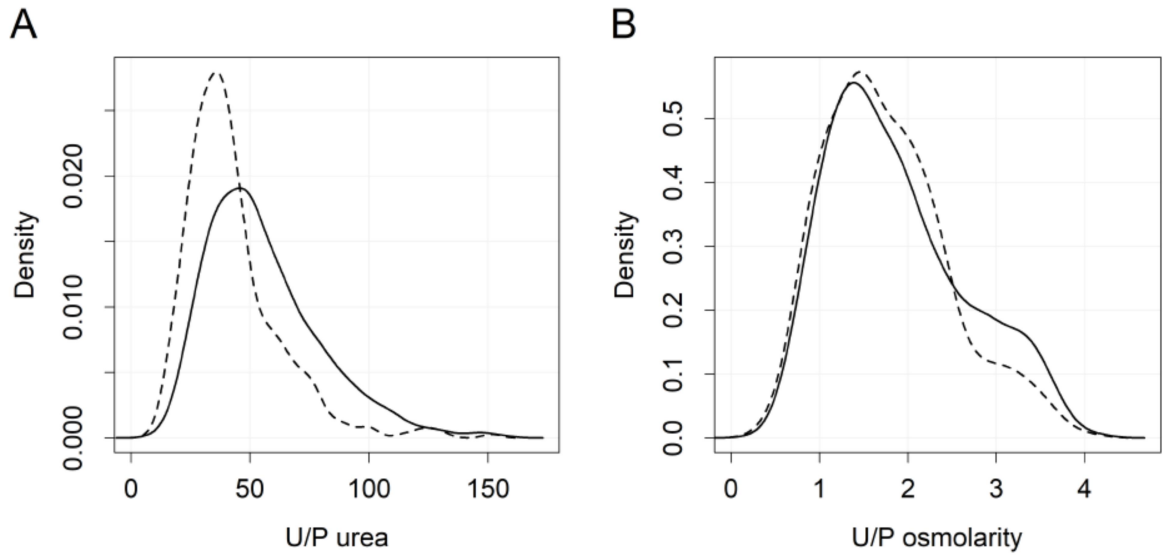

Figure 3. A and B: Kernel density distribution of the U/P urea concentration ratio **(A)** and of the U/P osmolarity ratio **(B)** in SKIPOGH 1 participants, stratified by eGFR-EPI clinical threshold. Solid line, eGFR-EPI ≥ 90 ml/min per 1.73m^2; dashed line, eGFR-EPI < 90 ml/min per 1.73m^2.

Figure 3. A and B: Kernel density distribution of the U/P urea concentration ratio **(A)** and of the U/P osmolarity ratio **(B)** in SKIPOGH 1 participants, stratified by eGFR-EPI clinical threshold. Solid line, eGFR-EPI > 90 ml/min per 1.73m^2; dashed line, eGFR-EPI ≤ 90 ml/min per 1.73m^2.

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Figure 4 *Petrovic et al. U/P urea ratio and eGFR decline.....*

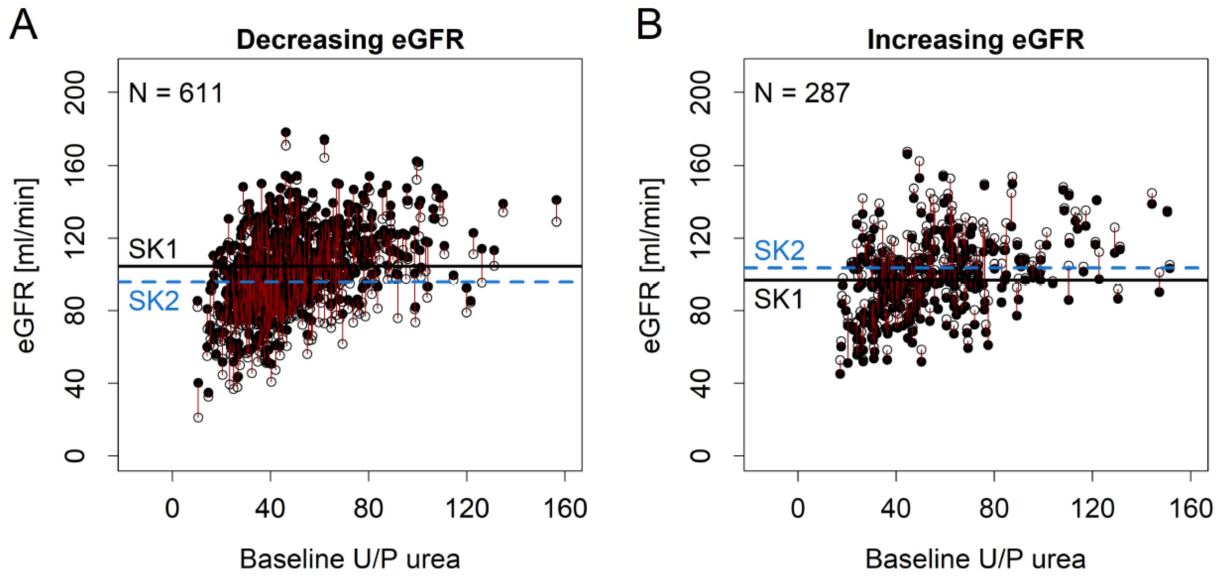

Figure 4. **A and B**: Relationship of eGFR at SKIPOGH 1 (closed circles) and SKIPOGH 2 (open circles) with baseline U/P urea ratio in participants in whom eGFR decreased **(A)** or increased **(B)** between the two waves. Thin vertical red lines join SKIPOGH 1 and SKIPOGH 2 values observed in each participant. The horizontal lines show the mean of eGFR at SKIPOGH 1 (black solid line) and SKIPOGH 2 (blue dashed line). The number of participants (N) is shown in the upper left corner for each subgroup.

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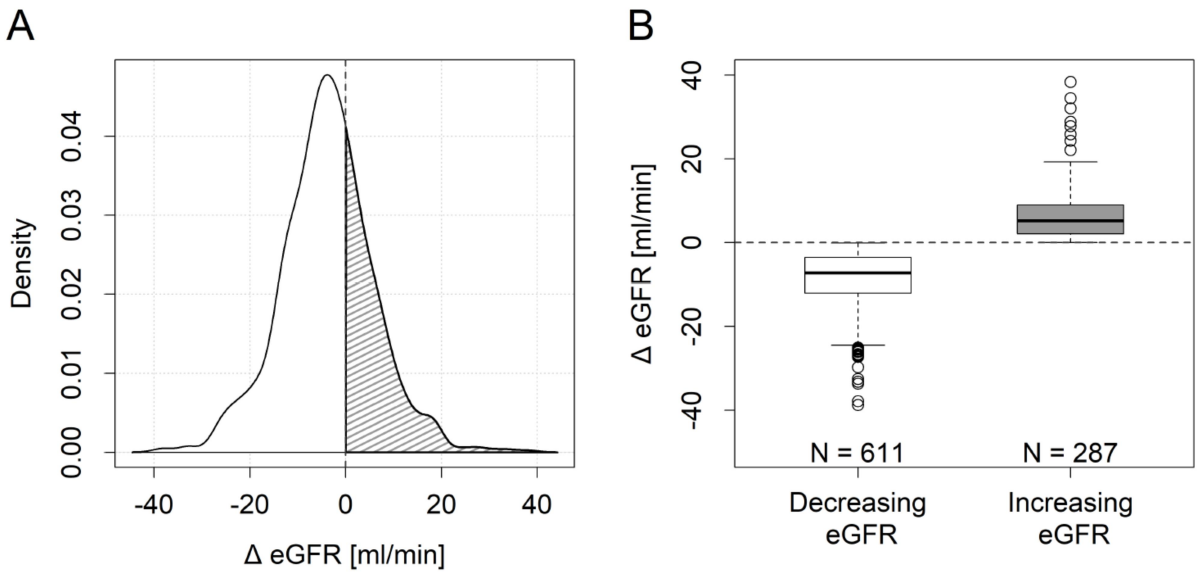

Figure 5. **A**: Kernel density distribution of the change in eGFR (Δ eGFR) between SKIPOGH 2 and SKIPOGH 1. A larger proportion of participants show a negative than a positive Δ eGFR (clear and shaded areas, respectively). Chi2 test: $\chi 2 = 111.83$, $P < 0.001$. **B.** Boxplots showing the distribution of the change in eGFR (Δ eGFR) across individuals with decreasing (Δ eGFR < 0) or increasing eGFR (Δ eGFR ≥ 0) between SKIPOGH 2 and SKIPOGH 1. The number of participants (N) is shown for each subgroup.

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Figure 6

Petrovic et al. U/P urea ratio and eGFR decline.....

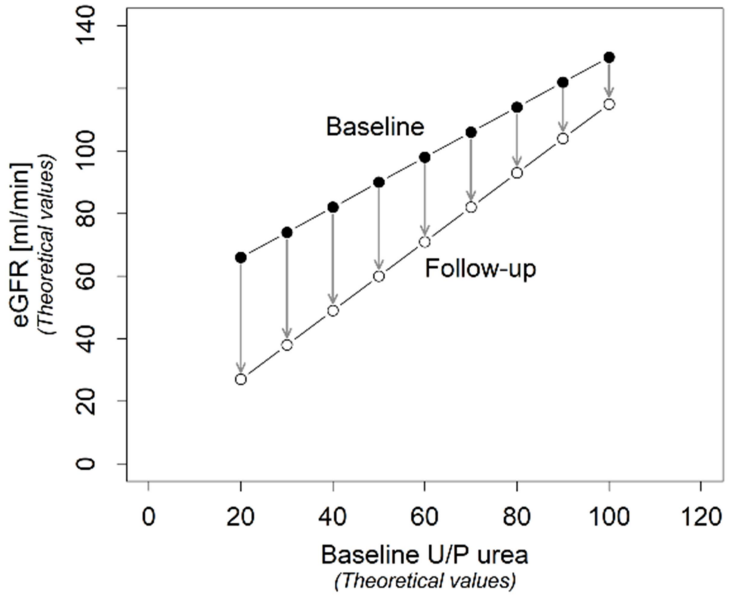

Figure 6. Modelization of the association between eGFR values at SKIPOGH 1 and SKIPOGH 2 plotted against the baseline U/P urea ratio (theoretical values). This figure illustrates the decline in eGFR between the two waves (shown as thin vertical arrows). This decline is larger in participants showing a lower U/P urea ratio at baseline, and smaller in those with a higher U/P urea ratio at baseline.

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Table 1 : Baseline characteristics of SKIPOGH 1 participants (N=1043)

Age (years)	48 (±17)
Recruitement center, N(%)	
Lausanne	350 (34%)
Geneva	414 (40%)
Bern	279 (27%)
Body weight (kg)	73 (±15)
BMI (kg/m^2)	25.1 (±4.5)
Body surface area (m^2)	1.84 (±0.21)
eGFR-EPI (ml/min x 1.73m^2)	96.38 (±17.87)
eGFR (ml/min)	102.65 (±22.25)
Systolic blood pressure (mmHg) [a]	118.1 (±16.7)
Diastolic blood pressure (mmHg) [a]	75.8 (±9.6)
Current smoking, N(%) [b]	250 (24%)
Kidney disease, N(%) [b]	133 (13%)
Diabetes, N(%) [b]	47 (5%)
Hypertension, N(%) [b]	328 (31%)
Plasma osmolarity (mmol/L)	279.6 (±5.4)
Urinary volume (ml/24h)	1709 (±745)
Urinary osmolarity (mOsm/L)	513 (±211)
Urinary osmolar excr. (mmol/24h)	770 (±246)
Plasma urea conc. (mmol/L)	4.92 (±1.56)
Plasma sodium conc. (mmol/L)	140.4 (±2.5)
Plasma potassium conc. (mmol/L)	4.08 (±0.34)
Plasma uric acid conc. (µmol/L)	308 (±76)
Plasma creatinine conc. (µmol/L)	73 (±14)
Plasma copeptin conc. (pmol/L)	4.91 (±3.48)
Urinary urea ~~concentration~~ conc. (mmol/L)	243 (±112)
Urinary sodium ~~concentration~~ conc. (mmol/L)	93 (±44)
Urinary potassium ~~concentration~~ conc. (mmol/L)	42 (±18)
Urinary uric acid ~~concentration~~ conc. (mmol/L)	2.20 (±1.10)
Urinary creatinine ~~concentration~~ conc. (mmol/L)	8.85 (±4.73)

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Urinary urea excr. (mmol/24h)	359 (±119)
Urinary sodium excr. (mmol/24h)	142 (±61)
Urinary potassium excr. (mmol/24h)	64 (±23)
Urinary uric acid excr. (mmol/24h)	3.22 (±1.07)
Urinary creatinine excr. (mmol/24h)	12.74 (±4.17)
Urinary albumin excr. (mg/24h)	16.29 (±117.62)
U/P urea ratio	51.3 (±23.7)
U/P sodium ratio	0.66 (±0.32)
U/P potassium ratio	10.29 (±4.48)
U/P uric acid ratio	7.42 (±3.86)
U/P creatinine ratio	121 (±62)
U/P osmolarity ratio	1.83 (±0.75)

Data are mean ± SD for continuous variables and N (%) for categorical variables
eGFR = estimated Glomerular Filtration Rate (non-indexed for body surface area)
eGFR-EPI = estimated Glomerular Filtration Rate (based on Chronic Kidney Disease Epidemiology consortium)
U/P = 24h Urine (U) / Plasma (P) concentration ratio. Excr = excretion; conc = concentration
a: Systolic and diastolic blood pressure are expressed as the mean of five successive blood pressure measurement at study examination
b: Current smoking and kidney disease were exclusively based on self-report, diabetes was either self-reported, based on blood glucose levels (≥7mmol/L) at clinical visit, or self-report of anti-diabetes medication intake, hypertension was either self-reported, based on systolic/diastolic blood pressure (≥140/90mmHg) at clinical visit, or self-report of anti-hypertensive medication intake

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Table 2: Regression model for the associations between urine/plasma urea concentration ratio (dependant variable) and demographic and physiological factors (independent variables), SKIPOGH 1 (N=1043)

	β [95%CI] [a]	*P* [a]
Male sex (cat.)	-2.83 [-5.98;0.32]	0.081
Age (years)	-0.39 [-0.51;-0.28]	**<0.001**
BMI (kg/m2)	0.27 [-0.07;0.60]	0.121
Study center - Geneva (cat.)	16.57 [13.29;19.85]	**<0.001**
Study center - Lausanne (cat.)	6.87 [3.35;10.39]	**<0.001**
Current smoking (cat.)	0.76 [-2.08;3.62]	0.602
Diabetes (cat.)	-2.65 [-8.82;3.55]	0.403
Systolic blood pressure (mmHg)	-0.05 [-0.17;0.07]	0.402
Systolic blood pressure (mmHg)	0.10 [-0.08;0.29]	0.293
Urinary albumin excretion (mg/24h)	-0.01 [-0.02;0.00]	**0.006**
Plasma copeptin (pmol/L)	1.51 [1.12;1.9]	**<0.001**
Urinary urea excretion (mmol/24h)	0.01 [0.00;0.02]	0.063
eGFR (ml/min)	0.19 [0.10;0.28]	**<0.001**

U/P = 24h Urine (U) / Plasma (P) concentration ratio
eGFR = estimated Glomerular Filtration Rate (non-indexed for body surface area)
Cat. = categorical variable (i.e. Study center, ref: Bern)
a: Mixed linear regression models for the association between urine/plasma urea concentration ratios (dependant variable, original units) and listed demographic and physiological factors (independant variables, original units), subsequently adjusting for familial structure (random-effect covariable)

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Table 3: Regression models for the associations between urine/plasma concentration ratios and renal function markers, SKIPOGH 1 (N=1043)

	β [95%CI] [a]	*P* [a]
U/P urea		
eGFR	0.08 [0.04;0.13]	**<0.001**
eGFR-EPI	0.09 [0.05;0.14]	**<0.001**
U/P sodium		
eGFR	0.00 [-0.05;0.05]	0.994
eGFR-EPI	0.01 [-0.04;0.06]	0.600
U/P potassium		
eGFR	-0.01 [-0.05;0.03]	0.607
eGFR-EPI	0.00 [-0.05;0.04]	0.906
U/P uric acid		
eGFR	0.04 [0.00;0.08]	**0.037**
eGFR-EPI	0.06 [0.01;0.10]	**0.012**
U/P osmolarity		
eGFR	0.01 [-0.04;0.05]	0.752
eGFR-EPI	0.00 [-	0.84

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U/P = 24h Urine (U) / Plasma (P) concentration ratio
eGFR = estimated Glomerular Filtration Rate (non-indexed for body surface area)
eGFR-EPI = estimated Glomerular Filtration rate (based on Chronic Kidney Disease Epidemiology consortium)
a: Linear regression models for the association between urine/plasma concentration ratios (scaled predictors) and renal function markers (scaled outcomes), adjusting for age, sex, study center, BMI, 24h urinary albumin excretion, 24h urinary excretion of related solutes (i.e. U/P sodium: 24h sodium excretion), tobacco smoking, diabetes, systolic and diastolic blood pressure, plasma copeptin, and familial structure

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Table 4: Baseline characteristics of SKIPOGH 1 participants, stratified by eGFR-EPI clinical threshold of 90 ml/min per 1.73m^2

	LOW-participants	NORM-participants	Ratio [a]	*P* [b,c]
N	**357**	**686**		
Age (years)	61 (±14)	40 (±15)	1.53	**<0.001**
Recruitement center, N(%)				
Lausanne	154 (43%)	196 (29%)	0.79	**<0.001**
Geneva	124 (35%)	290 (42%)	0.43	
Bern	79 (22%)	200 (29%)	0.40	
Body weight (kg)	75 (±14)	72 (±15)	1.04	**<0.001**
BMI (kg/m^2)	26.3 (±4.3)	24.4 (±4.5)	1.08	**<0.001**
Body surface area (m^2)	1.85 (±0.20)	1.84 (±0.21)	1.01	0.283
eGFR-EPI (ml/min x 1.73m^2)	76.89 (±10.75)	106.52 (±11.17)	0.72	**<0.001**
eGFR (ml/min)	82.34 (±14.97)	113.22 (±17.59)	0.73	**<0.001**
Systolic blood pressure (mmHg) [d]	125.3 (±18.4)	114.3 (±14.4)	1.10	**<0.001**
Diastolic blood pressure (mmHg) [d]	77.4 (±9.2)	74.9 (±9.8)	1.03	**<0.001**
Current smoking, N(%) [e]	60 (17%)	190 (28%)	0.93	**<0.001**
Kidney disease, N(%) [e]	63 (18%)	70 (10%)	2.51	**<0.001**
Diabetes, N(%) [e]	29 (8%)	18 (3%)	9.78	**<0.001**
Hypertension, N(%) [e]	176 (49%)	152 (22%)	1.16	**<0.001**
Plasma osmolarity (mmol/L)	281.4 (±5.3)	278.6 (±5.2)	1.01	**<0.001**
Urinary volume (ml/24h)	1650 (±731)	1740 (±751)	0.95	0.05

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				6
Urinary osmolarity (mOsm/L)	495 (±198)	522 (±217)	0.95	0.13 8
Urinary osmolar excr. (mmol/24h)	725 (±234)	794 (±248)	0.91	**<0.0 01**
Plasma urea conc. (mmol/L)	5.64 (±1.83)	4.54 (±1.24)	1.24	**<0.0 01**
Plasma sodium conc. (mmol/L)	140.8 (±2.6)	140.2 (±2.5)	1.00	**<0.0 01**
Plasma potassium conc. (mmol/L)	4.13 (±0.37)	4.05 (±0.32)	1.02	**<0.0 01**
Plasma uric acid conc. (µmol/L)	329 (±80)	297 (±72)	1.11	**<0.0 01**
Plasma creatinine conc. (µmol/L)	83 (±15)	69 (±11)	1.20	**<0.0 01**
Plasma copeptin conc. (pmol/L)	5.29 (±3.80)	4.71 (±3.28)	1.12	**0.02 1**
Urinary urea conc. (mmol/L)	233 (±108)	248 (±114)	0.94	0.06 7
Urinary sodium conc. (mmol/L)	89 (±41)	95 (±46)	0.94	0.06 4
Urinary potassium conc. (mmol/L)	42 (±17)	42 (±19)	1.00	0.13 8
Urinary uric acid conc. (mmol/L)	2.07 (±1.03)	2.27 (±1.14)	0.91	**0.00 9**
Urinary creatinine conc. (mmol/L)	8.42 (±4.37)	9.08 (±4.89)	0.93	0.06 6
Urinary urea excr. (mmol/24h)	335 (±116)	372 (±118)	0.90	**<0.0 01**
Urinary sodium excr. (mmol/24h)	132 (±59)	147 (±62)	0.90	**<0.0 01**
Urinary potassium excr. (mmol/24h)	63 (±21)	64 (±24)	0.98	0.64 7
Urinary uric acid excr. (mmol/24h)	2.95 (±1.00)	3.36 (±1.08)	0.88	**<0.0 01**
Urinary creatinine excr. (mmol/24h)	11.81 (±3.75)	13.22 (±4.30)	0.89	**<0.0 01**
Urinary albumin excr. (mg/24h)	23.30 (±179.56)	12.63 (±65.19)	1.84	0.85 3
U/P urea ratio	42.7 (±20.1)	55.8 (±24.1)	0.77	**<0.0**

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				01
U/P sodium ratio	0.63 (±0.29)	0.68 (±0.33)	0.93	**0.04 7**
U/P potassium ratio	10.31 (±4.16)	10.28 (±4.64)	1.00	0.34 8
U/P uric acid ratio	6.52 (±3.36)	7.88 (±4.01)	0.83	**<0.0 01**
U/P creatinine ratio	102 (±50)	131 (±64)	0.78	**<0.0 01**
U/P osmolarity ratio	1.76 (±0.70)	1.87 (±0.78)	0.94	0.06 7

Data are mean ± SD for continuous variables and N (%) for categorical variables
eGFR = estimated Glomerular Filtration Rate (non-indexed for body surface area)
eGFR-EPI = estimated Glomerular Filtration Rate (based on Chronic Kidney Disease Epidemiology consortium)
U/P = 24h Urine (U) / Plasma (P) concentration ratio. Excr = excretion; conc = concentration
LOW = Participants with decreased renal function (eGFR-EPI < 90 ml/min x 1.73m^2)
NORM = Participants with normal renal function (eGFR-EPI ≥ 90 ml/min x 1.73m^2)
a: Ratio between average values in LOW over NORM participants
b: The Mann-Whitney U-test was performed between the two groups for continuous variables.
c: The $\chi 2$ contingency test was performed between the two groups for categorical variables.
d: Systolic and diastolic blood pressure are expressed as the mean of five successive blood pressure measurement at study examination
e: Current smoking and kidney disease were exclusively based on self-report, diabetes was either self-reported, based on blood glucose levels (≥7mmol/L) at clinical visit, or self-report of anti-diabetes medication intake, hypertension was either self-reported, based on systolic/diastolic blood pressure (≥140/90mmHg) at clinical visit, or self-report of anti-hypertensive medication intake

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Table 5: Regression models for the associations between urine/plasma concentration ratios and renal function markers, stratified by eGFR-EPI clinical threshold of 90 ml/min per 1.73m^2, SKIPOGH 1

	LOW-participants (N = 357)		NORM-participants (N = 686)	
	β [95%CI] [a]	***P* [a]**	**β [95%CI] [a]**	***P* [a]**
U/P urea				
eGFR	0.24 [0.15;0.32]	**<0.001**	0.03 [-0.02;0.08]	0.228
eGFR-EPI	0.22 [0.12;0.32]	**<0.001**	0.06 [0.00;0.12]	0.073
U/P sodium				
eGFR	0.09 [0.00;0.19]	0.067	-0.05 [-0.11;0.00]	0.057
eGFR-EPI	0.09 [-0.03;0.21]	0.151	-0.03 [-0.11;0.04]	0.360
U/P potassium				
eGFR	0.08 [-0.01;0.17]	0.072	-0.05 [-0.10;0.00]	**0.034**
eGFR-EPI	0.07 [-0.04;0.17]	0.221	-0.04 [-0.10;0.03]	0.269
U/P uric acid				
eGFR	0.18 [0.10;0.27]	**<0.001**	-0.03 [-0.08;0.02]	0.199
eGFR-EPI	0.20 [0.10;0.30]	**<0.001**	-0.02 [-0.08;0.04]	0.545
U/P osmolarity				
eGFR	0.12 [0.03;0.21]	**0.013**	-0.04 [-0.09;0.01]	0.129
eGFR-EPI	0.09 [-0.02;0.20]	0.117	-0.04 [-0.10;0.03]	0.294

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U/P = 24h Urine (U) / Plasma (P) concentration ratio
eGFR = estimated Glomerular Filtration Rate (non-indexed for body surface area)
eGFR-EPI = estimated Glomerular Filtration rate (based on Chronic Kidney Disease Epidemiology consortium)
LOW = Participants with decreased renal function (eGFR-EPI < 90 ml/min x $1.73m^2$)
NORM = Participants with normal renal function (eGFR-EPI ≥ 90 ml/min x $1.73m^2$)
a: Linear regression models for the association between urine/plasma concentration ratios (scaled predictors) and renal function markers (scaled outcomes), adjusting for age, sex, study center, BMI, 24h urinary albumin excretion, 24h urinary excretion of related solutes (i.e. U/P sodium: 24h sodium excretion), tobacco smoking, diabetes, systolic and diastolic blood pressure, plasma copeptin, and familial structure

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Table 6: Regression models for the associations between urine/plasma concentration ratios at baseline and eGFR difference (Δ eGFR) between SKIPOGH 2 and SKIPOGH 1 (N=898)

	β [95%CI] [a]	***P* [a]**
U/P urea	0.08 [0.01;0.15]	**0.036**
U/P sodium	-0.03 [-0.11;0.05]	0.459
U/P potassium	0.07 [0.00;0.14]	0.068
U/P uric acid	-0.01 [-0.08;0.06]	0.797
U/P osmolarity	-0.28 [-1.75;1.20]	0.713

U/P = 24h Urine (U) / Plasma (P) concentration ratio
eGFR = estimated Glomerular Filtration Rate (non-indexed for body surface area)
Δ eGFR defined as the arithmetic difference between eGFR at SK1 and eGFR at SK2, divided by the number of months of follow-up
a: Linear regression model for the association between urine/plasma ratio at baseline (predictor) and eGFR difference (Δ eGFR), adjusting for sex, center, follow-up time difference, familial structure (random-effect covariable), eGFR (SK1), age (SK1), BMI (SK1), smoking (SK1), diabetes status (SK1), systolic and diastolic blood pressure (SK1), 24h urinary albumin excretion (SK1), plasma copeptin concentration (SK1), and 24h-related urinary excretion (SK1; i.e. U/P sodium: 24h sodium urinary excretion)

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Table 7: Regression models for the associations between urine/plasma concentration ratios at baseline and eGFR difference (Δ eGFR) between SKIPOGH 2 and SKIPOGH 1, stratified by eGFR-EPI clinical threshold of 90 ml/min per $1.73m^2$

	LOW-participants (N=315)		**NORM-participants (N=583)**	
	β [95%CI] [a]	***P*** **[a]**	**β [95%CI] [a]**	***P*** **[a]**
U/P urea	0.18 [0.04;0.33]	**0.016**	0.04 [-0.04;0.13]	0.340
U/P sodium	0.14 [-0.01;0.29]	0.080	-0.09 [-0.18;0.01]	0.077
U/P potassium	0.15 [0.02;0.28]	**0.026**	0.03 [-0.05;0.12]	0.434
U/P uric acid	0.1 [-0.04;0.24]	0.179	-0.05 [-0.13;0.03]	0.241
U/P osmolarity	-0.09 [-2.96;2.81]	0.951	0.15 [-1.58;1.89]	0.867

U/P = 24h Urine (U) / Plasma (P) concentration ratio
eGFR = estimated Glomerular Filtration Rate (non-indexed for body surface area)
eGFR-EPI = estimated Glomerular Filtration Rate (based on Chronic Kidney Disease Epidemiology consortium)
Δ eGFR defined as the arithmetic difference between eGFR at SK1 and eGFR at SK2, divided by the number of months of follow-up
LOW = Participants with decreased renal function (eGFR-EPI < 90 ml/min x $1.73m^2$)
NORM = Participants with normal renal function (eGFR-EPI ≥ 90 ml/min x $1.73m^2$)
a: Linear regression model for the association between urine/plasma ratio at baseline (predictor) and eGFR difference (Δ eGFR), adjusting for the following factors at SK1: sex, center, follow-up time difference, familial structure (random-effect covariable), eGFR, age, BMI, smoking, diabetes status, systolic and diastolic blood pressure, 24h urinary albumin excretion, plasma copeptin concentration (S), and related 24h urinary excretion (i.e., for U/P sodium, adjusted for 24h urinary sodium excretion).

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