

LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE



LSHTM Research Online

Kovesdy, CP; Matsushita, K; Sang, Y; Brunskill, NJ; Carrero, JJ; Chodick, G; Hasegawa, T; Heerspink, HL; Hirayama, A; Landman, GWD; +8 more... Levin, A; Nitsch, D; Wheeler, DC; Coresh, J; Hallan, SI; Shalev, V; Grams, ME; CKD Prognosis Consortium; (2018) Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. European heart journal. ISSN 0195-668X DOI: <https://doi.org/10.1093/eurheartj/ehy100>

Downloaded from: <http://researchonline.lshtm.ac.uk/4647056/>

DOI: <https://doi.org/10.1093/eurheartj/ehy100>

**Usage Guidelines:**

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact [researchonline@lshtm.ac.uk](mailto:researchonline@lshtm.ac.uk).

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

# **Serum Potassium and Adverse Outcomes Across the Range of Kidney Function: A CKD Prognosis Consortium Meta-Analysis**

Csaba P Kovesdy, MD,<sup>a</sup> Kunihiro Matsushita, MD, PhD,<sup>b</sup> Yingying Sang, MS,<sup>b</sup> Nigel J. Brunskill, MD, PhD,<sup>c</sup> Juan J Carrero, PharmD, PhD,<sup>d</sup> Gabriel Chodick, PhD,<sup>e</sup> Takeshi Hasegawa, MD, MPH, PhD,<sup>f</sup> Hiddo L. Heerspink, PharmD, PhD,<sup>g</sup> Atsushi Hirayama, MD,<sup>h</sup> Gijs W. D. Landman, MD,<sup>i</sup> Adeera Levin, MD,<sup>j</sup> Dorothea Nitsch, MD, MSc,<sup>k</sup> David C. Wheeler, MD,<sup>l</sup> Josef Coresh, MD, PhD,<sup>b</sup> Stein I. Hallan, MD, PhD,<sup>m</sup> Varda Shalev, MD,<sup>e</sup> Morgan E. Grams, MD, PhD<sup>b</sup> for the **CKD Prognosis Consortium**

<sup>a</sup>University of Tennessee Health Science Center, Memphis, TN and Memphis Veterans Affairs Medical Center, Memphis, TN, USA

<sup>b</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

<sup>c</sup>Department of Infection Immunity and Inflammation, University of Leicester, UK and John Walls Renal Unit, University Hospitals of Leicester, UK

<sup>d</sup>Department of Medical Epidemiology and Biosatistics (MEB), Karolinska Institutet, Stockholm, Sweden

<sup>e</sup>Medical Division, Maccabi Healthcare Services, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

<sup>f</sup>Showa University, Office for Promoting Medical Research, Tokyo, and Showa University Fujigaoka Hospital, Division of Nephrology, Department of Internal Medicine, Yokohama, and Fukushima Medical University, Center for Innovative Research for Communities and Clinical Excellence, Fukushima, and Kyoto University Graduate School of Public Health, Department of Healthcare Epidemiology, Kyoto, Japan

<sup>g</sup>Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, the Netherlands

<sup>h</sup>Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan

<sup>i</sup>Diabetes Centre Zwolle, Isala hospital, Zwolle, the Netherlands

<sup>j</sup>BC Provincial Renal Agency and University of British Columbia, Canada

<sup>k</sup>Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

<sup>l</sup>Centre for Nephrology, University College London, London, UK

<sup>m</sup>Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science Technology, Trondheim and Division of Nephrology, Department of Medicine, St Olav University Hospital, Trondheim, Norway

Word Count: abstract: 250; text (introduction to conclusion, plus references and figure legends): 5419

Brief title: Serum potassium and outcomes

Address for correspondence: Chronic Kidney Disease Prognosis Consortium Data Coordinating Center (Principal Investigator, Josef Coresh, MD, PhD), 2024 E. Monument Street, Baltimore, MD 21205; Tel: 410-955-9917, Fax: 410-955-8086, E-mail: [ckdpc@jhmi.edu](mailto:ckdpc@jhmi.edu)

## **ABSTRACT**

**Aims:** Both hypo- and hyperkalemia can have immediate deleterious physiologic effects; less is known about long-term risks. The objective was to determine the risks of all-cause mortality, cardiovascular mortality and end-stage renal disease associated with potassium levels across the range of kidney function and evaluate for consistency across cohorts in a global consortium.

**Methods & Results:** We performed an individual-level data meta-analysis of 27 international cohorts (10 general population, 7 high cardiovascular risk, and 10 CKD) in the CKD Prognosis Consortium. We used Cox regression followed by random-effects meta-analysis to assess the relationship between baseline potassium and adverse outcomes, adjusted for demographic and clinical characteristics, overall and across strata of eGFR and albuminuria. We included 1,217,986 participants followed for a mean of 6.9 years. Average age was  $55\pm 16$  years, average eGFR was  $83\pm 23$  ml/min/1.73 m<sup>2</sup>, and 17% had moderate- to severely-increased albuminuria. Mean baseline potassium was  $4.2\pm 0.4$  mmol/L. The risk of serum potassium of  $>5.5$  mmol/L was related to lower eGFR and higher albuminuria. The risk-relationship between potassium levels and adverse outcomes was U-shaped with the lowest risk at serum potassium 4-4.5 mmol/L. Compared to a reference of 4.2 mmol/L, the adjusted hazard ratio for all-cause mortality was 1.22 (95% CI: 1.15-1.29) at 5.5 mmol/L and 1.49 (95% CI: 1.26-1.76) at 3.0 mmol/L. Risks were similar by eGFR, albuminuria, renin-angiotensin-aldosterone system inhibitor use, and across cohorts.

**Conclusions:** Outpatient potassium levels both above and below the normal range are consistently associated with adverse outcomes, with similar risk relationships across eGFR and albuminuria.

**Key words:** potassium, estimated glomerular filtration rate, albuminuria, end-stage renal disease, mortality

## INTRODUCTION

Abnormal serum potassium levels represent one of the most important electrolyte disturbances in clinical practice. Potassium plays a crucial role in normal cell membrane electrophysiology, with both hyperkalemia and hypokalemia resulting in electrophysiologic perturbations, most importantly in the cardiac system. Abnormalities in myocardial resting membrane potential, cardiac depolarization, and myocardial excitability can result in conduction system abnormalities, including malignant arrhythmias.<sup>1-3</sup>

The kidneys play a central role in potassium homeostasis, with chronic kidney disease (CKD) being an especially prominent risk factor for hyperkalemia.<sup>4,5</sup> Other risk factors for hyperkalemia commonly occur in combination with CKD, including clinical conditions such as acute kidney injury, cardiovascular disease (CVD), and diabetes mellitus (DM), and various medication classes which affect physiologic processes involved in potassium regulation, such as inhibitors of the renin-angiotensin aldosterone system (RAASi).<sup>6</sup> There is wide variation in the estimates of hyperkalemia incidence and prevalence reported in studies of CKD patients, ranging from as low as 7.7% to as high as 73%.<sup>7-10</sup> Although patients in the general population are reported to have lower risk of hyperkalemia than patients with CKD, with prevalence values ranging from 2.6% to 3.5% in Canadian and US studies, many of these studies are limited by small sample size or select populations.<sup>4,10,11</sup> There are less data on hypokalemia in general. The increasing worldwide prevalence of CKD and associated conditions compels a careful assessment of the prevalence and long-term risks associated with abnormal potassium levels in diverse international populations.<sup>12,13</sup>

Hyperkalemia and hypokalemia have been consistently associated with higher short-term all-cause mortality in observational studies.<sup>8,14-18</sup> Some, but not all, have suggested that risks

associated with hyperkalemia are greater in individuals with normal kidney function than in those with CKD.<sup>10</sup> Notwithstanding the putative role of cardiac arrhythmias in the mortality associated with hypo- and hyperkalemia,<sup>19</sup> few studies have examined the long-term association of abnormal potassium levels with CVD-associated mortality. Furthermore, the effects of abnormal serum potassium levels on outcomes in other organ systems, such as the kidneys, remain less well studied. In order to better guide clinical practice and future clinical trials, we performed a meta-analysis of the prevalence of abnormal potassium levels, risk factors of abnormal potassium levels, and long-term associations between potassium levels, all-cause mortality, CVD-associated mortality, and end stage renal disease (ESRD) in 27 large and diverse international cohorts. For the latter aim, we also evaluated whether risks varied by level of kidney function and other clinically relevant characteristics.

## **METHODS**

### **Participating cohorts**

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) has been described previously; additional information is available in Appendices 1-2.<sup>20-24</sup> Briefly, CKD-PC incorporates cohorts with at least 1,000 participants (at least 500 participants for those cohorts predominantly enrolling persons with CKD [CKD cohorts]), data on serum creatinine and albuminuria, and 50 or more events of the outcome of interest (mortality or kidney outcomes). The present study included 27 cohorts: 10 general population cohorts, 7 high-risk cohorts in terms of cardiovascular risk, and 10 CKD cohorts. Meta-analyses were restricted to participants aged  $\geq 18$  years old with an available value of potassium at baseline. This study was approved by

the institutional review board at the Johns Hopkins Bloomberg School of Public Health (Baltimore, Maryland, USA).

## **Procedures**

Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI creatinine equation.<sup>25</sup> In cohorts where the creatinine measurement was not standardized to isotope dilution mass spectrometry (IDMS), values were multiplied by 0.95 before eGFR calculation.<sup>26</sup> We defined diabetes as fasting glucose  $\geq 7.0$  mmol/L (126 mg/dL), non-fasting glucose  $\geq 11.1$  mmol/L (200 mg/dL), hemoglobin A1c  $\geq 6.5\%$ , use of glucose lowering drugs, or self-reported diabetes. Participants with a history of myocardial infarction, coronary revascularization, heart failure, or stroke were considered to have a history of CVD. Measures of albuminuria were the urine albumin-to-creatinine ratio (ACR), urine albumin excretion rate, urine protein-to-creatinine ratio, or semi-quantitative dipstick protein; urine protein-to-creatinine ratio was converted to ACR as previously described.<sup>27</sup>

The outcomes of interest were all-cause mortality, CVD-associated mortality and ESRD. We defined ESRD as initiation of renal replacement therapy.

## **Statistical analysis**

We applied a two-stage meta-analysis, with each study first analyzed individually, and followed by a random-effects meta-analysis. The overview of the analysis and analytic notes for individual studies are provided in Appendix 2 in the Supplement. We imputed missing values of covariates using cohort-specific mean values. Potassium levels, serum creatinine and albuminuria, as well as the demographic variables age, gender and race were not imputed. We quantified heterogeneity with the  $I^2$  statistic and Cochran's  $Q$  test. Since the risk of abnormal serum potassium levels and their associated outcomes might vary substantially depending on the

type of patient population, analyses were stratified by type of cohort (general population/high cardiovascular risk or CKD).

To assess the cross-sectional associations between kidney function and level of potassium, we plotted the distribution of baseline serum potassium levels within categories of eGFR using kernel density plots. Next, we modeled the risk of potassium  $>5.0$ ,  $>5.5$  and  $<3.5$  mmol/L using logistic regression, adjusting for age, race, sex, systolic blood pressure, antihypertensive drugs, total cholesterol, diabetes mellitus, body mass index, smoking, history of coronary heart disease or stroke, history of heart failure, eGFR (linear spline with knots at 30 and 60) and albuminuria (log transformed ACR, or categories of dipstick). For eGFR and ACR, the reference point was placed at eGFR 80 ml/min/1.73 m<sup>2</sup> and ACR 10 mg/g in the general population/high-risk cohorts and eGFR 50 ml/min/1.73 m<sup>2</sup> and ACR 50 mg/g in the CKD cohorts, with statistical significance at other points determined by the meta-analyzed beta coefficient and standard error. We tested whether the relationship between kidney function and abnormal potassium levels differed by subgroups of age, race, sex, and diabetes status, by including the relevant product term in the regression model, determining statistical significance by evaluating the ratio of odds ratios between subgroups at each 1 ml/min/1.73 m<sup>2</sup> and 8% increment of ACR (pointwise interaction), as done previously.<sup>20,28,29</sup> In addition, we assessed the relationship between potassium levels  $>5.5$  mmol/L and CKD stages (G1-G5 and A1-A3), with the reference placed as G2/A1 in the general population/high risk cohorts and G3b/A2 in CKD cohorts.

To assess the relationship between baseline serum potassium and subsequent adverse outcomes, we modeled the adjusted hazard ratios (HRs) of the studied outcomes as a spline function of serum potassium concentration, fitting piece-wise linear splines for serum potassium

with knots placed at 3.5, 4, 4.5, 5, and 5.5 mmol/L, and adjusting for the same set of covariates. Given the importance of kidney function on potassium homeostasis, analyses were performed overall and with interaction between potassium and eGFR strata of 60+, 30-59, and <30 ml/min/1.73 m<sup>2</sup>, albuminuria levels of <30, 30-299 and ≥300 mg/g, as well as age, race, sex, diabetes, status, RAASi use, and diuretic use, determining statistical significance for the pointwise interaction at each 0.05 mmol/L of potassium. Analyses were performed using Stata/MP 14.2 software for Windows ([www.stata.com](http://www.stata.com)). We considered *P*-values <0.05 statistically significant.

## RESULTS

There were a total of 1,217,986 participants with baseline potassium, eGFR, and albuminuria levels across 27 cohorts, followed for an average of 6.9 years (range 2.0 - 19). Average (mean ± standard deviation) age was 55±16 years, 40% were female, and 14% were black (**Table 1**). Average eGFR was 83±23 ml/min/1.73 m<sup>2</sup>, 17% had moderate to severely-increased albuminuria, and 46% were on antihypertensive medications. Angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and potassium sparing diuretics were used in 31%, 11%, and 3% of individuals at baseline, respectively. Non-steroidal anti-inflammatory drugs (NSAID) use was reported by 15% (**Table S1**).

### **Prevalence and risk factors of hyperkalemia and hypokalemia**

Overall, average baseline potassium was 4.2±0.4 mmol/L; potassium was higher with lower baseline eGFR in both the general population/high cardiovascular risk cohorts (**Figure 1**) and in the CKD cohorts (**Figure S1**). The prevalence of serum potassium >5.0 mmol/L, serum potassium >5.5 mmol/L, serum potassium <4.0 mmol/L, and serum potassium <3.5 mmol/L was

3.31% (95% CI: 3.28-3.34%), 0.49% (95% CI: 0.48-0.50%), 23.57% (95% CI: 23.49-23.64%), and 1.91% (95% CI: 1.89-1.94%) of individuals in general population/high cardiovascular risk cohorts and 17.94% (95% CI: 17.58-18.31%), 4.23% (95% CI: 4.03-4.42%), 12.61% (95% CI: 12.29-12.93%), and 2.03% (95% CI: 1.90-2.17%) of individuals in CKD cohorts. In the general population/high cardiovascular risk cohorts, risk factors for hyperkalemia included male gender, non-black race, diabetes mellitus, lower BMI, active smoking, history of coronary heart disease or stroke, lower eGFR, higher ACR, use of ACEi, ARB or potassium sparing diuretics, and non-use of thiazide or loop diuretics (**Table S2**). The relationship between eGFR and serum potassium >5.5 mmol/L was nearly linear; higher ACR was a weaker but independent risk factor at levels >37 mg/g (**Figure 2A & B**). There were no meaningful differences in the relationship between eGFR or ACR and potassium levels >5.5 mmol/L among patients with different age (<65 years, ≥65 years), gender, race (black, non-black), and presence/absence of diabetes mellitus (**Figures S2-S5**). Relationships between eGFR, ACR, and potassium >5.5 mmol/L were also similar in the CKD cohorts (**Figure S6**), as were the direction of associations with most risk factors (**Table S3**). Categorical analysis revealed that lower eGFR was associated with higher risk of potassium level >5.5 mmol/L independent of ACR levels, whereas the association between ACR and hyperkalemia was most apparent at higher levels of eGFR and null at eGFR <15 ml/min/1.73m<sup>2</sup> (**Table S4**). Similarly, in CKD cohorts, lower eGFR was a strong risk factor for potassium >5.5 mmol/L, whereas higher ACR was weak to null (**Table S5**).

Risk factors for hypokalemia in the general population/high cardiovascular risk cohorts included younger age, female gender, black race, higher systolic blood pressure, the use of thiazide or loop diuretics, lower serum cholesterol, lower BMI, and higher ACR; the use of ACEi, ARB, or potassium-sparing diuretics, the presence of diabetes mellitus, and a history of

CHD or stroke were protective (**Table S2**). The association of higher albuminuria level with the risk of hypokalemia was weak but nearly linear; the association between eGFR and potassium <3.5 mmol/L was fairly flat (**Figure 2**). Risk factor associations with potassium <3.5 mmol/L were generally consistent in direction if weaker in the CKD cohorts, with the exception of the use of RAASi medications, which was a stronger protective factor for hypokalemia <3.5 mmol/L in the CKD cohorts (**Table S3**). Neither eGFR nor ACR were significantly associated with potassium <3.5 mmol/L in CKD cohorts (**Figure S6**).

### **Outcomes associated with serum potassium level**

We observed a total of 151,153 all-cause deaths in 26 cohorts, 9,672 cardiovascular deaths in 13 cohorts, and 14,266 ESRD events in 16 cohorts during a mean follow-up period of  $6.9 \pm 4.1$  years (**Table S6**). The risk-relationship between potassium and all-cause mortality demonstrated lowest risk with serum potassium levels between 4 and 4.5 mmol/L, and higher risk outside of the 3.5-5 mmol/L range (**Figure 3A**). Compared to a reference of 4.2 mmol/L, the overall adjusted hazard ratio for all-cause mortality was 1.22 (95% CI: 1.15-1.29) at serum potassium 5.5 mmol/L and 1.49 (95% CI: 1.26-1.76) at serum potassium 3.0 mmol/L. These associations were qualitatively consistent in the individual cohorts (**Figure 4**) and there was no difference in the risk of all-cause mortality associated with potassium by level of eGFR (**Figure 3B**). Risk relationships were similarly U-shaped for cardiovascular mortality and end-stage renal disease (**Figure 3C & 3D**) with qualitative consistency in point estimates (**Figures S7 & S8**). Although confidence intervals were wide, there appeared to be no difference in potassium-cardiovascular risk relationships by level of GFR (**Figure S9A**). In contrast, higher levels of potassium had a weaker relationship with ESRD in individuals with eGFR <30 ml/min/1.73 m<sup>2</sup>

(**Figure S9B**). The associations of serum potassium with the studied outcomes were broadly similar in individuals of different sex, race, levels of albuminuria, history of diabetes mellitus, and ACEi/ARB/potassium-sparing diuretic use; however, the association between lower levels of potassium and all-cause mortality appeared slightly weaker in older individuals and those using diuretics (**Figures S10-S16**). Results were also broadly similar in CKD cohorts (**Figures S17-S25**).

## **DISCUSSION**

In this international meta-analysis of 1,215,347 participants in 26 diverse cohorts, we describe the prevalence, risk factors and long-term outcomes associated with abnormal potassium concentrations. Hyperkalemia and hypokalemia were relatively infrequent in the studied populations, especially in participants with normal kidney function. Lower eGFR was a strong risk factor for hyperkalemia but not hypokalemia; higher albuminuria was a relatively weak risk factor for both. Both hyper- and hypokalemia were associated with significantly higher long-term risk of all-cause and CV mortality, and of ESRD. Ideal outcomes were observed with serum potassium concentrations of 4-4.5 mmol/L. While abnormal potassium levels were more common in individuals with lower estimated GFR and higher albuminuria levels, the relative risks associated with hyperkalemia and hypokalemia were similar in patients with various levels of kidney function, and in various subgroups divided by age, gender, race, diabetes mellitus or treatment with ACEi or ARB.

Abnormal potassium homeostasis is often mediated by a combination of conditions affecting potassium intake, distribution and excretion, including demographic characteristics, comorbidities and various medications.<sup>6,30</sup> Our results confirm the diversity of the risk factors

determining hyper- and hypokalemia (including comorbidities such as CHF and DM,<sup>3</sup> and therapeutic interventions like diuretic use and RAAS inhibitors<sup>31</sup>), and emphasize the central role played by the kidneys in potassium homeostasis. Similar to our findings, previous studies have found a low prevalence of hyperkalemia in patients with normal kidney function, and markedly elevated frequencies in various cohorts with CKD, especially in patients with diabetes mellitus, in those with more advanced stages of CKD<sup>7,8,10</sup> and in kidney transplant recipients.<sup>9</sup> As opposed to the widely accepted role of lower eGFR as a risk factor for hyperkalemia, the role of albuminuria in engendering this condition has not been previously studied. Our results suggest that patients with higher levels of albuminuria had a higher prevalence of both hyperkalemia and hypokalemia, although the magnitude of this association was smaller than the relationship between eGFR and potassium abnormalities, at least for hyperkalemia. This finding has important practical relevance, since patients with higher levels of albuminuria often benefit from therapy with RAAS inhibitor medications to slow progression of CKD,<sup>32-37</sup> but which also increase the risk of hyperkalemia.<sup>31,38,39</sup> A secondary analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study showed that hyperkalemia after losartan therapy attenuated the renoprotective effect of losartan, suggesting that prevention of hyperkalemia might allow for enhanced renoprotection by RAAS inhibitors.<sup>40</sup> Current clinical guidelines recommend concerted efforts to resume RAAS inhibitor therapy in patients with CHF, even after episodes of severe hyperkalemia (>6 mEq/l), once the hyperkalemia was treated and precautions are taken to monitor serum potassium.<sup>31</sup> Recent clinical trials suggest that the use of potassium binder medications may allow the use of RAAS inhibitors in patients prone to hyperkalemia,<sup>41-45</sup> although the long term benefit of such strategies on clinical outcomes is yet to be demonstrated.<sup>46</sup>

While the prevalence of serum potassium  $<3.5$  was relatively low, milder forms of hypokalemia were very common, especially in general population/high cardiovascular risk cohorts. Even mild hypokalemic episodes are clinically relevant in patients at high risk for ventricular arrhythmias and sudden cardiac death, such as patients with CHF or DM.<sup>3,31,47</sup> Correction of hypokalemia is relatively easy with dietary or medicinal measures,<sup>48</sup> and it is recommended as part of strategies to prevent these complications.<sup>3</sup>

The U-shaped association of serum potassium levels with clinical outcomes described in this study confirm findings from previous studies indicating similar associations with all-cause mortality,<sup>8,10,14-18</sup> and extends them to an outpatient, large and diverse international population. The association between hypo- and hyperkalemia and mortality could be explained by the induction of malignant arrhythmias<sup>3,19</sup> and their consequences, such as hypotension, myocardial ischemia and sudden cardiac death.<sup>3,17</sup> In addition, hypokalemia and low dietary potassium intake is also associated with hypertension and consequent cardiovascular outcomes such as strokes.<sup>48</sup> This hypothesis is also supported by the association of hypo- and hyperkalemia with cardiovascular mortality in our study. It is perhaps not surprising to see an association of serum potassium levels with ESRD, which has been inconsistently detected previously in smaller cohort studies.<sup>8,40,49,50</sup> Hyperkalaemia that is resistant to treatment is an indication of dialysis start and patients who require very high diuretic doses due to volume overload may have lower potassium levels and may be started earlier on dialysis. In addition to its link with hypertension, hypokalemia is also a risk factor for tubulointerstitial fibrosis and renal cyst formation,<sup>51-54</sup> thus contributing to the development and progression of CKD. Conversely, hyperkalemia may be a surrogate marker of more severe CKD. Further studies are needed to determine if correction of hypo- and hyperkalemia could result in improved renal outcomes.

Our study is notable for its large size, international representation and diverse patient population. Despite its advantages, this study also has limitations. Variation in design across cohorts introduces heterogeneity and prevents using time-updated potassium levels, but our consistent results across diverse cohorts suggest the robust and empirical long-term association of a single measurement, relevant to clinical practice. Our results were driven largely by findings from general population cohorts, with high cardiovascular risk and CKD cohorts contributing relatively fewer participants. However, the causes and consequences of abnormal serum potassium have been least studied in the general population, hence our emphasis on this segment fills an important void. We adjusted for many confounders, but the effect of unmeasured confounders (e.g. serum calcium, magnesium and blood pH levels) cannot be ruled out. We could not limit the studied medications (e.g. RAAS inhibitors) to new prescriptions, which may explain their lack of association with outcomes.

## **Conclusions**

The risk factors of abnormal potassium values are diverse, and include low estimated GFR, albuminuria, the use of various medications and comorbid conditions such as diabetes mellitus. The incorporation of these findings in clinical prediction tools in future studies could enhance our ability to risk-stratify patients and to proactively manage hypo- and hyperkalemia. Hypo- and hyperkalemia are independently associated with significantly higher all-cause and CV mortality, and with higher risk of ESRD, with the best outcomes seen with serum potassium levels of 4-4.5 mmol/L. Future research is needed, preferably in the form of a randomized controlled clinical trial, to determine if correction of abnormal serum potassium levels can result in improvement in mortality and delay onset of dialysis.

**Contributors:**

CPK, KM, JC, SH, VS, and MEG conceived of the study concept and design. KM, JC, MEG and the CKD-PC investigators/collaborators listed below acquired the data. YS and the Data Coordinating Center members listed below analyzed the data. All authors took part in the interpretation of the data. CPK, KM, YS, and MEG drafted the manuscript, and all authors provided critical revisions of the manuscript for important intellectual content. All collaborators shared data and were given the opportunity to comment on the manuscript. JC obtained funding for CKD-PC and individual cohort and collaborator support is listed in appendix 3 in the Supplement.

**Funding:** The CKD-PC Data Coordinating Center is funded in part by a program grant from the US National Kidney Foundation (NKF funding sources include Relypsa) and the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK100446-01). A variety of sources have supported enrollment and data collection including laboratory measurements, and follow-up in the collaborating cohorts of the CKD-PC. These funding sources include government agencies such as National Institutes of Health and medical research councils as well as foundations and industry sponsors listed in appendix 3 in the supplement. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## **Acknowledgements**

**CKD-PC investigators/collaborators** (study acronyms/abbreviations are listed in appendix 2 in the Supplement):

**AASK:** Brad Astor, Larry Appel, Tom Greene, Teresa Chen; **ADVANCE:** John Chalmers, Mark Woodward, Hisatomi Arima, Vlado Perkovic; **BC CKD:** Adeera Levin, Ognjenka Djurdjev; **Beijing:** Luxia Zhang, Lisheng Liu, Minghui Zhao, Fang Wang, Jinwei Wang; **CanPREDDICT:** Adeera Levin, Ognjenka Djurdjev, Mila Tang; **CIRCS:** Hiroyasu Iso, Kazumasa Yamagishi, Mitsumasa Umesawa, Isao Muraki; **CKD-JAC:** Masafumi Fukagawa, Shoichi Maruyama, Takayuki Hamano, Takeshi Hasegawa, Naohiko Fujii; **CRIB:** David Wheeler, John Emberson, John Townend, Martin Landray; **Geisinger:** Jamie Green, H Lester Kirchner, Alex R Chang; **Gubbio:** Massimo Cirillo; **KHS:** Sun Ha Jee, Heejin Kimm, Yejin Mok; **Maccabi:** Gabriel Chodick, Varda Shalev; **MASTERPLAN:** Jack F. M. Wetzels, Peter J

Blankestijn, Arjan D van Zuilen, M Bots; **MDRD:** Mark Sarnak, Lesley Inker; **MRC:** Dorothea Nitsch, Paul Roderick, Astrid Fletcher; **Mt Sinai BioMe:** Erwin Bottinger, Girish N Nadkarni, Stephen B Ellis, Rajiv Nadukuru; **NHANES:** Yingying Sang; **PSP-CKD:** Nigel Brunskill, Rupert Major, David Shepherd, James Medcalf; **PREVEND:** Ron T Gansevoort, Stephan JL Bakker, Hiddo J Lambers Heerspink; **Rancho Bernardo:** Simerjot K Jassal, Jaclyn Bergstrom, Joachim H Ix, Elizabeth Barrett-Connor; **RCAV:** Csaba Kovesdy, Kamyar Kalantar-Zadeh; **RENAAL:** Hiddo J Lambers Heerspink, Dick de Zeeuw, Barry Brenner; **SCREAM:** Juan J Carrero, Alessandro Gasparini, Carl-Gustaf Elinder, Peter Barany; **SRR-CKD:** Marie Evans, Mårten Segelmark, Maria Stendahl, Staffan Schön; **Sunnybrook:** Navdeep Tangri, Maneesh Sud, David Naimark; **Taiwan MJ:** Chi-Pang Wen, Chwen-Keng Tsao, Min-Kugng Tsai, Chien-Hua Chen; **Takahata:** Tsuneo Konta, Atsushi Hirayama, Kazunobu Ichikawa; **ZODIAC:** Henk J.G. Bilo, Gijs W.D. Landman, Kornelis J.J. van Hateren, Nanne Kleefstra

**CKD-PC Steering Committee:** Josef Coresh (Chair), Ron T Gansevoort, Morgan E. Grams, Stein Hallan, Csaba P Kovesdy, Andrew S Levey, Kunihiro Matsushita, Varda Shalev, Mark Woodward

**CKD-PC Data Coordinating Center:** Shoshana H Ballew (Assistant Project Director), Jingsha Chen (Programmer), Josef Coresh (Principal Investigator), Morgan E Grams (Director of Nephrology Initiatives), Lucia Kwak (Programmer), Kunihiro Matsushita (Director), Yingying Sang (Lead Programmer), Mark Woodward (Senior Statistician)

Some of the data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government.

**Conflict of Interest Disclosures:** All authors will complete and submit the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Kovesdy reports grants from NIH, during the conduct of the study; personal fees from Astra Zeneca, personal fees from Relypsa, personal fees from ZS Pharma outside the submitted work. Dr. Matsushita reports grants and personal fees from Kyowa Hakko Kirin outside the submitted work. Dr. Brunskill reports grants from UK National Institute for Health Research during the conduct of the study; grants from Baxter Healthcare outside the submitted work. Dr. Carrero reports grants from AstraZeneca and grants from ViforPharma outside the submitted work. Dr. Hasegawa reports grants from JSPS KAKENHI and personal fees from Kyowa Hakko Kirin outside the submitted work. Dr. L Heerspink reports other support from Abbvie, grants and other support from AstraZeneca, other support from Astellas, grants and other support from Boehringer Ingelheim, grants and other support from Janssen, other support from Fresenius, and other support from Merck outside the submitted work. Dr. Wheeler reports grants and personal fees from AstraZeneca, and personal fees from Vifor Fresenius outside the submitted work. Dr. Coresh reports grants from NIH and grants from NKF during the conduct of the study; grants from NIH and grants from NKF outside the submitted work; In addition, Dr. Coresh has a patent PCT/US2015/044567 Provisional patent [Coresh, Inker and Levey] filed 8/15/2014 -- Precise estimation of glomerular filtration rate from multiple biomarkers issued.

Ms. Sang and Drs. Chodick, Hirayama, Landman, Levin, Nitsch, Hallan, Shalev, and Grams  
have nothing to disclose.

## References

1. Dittrich KL, Walls RM. Hyperkalemia: ECG manifestations and clinical considerations. *J Emerg Med* 1986;**4**:449-55.
2. Parham WA, Mehdiraz AA, Biermann KM, Fredman CS. Hyperkalemia revisited. *Tex Heart Inst J* 2006;**33**:40-7.
3. Priori SG, Blomstrom-Lundqvist C. 2015 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *Eur Heart J* 2015;**36**:2757-9.
4. Drawz PE, Babineau DC, Rahman M. Metabolic complications in elderly adults with chronic kidney disease. *J Am Geriatr Soc* 2012;**60**:310-5.
5. Bourgoignie JJ, Kaplan M, Pincus J, Gavellas G, Rabinovitch A. Renal handling of potassium in dogs with chronic renal insufficiency. *Kidney Int* 1981;**20**:482-490.
6. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. *Nat Rev Nephrol* 2014;**10**:653-62.
7. Sarafidis PA, Blacklock R, Wood E, Rumjon A, Simmonds S, Fletcher-Rogers J, Ariyanayagam R, Al-Yassin A, Sharpe C, Vinen K. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin J Am Soc Nephrol* 2012;**7**:1234-41.
8. Hayes J, Kalantar-Zadeh K, Lu JL, Turban S, Anderson JE, Kovesdy CP. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. *Nephron Clin Pract* 2012;**120**:c8-16.
9. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 2004;**351**:585-92.
10. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL, Weir MR, Fink JC. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;**169**:1156-62.
11. Fleet JL, Shariff SZ, Gandhi S, Weir MA, Jain AK, Garg AX. Validity of the International Classification of Diseases 10th revision code for hyperkalaemia in elderly patients at presentation to an emergency department and at hospital admission. *BMJ Open* 2012;**2**.
12. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;**298**:2038-47.
13. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, Chen J, He J. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 2015;**88**:950-7.
14. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 1990;**15**:458-82.
15. Iseki K, Uehara H, Nishime K, Tokuyama K, Yoshihara K, Kinjo K, Shiohira Y, Fukiyama K. Impact of the initial levels of laboratory variables on survival in chronic dialysis patients. *Am J Kidney Dis* 1996;**28**:541-8.
16. Kovesdy CP, Regidor DL, Mehrotra R, Jing J, McAllister CJ, Greenland S, Kopple JD, Kalantar-Zadeh K. Serum and dialysate potassium concentrations and survival in hemodialysis patients. *Clin J Am Soc Nephrol* 2007;**2**:999-1007.

17. Goyal A, Spertus JA, Gosch K, Venkitachalam L, Jones PG, Van den Berghe G, Kosiborod M. Serum potassium levels and mortality in acute myocardial infarction. *JAMA* 2012;**307**:157-64.
18. Korgaonkar S, Tilea A, Gillespie BW, Kiser M, Eisele G, Finkelstein F, Kotanko P, Pitt B, Saran R. Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. *Clin J Am Soc Nephrol* 2010;**5**:762-9.
19. Epstein FH. Signs and symptoms of electrolyte disorders. In: Maxwell MH, Kleeman CR, (eds). *Clinical disorders of fluid and electrolyte metabolism*. 3rd ed. New York: McGraw-Hill; 1980, 499-516.
20. Grams ME, Sang Y, Ballew SH, Gansevoort RT, Kimm H, Kovesdy CP, Naimark D, Oien C, Smith DH, Coresh J, Sarnak MJ, Stengel B, Tonelli M, CKD Prognosis Consortium. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Age, Race, and Sex With Acute Kidney Injury. *Am J Kidney Dis* 2015;**66**:591-601.
21. Grams ME, Sang Y, Levey AS, Matsushita K, Ballew S, Chang AR, Chow EK, Kasiske BL, Kovesdy CP, Nadkarni GN, Shalev V, Segev DL, Coresh J, Lentine KL, Garg AX, Chronic Kidney Disease Prognosis Consortium. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. *N Engl J Med* 2016;**374**:411-21.
22. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, Chodick G, Collins AJ, Djurdjev O, Elley CR, Evans M, Garg AX, Hallan SI, Inker LA, Ito S, Jee SH, Kovesdy CP, Kronenberg F, Heerspink HJ, Marks A, Nadkarni GN, Navaneethan SD, Nelson RG, Titze S, Sarnak MJ, Stengel B, Woodward M, Iseki K. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. *JAMA* 2016;**315**:164-74.
23. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, Arima H, Chadban SJ, Cirillo M, Djurdjev O, Green JA, Heine GH, Inker LA, Irie F, Ishani A, Ix JH, Kovesdy CP, Marks A, Ohkubo T, Shalev V, Shankar A, Wen CP, de Jong PE, Iseki K, Stengel B, Gansevoort RT, Levey AS, CKD Prognosis Consortium. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 2014;**311**:2518-31.
24. Kovesdy CP, Coresh J, Ballew SH, Woodward M, Levin A, Naimark DM, Nally J, Rothenbacher D, Stengel B, Iseki K, Matsushita K, Levey AS, CKD Prognosis Consortium. Past Decline Versus Current eGFR and Subsequent ESRD Risk. *J Am Soc Nephrol* 2016;**27**:2447-55.
25. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604-12.
26. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F, Collaboration fCKDE. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. *Clin Chem* 2007;**53**:766-772.
27. Miller WG, Bruns DE, Hortin GL, Sandberg S, Aakre KM, McQueen MJ, Itoh Y, Lieske JC, Secombe DW, Jones G, Bunk DM, Curhan GC, Narva AS. Current issues in measurement and reporting of urinary albumin excretion. *Clin Chem* 2009;**55**:24-38.
28. James MT, Grams ME, Woodward M, Elley CR, Green JA, Wheeler DC, de Jong P, Gansevoort RT, Levey AS, Warnock DG, Sarnak MJ, CKD Prognosis Consortium. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Diabetes Mellitus, and Hypertension With Acute Kidney Injury. *Am J Kidney Dis* 2015;**66**:602-12.
29. Hallan SI, Matsushita K, Sang Y, Mahmoodi BK, Black C, Ishani A, Kleefstra N, Naimark D, Roderick P, Tonelli M, Wetzels JF, Astor BC, Gansevoort RT, Levin A, Wen CP,

- Coresh J. Age and Association of Kidney Measures With Mortality and End-stage Renal Disease. *JAMA* 2012;**308**:2349-2360.
30. Kovesdy CP. Updates in hyperkalemia: Outcomes and therapeutic strategies. *Rev Endocr Metab Disord* 2016.
31. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891-975.
32. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861-9.
33. Iino Y, Hayashi M, Kawamura T, Shiigai T, Tomino Y, Yamada K, Kitajima T, Ideura T, Koyama A, Sugisaki T, Suzuki H, Umemura S, Kawaguchii Y, Uchida S, Kuwahara M, Yamazaki T, Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients Study I. Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension--a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. *Hypertens Res* 2004;**27**:21-30.
34. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;**329**:1456-62.
35. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, Ponticelli C, Ritz E, Zucchelli P. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 1996;**334**:939-45.
36. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 1997;**349**:1857-63.
37. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, Jiang JP, Liang M, Wang GB, Liu ZR, Geng RW. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006;**354**:131-40.
38. Bozkurt B, Agoston I, Knowlton AA. Complications of inappropriate use of spironolactone in heart failure: when an old medicine spirals out of new guidelines. *J Am Coll Cardiol* 2003;**41**:211-4.
39. Shah KB, Rao K, Sawyer R, Gottlieb SS. The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. *J Am Coll Cardiol* 2005;**46**:845-9.
40. Miao Y, Dobre D, Heerspink HJ, Brenner BM, Cooper ME, Parving HH, Shahinfar S, Grobbee D, de Zeeuw D. Increased serum potassium affects renal outcomes: a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. *Diabetologia* 2011;**54**:44-50.

41. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ, Investigators P-H. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* 2011;**32**:820-8.
42. Buysse JM, Huang IZ, Pitt B. PEARL-HF: prevention of hyperkalemia in patients with heart failure using a novel polymeric potassium binder, RLY5016. *Future Cardiol* 2012;**8**:17-28.
43. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittes J, Christ-Schmidt H, Berman L, Pitt B, Investigators O-H. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015;**372**:211-21.
44. Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, Roger SD, Yang A, Lerma E, Singh B. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA* 2014;**312**:2223-33.
45. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, Qunibi W, Pergola P, Singh B. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med* 2015;**372**:222-31.
46. Kovesdy CP. Management of Hyperkalemia: An Update for the Internist. *Am J Med* 2015;**128**:1281-7.
47. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, De Backer G, Sirnes PA, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Baumgartner H, Betteridge J, Ceriello A, Fagard R, Funck-Brentano C, Gulba DC, Hasdai D, Hoes AW, Kjekshus JK, Knuuti J, Kolh P, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Ponikowski P, Reiner Z, Sattar N, Schachinger V, Scheen A, Schirmer H, Stromberg A, Sudzhaeva S, Tamargo JL, Viigimaa M, Vlachopoulos C, Xuereb RG. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;**34**:3035-87.
48. Kovesdy CP, Appel LJ, Grams ME, Gutkunst L, McCullough PA, Palmer BF, Pitt B, Sica DA, Townsend RR. Potassium Homeostasis in Health and Disease: A Scientific Workshop Cosponsored by the National Kidney Foundation and the American Society of Hypertension. *Am J Kidney Dis* 2017.
49. Nakhoul GN, Huang H, Arrigain S, Jolly SE, Schold JD, Nally JV, Jr., Navaneethan SD. Serum Potassium, End-Stage Renal Disease and Mortality in Chronic Kidney Disease. *Am J Nephrol* 2015;**41**:456-63.
50. Heerspink HJ, Gao P, de Zeeuw D, Clase C, Dagenais GR, Sleight P, Lonn E, Teo KT, Yusuf S, Mann JF. The effect of ramipril and telmisartan on serum potassium and its association with cardiovascular and renal events: results from the ONTARGET trial. *Eur J Prev Cardiol* 2014;**21**:299-309.
51. Cremer W, Bock KD. Symptoms and course of chronic hypokalemic nephropathy in man. *Clin Nephrol* 1977;**7**:112-9.

52. Elger M, Bankir L, Kriz W. Morphometric analysis of kidney hypertrophy in rats after chronic potassium depletion. *Am J Physiol* 1992;**262**:F656-67.
53. Riemenschneider T, Bohle A. Morphologic aspects of low-potassium and low-sodium nephropathy. *Clin Nephrol* 1983;**19**:271-9.
54. Torres VE, Young WF, Jr., Offord KP, Hattery RR. Association of hypokalemia, aldosteronism, and renal cysts. *N Engl J Med* 1990;**322**:345-51.

### **Figure Titles and Legends:**

**Figure 1.** Distribution of serum potassium concentrations, overall and by baseline estimated glomerular filtration rate in general population and high cardiovascular risk cohorts.

**Figure 2.** Continuous association of estimated GFR (panel A) and albuminuria (Panel B) with the risk of serum potassium level  $>5.5$  mmol/L, and of estimated GFR (panel C) and albuminuria (Panel D) with the risk of serum potassium level  $<3.5$  mmol/L, in general population and high cardiovascular risk cohorts. Black dots indicate statistical significance compared with the reference (diamond) estimated GFR of  $80$  ml/min/ $1.73\text{m}^2$  (panels A and C) and albuminuria of  $10$  mg/g (panels B and D). Adjusted for age, gender, race, systolic blood pressure, antihypertensive drugs, total cholesterol, diabetes, body mass index, smoking, history of coronary heart disease or stroke, history of heart failure.

**Figure 3.** Adjusted hazard ratio of all-cause mortality, cardiovascular mortality and end stage renal disease associated with serum potassium concentration in general population and high cardiovascular risk cohorts. Black dots indicate statistical significance compared with the reference (diamond) serum potassium of  $4.2$  mmol/L. Models adjusted for age, gender, race, systolic blood pressure, antihypertensive drugs, total cholesterol, diabetes, body mass index, smoking, eGFR, albuminuria, history of coronary heart disease or stroke, history of heart failure.

**Figure 4.** Adjusted relative hazard of all-cause mortality for potassium of 3.0 mmol/L (A) and 5.5 mmol/L (B), compared to a potassium of 4.2 mmol/L in individual general population/high risk cohorts