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CLINICAL RESEARCH
Prevention and epidemiology

Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis

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Aims Both hypo- and hyperkalaemia can have immediate deleterious physiological effects, and 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 and results We performed an individual-level data meta-analysis of 27 international cohorts [10 general population, 7 high cardiovascular risk, and 10 chronic kidney disease (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 estimated glomerular filtration rate (eGFR) and albuminuria. We included 1 217 986 participants followed up for a mean of 6.9 years. The average age was 55 ± 16 years, average eGFR was 83 ± 23 mL/min/1.73 m^2, and 17% had moderate- to-severe increased albuminuria levels. The mean baseline potassium was 4.2 ± 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 of 4–4.5 mmol/L. Compared with a reference of 4.2 mmol/L, the adjusted hazard ratio for all-cause mortality was 1.22 [95% confidence interval (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.

Keywords Potassium • Estimated glomerular filtration rate • Albuminuria • End-stage renal disease • Mortality

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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 hyperkalaemia and hypokalaemia resulting in electrophysiological 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.[1–3]

The kidneys play a central role in potassium homeostasis, with chronic kidney disease (CKD) being an especially prominent risk factor for hyperkalaemia.[4,5] Other risk factors for hyperkalaemia 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 that affect physiological processes involved in potassium regulation, such as inhibitors of the renin–angiotensin–aldosterone system (RAASi).[6] There is wide variation in the estimates of hyperkalaemia incidence and prevalence reported in studies of CKD patients, ranging from as low as 7.7% to as high as 73%.[7–10] Although patients in the general population are reported to have lower risk of hyperkalaemia 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.[4,10,11] There are less data on hypokalaemia 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.[12,13]

Hyperkalaemia and hypokalaemia have been consistently associated with higher short-term all-cause mortality in observational studies.[8,14–18] Some, but not all, have suggested that risks associated with hyperkalaemia are greater in individuals with normal kidney function than in those with CKD.[10] Notwithstanding the putative role of cardiac arrhythmias in the mortality associated with hypo- and hyperkalaemia,[19] 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. 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 the 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 Supplementary material online, *Appendices S1 and S2*.[20–24] Briefly, CKD-PC incorporates cohorts with at least 1000 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 (CV) risk, and 10 CKD cohorts. Meta-analyses were restricted to participants aged ≥18 years 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, MD, USA).

Procedures

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease–Epidemiology Collaboration (CKD–EPI) creatinine equation.[25] In cohorts where the creatinine measurement was not standardized to isotope dilution mass spectrometry, values were multiplied by 0.95 before eGFR calculation.[26] We defined diabetes as fasting glucose ≥7.0 mmol/L (126 mg/dL), non-fasting glucose ≥11.1 mmol/L (200 mg/dL), haemoglobin A1c ≥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.[27]

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 analysed individually, followed by a random-effects meta-analysis. The overview of the analysis and analytic notes for individual studies are provided in Supplementary material, *Appendix S2*. 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. Because 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 the type of cohort (general population/high CV 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 modelled the risk of potassium >5.0, >5.5, and <3.5 mmol/L using logistic regression, adjusting for age, race, gender, 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 of 80 mL/min/1.73 m^2 and ACR of 10 mg/g in the general population/high CV risk cohorts and eGFR of 50 mL/min/1.73 m^2 and ACR of 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, gender, 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^2 and 8% increment of ACR (pointwise interaction), as done previously.[20,28,29] 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 CV risk cohorts and G3b/A2 in the CKD cohorts.

To assess the relationship between baseline serum potassium and subsequent adverse outcomes, we modelled the adjusted hazard ratios (HRs) of the studied outcomes as a spline function of serum potassium concentration, fitting piecewise 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^2; albuminuria levels of <30, 30–299, and ≥300 mg/g as well as age, race, gender, 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). We considered *P*-values <0.05 as statistically significant.

Results

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

Prevalence and risk factors of hyperkalaemia and hypokalaemia

Overall, the average baseline potassium was 4.2 ± 0.4 mmol/L; potassium was higher with lower baseline eGFR in both the general population/high CV risk cohorts (*Figure 1*) and the CKD cohorts (Supplementary material online, *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% confidence interval (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 CV 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 the CKD cohorts. In the general population/high CV risk cohorts, risk factors for hyperkalaemia included male gender, non-Black race, DM, lower body mass index (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 (Supplementary material online, *Table S2*). The relationship between eGFR and serum potassium >5.5 mmol/L was nearly linear; higher ACR was a weaker but an independent risk factor at levels >37 mg/g (*Figure 2A* and *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 and ≥65 years), gender, race (Black and non-Black), and presence/absence of DM (Supplementary material online, *Figures S2*). Relationships between eGFR, ACR, and potassium >5.5 mmol/L were also similar in the CKD cohorts (Supplementary material online, *Figure S6*), as were the direction of associations with most risk factors (Supplementary material online, *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 hyperkalaemia was most apparent at higher levels of eGFR and null at eGFR <15 mL/min/1.73 m^2 (Supplementary material online, *Table S4*). Similarly, in the CKD cohorts, lower eGFR was a strong risk factor for potassium >5.5 mmol/L, whereas higher ACR was weak to null (Supplementary material online, *Table S5*).

Risk factors for hypokalaemia in the general population/high CV 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 DM; and a history of CHD or stroke were protective (Supplementary material online, *Table S2*). The association of higher albuminuria level with the risk of hypokalaemia 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 hypokalaemia <3.5 mmol/L in the CKD cohorts (Supplementary material online, *Table S3*). Neither eGFR nor ACR were significantly associated with potassium <3.5 mmol/L in the CKD cohorts (Supplementary material online, *Figure S6*).

Outcomes associated with serum potassium level

We observed a total of 151 153 all-cause deaths in 26 cohorts, 9672 CV deaths in 13 cohorts, and 14 266 ESRD events in 16 cohorts during a mean follow-up period of 6.9 ± 4.1 years (Supplementary material online, *Table S6*). The risk relationship between potassium and all-cause mortality demonstrated lowest risk with serum potassium levels between 4 mmol/L and 4.5 mmol/L and higher risk outside of the 3.5–5 mmol/L range (*Figure 3A*). Compared with a reference of 4.2 mmol/L, the overall adjusted HR 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 CV mortality and end-stage renal disease (*Figure 3C* and *D*) with qualitative consistency in point estimates (Supplementary material online, , *Figures S7* and *S8*). Although confidence intervals were wide, there appeared to be no difference in potassium–CV risk relationships by the level of eGFR (Supplementary material online, *Figure S9A*). In contrast, higher levels of potassium had a weaker relationship with ESRD in individuals with eGFR <30 mL/min/1.73 m^2 (Supplementary material online, *Figure S9B*). The associations of serum potassium with the studied outcomes were broadly similar in individuals of different gender, race, levels of albuminuria, history of DM, 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 (Supplementary material online, *Figures S10–S16*). Results were also broadly similar in the CKD cohorts (Supplementary material online, *Figures S17–S25*).

Table 1 **Baseline characteristics**

Study	Region	*n*	Potassium (mmol/L)	eGFR, (mL/min/1.73 m^2)	Albuminuria >30 mg/g[a]	Age (years)	% Female	% Blacks	% DM	% History of CHD and/or stroke	% History of HF	% Current smoker	% HTN	SBP (mmHg)	DBP (mmHg)	BMI (kg/m^2)	Chol (mmol/L)
General population																	
Beijing	China	1528	4.5 (0.5)	83 (14)	87 (6%)	60 (10)	772 (51%)	0 (0%)	420 (29%)	281 (18%)	—	360 (24%)	682 (45%)	125 (18)	77 (10)	25 (3)	5.3 (1.1)
CIRCS	Japan	8034	4.2 (0.4)	89 (15)	216 (3%)	54 (9)	4990 (62%)	0 (0%)	96 (1%)	88 (1%)	—	2010 (25%)	2630 (33%)	130 (18)	79 (11)	23 (3)	5.1 (0.9)
Gubbio	Italy	1683	4.2 (0.4)	84 (12)	70 (4%)	54 (6)	933 (55%)	0 (0%)	90 (5%)	164 (10%)	34 (2%)	524 (31%)	663 (39%)	130 (18)	78 (10)	28 (4)	5.9 (1.0)
KHS	South Korea	111532	4.2 (0.3)	86 (15)	4248 (4%)	46 (10)	41692 (37%)	0 (0%)	7208 (6%)	3219 (3%)	—	38734 (35%)	29159 (26%)	122 (18)	75 (12)	24 (3)	5.0 (0.9)
MRC	UK	11840	4.4 (0.6)	57 (15)	892 (8%)	81 (5)	7221 (61%)	0 (0%)	917 (8%)	2058 (18%)	2 (100%)	1343 (11%)	4006 (34%)	149 (22)	74 (13)	26 (4)	—
NHANES	USA	46526	4.0 (0.3)	97 (25)	5543 (12%)	47 (20)	24212 (52%)	10365 (22%)	5336 (11%)	4094 (9%)	1366 (3%)	8318 (19%)	15937 (35%)	124 (20)	71 (13)	28 (6)	5.2 (1.1)
PREVEND	Netherlands	7319	4.4 (0.7)	96 (16)	750 (10%)	50 (13)	3768 (51%)	66 (1%)	263 (4%)	397 (5%)	19 (0%)	2440 (33%)	2443 (34%)	129 (20)	74 (10)	26 (4)	5.6 (1.1)
Rancho Bernardo	USA	1481	4.3 (0.4)	66 (16)	217 (15%)	71 (12)	884 (60%)	1 (0%)	212 (14%)	206 (14%)	50 (3%)	115 (8%)	749 (51%)	135 (22)	76 (10)	26 (4)	5.5 (1.0)
Taiwan MJ	Taiwan	140488	4.1 (0.3)	86 (18)	3763 (3%)	44 (15)	73278 (52%)	0 (0%)	8053 (6%)	5331 (5%)	—	24904 (26%)	29211 (21%)	122 (21)	74 (12)	23 (4)	5.0 (1.0)
Takahata	Japan	1923	4.3 (0.4)	97 (12)	250 (13%)	64 (10)	1064 (55%)	0 (0%)	176 (9%)	131 (7%)	—	307 (16%)	1111 (58%)	134 (16)	79 (10)	23 (3)	5.2 (0.8)
Subtotal		332 354	4.1 (0.4)	87 (19)	16 036 (5%)	47 (15)	158 814 (48%)	10 432 (19%)	22 771 (7%)	15 353 (5%)	1471 (3%)	79 055 (28%)	86 591 (26%)	124 (21)	74 (12)	24 (4)	5.1 (1.0)
High CV risk cohorts																	
ADVANCE	Multi	11 003	4.4 (0.5)	78 (17)	3400 (31%)	66 (6)	4681 (43%)	38 (0%)	11 003 (100%)	3099 (28%)	352 (3%)	—	9088 (83%)	145 (21)	80 (11)	28 (5)	5.2 (1.2)
Geisinger	USA	67023	4.3 (0.4)	80 (26)	23 507 (35%)	61 (15)	34798 (52%)	1600 (2%)	43 177 (64%)	17 076 (25%)	5487 (8%)	9960 (15%)	50 350 (75%)	131 (18)	75 (11)	33 (8)	4.8 (1.1)
Maccabi	Israel	254 379	4.4 (0.4)	86 (21)	40 885 (16%)	58 (14)	125 220 (49%)	0	90 676 (36%)	38 332 (15%)	5989 (2%)	5695 (2%)	140 464 (55%)	131 (18)	78 (10)	30 (12)	4.9 (1.1)
Mt Sinai BioMe	USA	8393	4.3 (0.6)	73 (28)	2043 (24%)	56 (14)	4810 (57%)	2773 (33%)	4244 (51%)	830 (10%)	1000 (12%)	1374 (18%)	6156 (73%)	132 (20)	77 (12)	31 (8)	4.8 (1.2)
RCAV	USA	277 226	4.3 (0.4)	77 (17)	746 27 (27%)	64 (11)	9213 (3%)	45 078 (16%)	218 374 (79%)	93 440 (34%)	18 581 (7%)	—	225 997 (82%)	133 (17)	75 (11)	32 (6)	4.4 (1.1)
SCREAM	Sweden	224 285	4.1 (0.4)	91 (24)	24 005 (11%)	49 (17)	123 720 (55%)	0	29 690 (13%)	23 711 (11%)	12 300 (5%)	—	49 250 (22%)	—	—	—	5.2 (1.1)
ZODIAC	Netherlands	1153	4.4 (0.4)	68 (17)	92 (8%)	67 (12)	632 (55%)	0	1153 (100%)	408 (35%)	—	217 (19%)	876 (76%)	152 (24)	83 (11)	29 (5)	5.5 (1.1)
Subtotal		843 462	4.3 (0.4)	84 (22)	168 559 (20%)	58 (15)	303 074 (36%)	49 489 (14%)	408 469 (48%)	176 233 (21%)	43 709 (5%)	17 246 (5%)	543 172 (64%)	132 (18)	76 (11)	31 (9)	4.8 (1.2)
CKD cohorts																	
AASK	USA	1081	4.2 (0.6)	46 (16)	591 (55%)	55 (11)	420 (39%)	1081 (100%)	0	535 (49%)	32 (3%)	317 (29%)	1081 (100%)	143 (22)	88 (14)	31 (7)	5.5 (1.2)
BC CKD	Canada	11 990	4.6 (0.6)	34 (17)	8660 (72%)	69 (14)	5473 (46%)	50 (0%)	7315 (61%)	3592 (30%)	1564 (13%)	635 (11%)	10 149 (85%)	137 (23)	73 (13)	28 (6)	4.6 (1.3)
CanPREDDICT	Canada	2017	4.6 (0.6)	27 (9)	1487 (74%)	68 (13)	755 (37%)	32 (2%)	1010 (50%)	640 (32%)	269 (13%)	—	1973 (98%)	134 (20)	71 (12)	30 (8)	4.2 (1.2)
CKD-JAC	Japan	2639	4.6 (0.6)	37 (17)	2335 (88%)	60 (11)	1001 (38%)	0	896 (34%)	407 (15%)	104 (4%)	385 (17%)	2472 (94%)	132 (19)	76 (12)	23 (4)	5.0 (1.1)
CRIB	UK	373	4.6 (0.6)	22 (11)	314 (84%)	62 (14)	130 (35%)	20 (5%)	64 (17%)	93 (25%)	—	47 (13%)	350 (94%)	152 (22)	84 (12)	27 (5)	5.6 (1.3)
MASTERPLAN	Netherlands	670	4.4 (0.6)	36 (15)	483 (72%)	60 (13)	207 (31%)	0	163 (24%)	171 (26%)	108 (17%)	138 (21%)	639 (95%)	139 (21)	80 (12)	27 (5)	4.8 (1.1)
MDRD	USA	832	4.4 (0.6)	33 (14)	619 (74%)	52 (12)	329 (40%)	64 (8%)	82 (10%)	90 (11%)	—	81 (10%)	724 (87%)	131 (19)	80 (10)	27 (4)	5.5 (1.3)
PSP-CKD	UK	16 828	4.6 (0.5)	51 (14)	5364 (32%)	76 (11)	10 138 (60%)	179 (1%)	5129 (30%)	5685 (34%)	1262 (7%)	1567 (14%)	16 271 (97%)	134 (16)	74 (10)	29 (6)	4.4 (1.2)
SRR-CKD	Sweden	2618	4.4 (0.6)	24 (11)	2061 (79%)	68 (14)	844 (32%)	0	990 (38%)	399 (15%)	379 (14%)	—	2526 (97%)	141 (23)	78 (12)	28 (5)	5.0 (1.5)
Sunnybrook	Canada	3122	4.4 (0.5)	56 (31)	2167 (69%)	61 (18)	1443 (46%)	0	1467 (47%)	244 (8%)	217 (7%)	414 (13%)	2397 (77%)	133 (20)	76 (12)	29 (12)	4.8 (1.4)
Subtotal		42 170	4.6 (0.6)	42 (19)	24 081 (57%)	70 (14)	20 740 (49%)	1426 (4%)	17 116 (42%)	11 856 (28%)	3935 (10%)	3584 (14%)	38 582 (91%)	135 (20)	75 (12)	28 (7)	4.6 (1.3)
Total		1 217 986	4.2 (0.4)	83 (23)	208 676 (17%)	55 (16)	482 628 (40%)	61 347 (14%)	448 356 (37%)	203 442 (17%)	49 115 (5%)	99 885 (16%)	66 8345 (55%)	129 (19)	76 (11)	29 (9)	4.9 (1.1)

CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; SBP, systolic blood pressure.
[a]By definition, all participants have a measure of albuminuria. Urine protein-to-creatinine ratio was converted to urine albumin-to-creatinine ratio by dividing by 2.655 for men and 1.7566 for women. Dipstick proteinuria was classified as <30 mg/g for values of negative and trace, 30–299 mg/g for 1+, and 300+ mg/g for 2+ and higher.

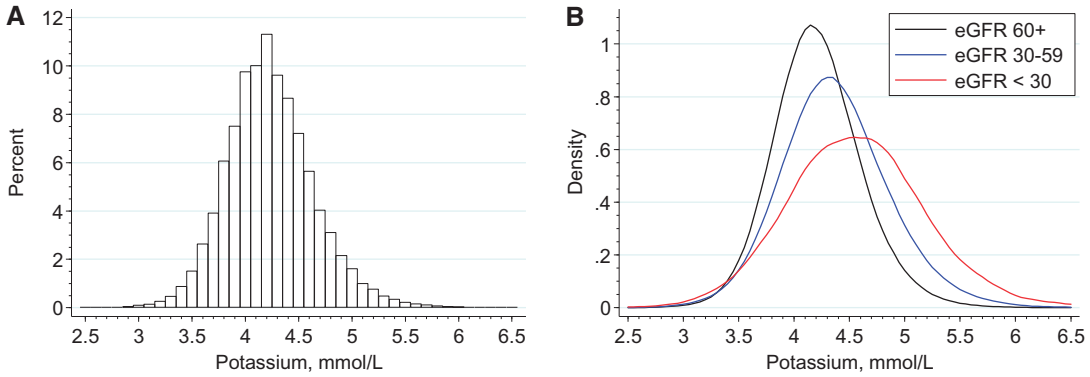

Figure 1 Distribution of serum potassium concentrations, overall and by baseline estimated glomerular filtration rate in the general population and high cardiovascular risk cohorts.

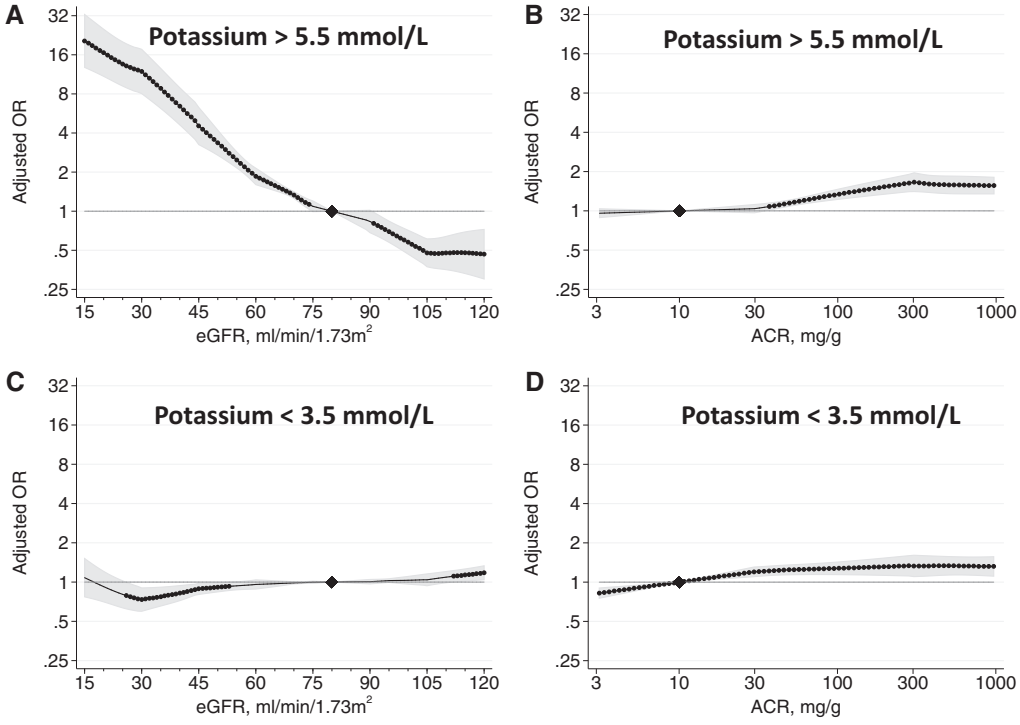

Figure 2 Continuous association of estimated glomerular filtration rate (*A*) and albuminuria (*B*) with the risk of serum potassium level >5.5 mmol/L and of estimated glomerular filtration rate (*C*) and albuminuria (*D*) with the risk of serum potassium level <3.5 mmol/L, in the general population and high cardiovascular risk cohorts. Black dots indicate statistical significance compared with the reference (diamond) estimated glomerular filtration rate of 80 mL/min/1.73 m^2 (*A* and *C*) and albuminuria of 10 mg/g (*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, and history of heart failure.

Discussion

In this international meta-analysis of 1 217 986 participants in 27 diverse cohorts, we describe the prevalence, risk factors, and long-term outcomes associated with abnormal potassium concentrations. Hyperkalaemia and hypokalaemia were relatively infrequent in the studied populations, especially in participants with normal kidney function. Lower eGFR was a strong risk factor for hyperkalaemia but not hypokalaemia; higher albuminuria was a relatively weak risk factor for both. Both hyper- and hypokalaemia 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 hyperkalaemia and hypokalaemia were similar in patients with various levels of kidney

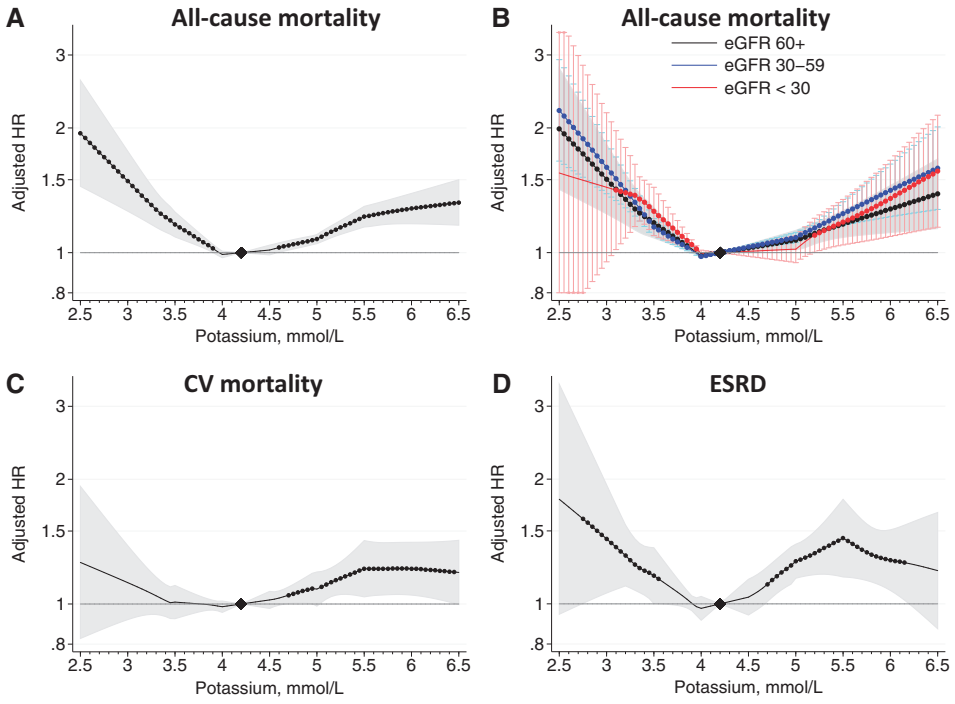

Figure 3 Adjusted hazard ratio of all-cause mortality, cardiovascular mortality, and end-stage renal disease associated with serum potassium concentration in the general population and high cardiovascular risk cohorts. Black dots indicate statistical significance compared with the reference (diamond) 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, estimated glomerular filtration rate, albuminuria, history of coronary heart disease or stroke, and history of heart failure.

function and in various subgroups divided by age, gender, race, DM, or treatment with ACEi or ARB.

Abnormal potassium homeostasis is more frequently mediated by a combination of conditions affecting potassium intake, distribution and excretion, including demographic characteristics, co-morbidities, and various medications.[6,30] Our results confirm the diversity of the risk factors determining hyper- and hypokalaemia [including co-morbidities such as congestive heart failure (CHF) and DM,[3] and therapeutic interventions such as diuretic use and RAASi[31]] and emphasize the central role played by the kidneys in potassium homeostasis. Similar to our findings, previous studies have found a low prevalence of hyperkalaemia in patients with normal kidney function and markedly elevated frequencies in various cohorts with CKD, especially in patients with DM, in those with more advanced stages of CKD[7,8,10] and in kidney transplant recipients.[9] As opposed to the widely accepted role of lower eGFR as a risk factor for hyperkalaemia, 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 hyperkalaemia and hypokalaemia, although the magnitude of this association was smaller than the relationship between eGFR and potassium abnormalities, at least for hyperkalaemia. This finding has important practical relevance, because patients with higher levels of albuminuria often benefit from therapy with RAASi medications to slow progression of CKD,[32–37] which also increase the risk of hyperkalaemia.[31,38,39] A secondary analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study showed that hyperkalaemia after losartan therapy attenuated the renoprotective effect of losartan, suggesting that prevention of hyperkalaemia might allow for enhanced renoprotection by RAASi.[40] Current clinical guidelines recommend concerted efforts to resume RAASi therapy in patients with CHF, even after episodes of severe hyperkalaemia (>6 mEq/l), once hyperkalaemia was treated and precautions are taken to monitor serum potassium.[31] Recent clinical trials suggest that the use of potassium binder medications may allow the use of RAASi in patients prone to hyperkalaemia,[41–45] although the long-term benefit of such strategies on clinical outcomes is yet to be demonstrated.[46]

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

The U-shaped association of serum potassium levels with clinical outcomes described in this study confirms the findings from previous studies, indicating similar associations with all-cause mortality,[8,10,14–18] and extends them to an outpatient, large and diverse international population. The association between hypo- and hyperkalaemia and mortality could be explained by the induction of malignant

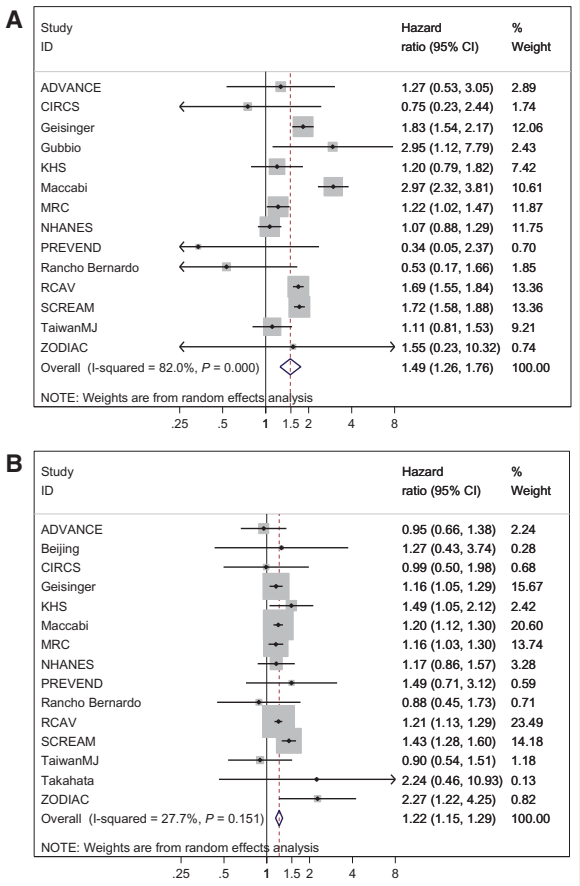

Figure 4 Adjusted relative hazard of all-cause mortality for potassium of 3.0 mmol/L (*A*) and 5.5 mmol/L (*B*) compared with a potassium of 4.2 mmol/L in individual general population/high cardiovascular risk cohorts.

arrhythmias[3,19] and their consequences, such as hypotension, myocardial ischaemia, and sudden cardiac death.[3,17] In addition, hypokalaemia and low dietary potassium intake are also associated with hypertension and consequent CV outcomes such as strokes.[48] This hypothesis is also supported by the association of hypo- and hyperkalaemia with CV 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.[8,40,49,50] 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, hypokalaemia is also a risk factor for tubulointerstitial fibrosis and renal cyst formation,[51–54] thus contributing to the development and progression of CKD. Conversely, hyperkalaemia may be a surrogate marker of more severe CKD. Further studies are needed to determine whether correction of hypo- and hyperkalaemia 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 CV 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. RAASi) 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 co-morbid conditions such as DM. 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 hyperkalaemia. Hypo- and hyperkalaemia 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 whether the correction of abnormal serum potassium levels can result in improvement in mortality and delayed onset of dialysis.

Authors' contributions

C.P.K., K.M., J.C., S.H., V.S., and M.E.G. conceived of the study concept and design. K.M., J.C., M.E.G. and the CKD-PC Investigators/Collaborators listed below acquired the data. Y.S. and the Data Coordinating Center members listed below analysed the data. All authors took part in the interpretation of the data. C.P.K., K.M., Y.S., and M.E.G. 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. J.C. obtained funding for CKD-PC and individual cohort and collaborator support is listed in Supplementary material online, *Appendix S3*.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Conflict of interest: C.P.K. reports grants from National Institutes of Health (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. K.M. reports grants and personal fees from Kyowa Hakko Kirin outside the submitted work. N.J.B. reports grants from the UK National Institute for Health Research during the conduct of the study; grants from Baxter Healthcare outside the submitted work. J.J.C. reports grants from AstraZeneca and grants from ViforPharma outside the submitted work. T.H. reports grants from JSPS KAKENHI and personal fees from Kyowa Hakko Kirin outside the submitted work. H.L.H. 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. D.C.W. reports grants and personal fees from AstraZeneca, and personal fees from Vifor Fresenius outside the submitted work. J.C. 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, J.C. 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. Y.S., G.C., A.H., G.W.D.L., A.L., D.N., S.I.H., V.S., and M.E.G. have nothing to disclose.

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