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Original Article

ORIGINAL ARTICLE

Gender-specific risk factors and outcomes of hyperkalemia in CKD patients: smoking as a driver of hyperkalemia in men

Jose M. Valdivielso [1], Sol Carriazo [2,3], Marisa Martin[1], Beatriz Fernandez-Fernandez[2,3], Marcelino Bermudez-López[1] and Alberto Ortiz [2,3,*]; on behalf of NEFRONA investigators*

[1]Vascular and Renal Translational Research Group, UDETMA, REDinREN del ISCIII, IRBLleida, University of Lleida, Lleida, Spain, [2]IIS-Fundacion Jimenez Diaz, School of Medicine, University Autonoma of Madrid, FRIAT and REDINREN, Madrid, Spain and [3]ISCIII RICORS2040 Kidney Disease Research Network, Madrid, Spain

*NEFRONA investigators: The NEFRONA study investigator group is listed in the appendix.
Correspondence to: Jose M. Valdivielso; E-mail: josemanuel.valdivielso@udl.cat or Alberto Ortiz; E-mail: AOrtiz@fjd.es

ABSTRACT

Background. Hyperkalemia is common among patients with chronic kidney disease (CKD) but there is scarce information on differential risk factors and outcomes for men and women. For instance, smoking has been suggested to be a risk factor for hyperkalemia, but specific analysis of the sex-specific impact of smoking on hyperkalemia in CKD is lacking.

Methods. We studied serum potassium levels in 2891 participants from the NEFRONA cohort: 483 controls (47% women) and 2408 CKD patients (38% women) without prior cardiovascular disease (CVD), assessing whether smoking is a risk factor for hyperkalemia, and if hyperkalemia is associated with outcomes separately for men and women.

Results. Median potassium levels and prevalence of hypo and hyperkalemia were higher in CKD participants than in controls. Serum potassium levels were higher and hyperkalemia and severe hyperkalemia more prevalent in men than in women with non-dialysis CKD (G3–G5). The highest prevalence of hyperkalemia for each gender was found in CKD G4-G5 and hemodialysis patients for men (46%) and in hemodialysis (54%) for women. Gender-specific etiological multivariate analysis identified current smoking as a risk factor for hyperkalemia only in men. Hyperkalemia was independently associated with stopping RAASi, an outcome which was more common in women. Hyperkalemia was also associated to higher risk of cardiovascular events within 4 years in men. In conclusion, hyperkalemia is common among men and women with CKD, but the prevalence, risk factors and outcomes may differ by gender. Specifically, current smoking is a driver of hyperkalemia in men.

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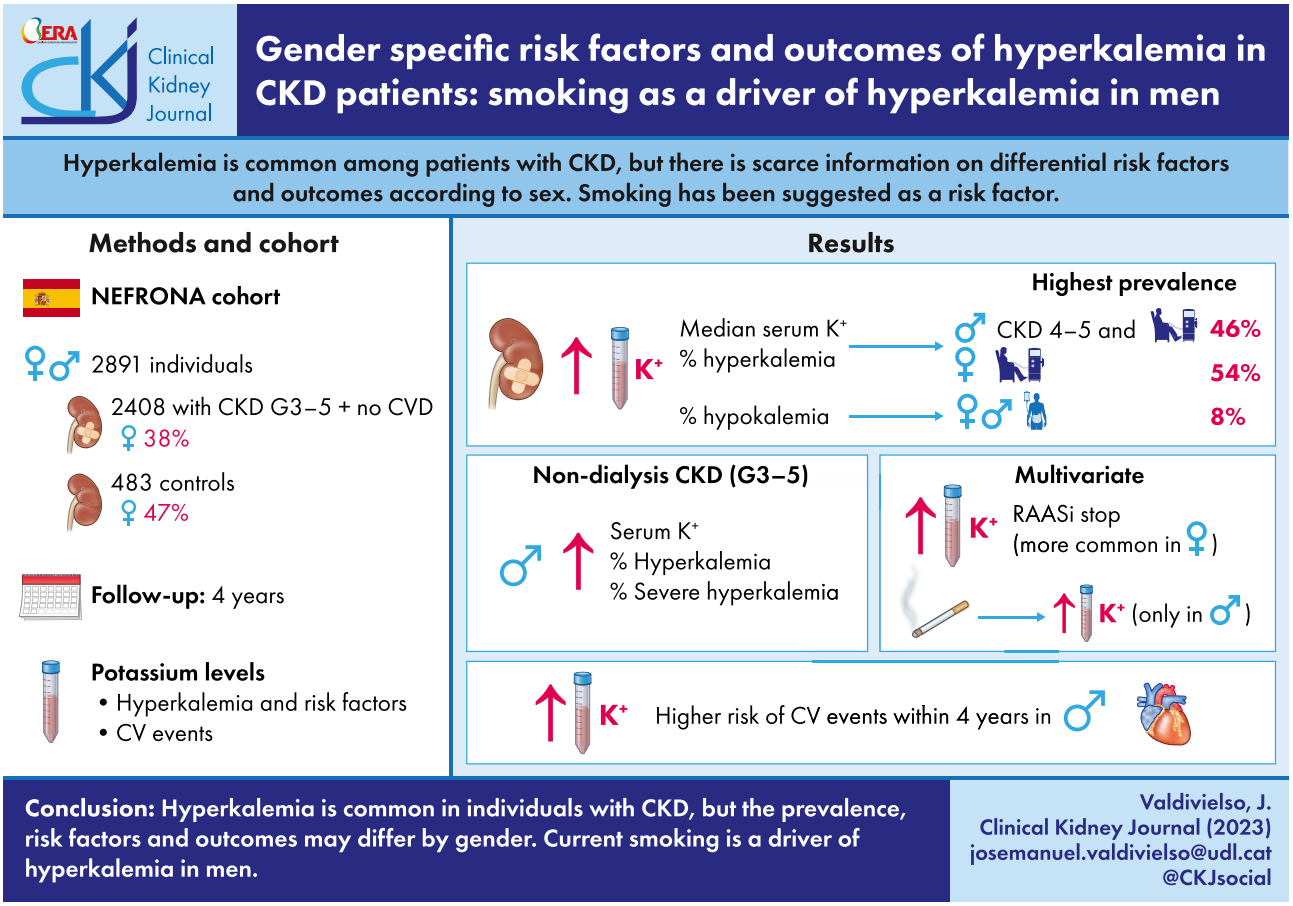
GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, gender, hyperkalemia, risk factors, smoking

KEY LEARNING POINTS

What was known:

- In individuals with chronic kidney disease (CKD), hyperkalemia is common, and associated with suboptimal dosing of drugs that provide kidney and cardiovascular protection and with adverse outcomes.
- However, studies usually included patients that may also have coexistent cardiovascular disease (CVD) and have not addressed gender-specific epidemiology, risk factors, and outcomes.
- The coexistence of CVD may be a confounding factor, as a majority of patients with CKD do not have established CVD, despite CVD being common.

This study adds:

- Hyperkalemia is more common in men than in women with non-dialysis CKD. Despite this, renin-angiotensin system blockers are stopped more frequently in women than in men. By contrast, hyperkalemia was more common in women than in men on hemodialysis.
- Hyperkalemia was also associated to higher risk of cardiovascular events within 4 years in men.
- In aetiological models, smoking was identified as a driver of hyperkalemia only in men.

Potential impact:

- Gender-specific approaches to the prevention and treatment of hyperkalemia may be needed.
- Specifically, men should have it explained that, on top of other benefits of quitting smoking, smoking may drive an increased risk of hyperkalemia.
- The reasons underlying the higher frequency of stopping renin-angiotensin system blockers in women with non-dialysis CKD, despite the lower prevalence of hyperkalemia, should be explored and corrective actions implemented.

INTRODUCTION

Hyperkalemia is common in individuals with chronic kidney disease (CKD), and it is associated with adverse cardiovascular events that can be life-threatening [1, 2]. CKD patients have several characteristics that make them more prone to hyperkalemia. First, decreased kidney function impairs the ability to excrete potassium in urine. Second, CKD patients are often treated with renin-angiotensin aldosterone system inhibitors (RAASi). Aldosterone promotes sodium reabsorption in the distal nephron in exchange with potassium secretion. Therefore, RAASi increase the risk of hyperkalemia. Furthermore, transcellular shifts may contribute to increase serum potassium in CKD patients. Potassium is the main intracellular osmolyte and small changes in its intra to extracellular distribution can cause hyperkalemia. Metabolic acidosis is common in CKD and increases the transcellular shift, as do hyperglycemia, beta2-adrenergic blockers or hyperosmolarity, favoring hyperkalemia [3].

Hyperkalemia is associated with adverse outcomes [4, 5]. Severe hyperkalemia may be lethal, and chronic milder hyperkalemia may be complicated by severe hyperkalemia episodes [6–9] or lead to down-titration or withdrawal of RAASi [10], depriving patients of their protective effects [11]. However, cardiovascular disease (CVD) is common in individuals with CKD and prior analyses have not dissociated the influence of CVD and of CKD on risk factors and outcomes for hyperkalemia.

Additionally, the gender-specific risk factors and epidemiology of hyperkalemia and hyperkalemia-associated outcomes have not been properly addressed in patients with CKD, although dimorphism is common in the kidney handling of electrolytes [12], a fact that could lead to differences in disease susceptibility [13]. In this regard, there are gender-related differences in CVD risk factors (i.e. smoking) and outcomes among patients with CKD.

The main objectives of the present study are to characterize the epidemiology and outcomes of hyperkalemia in men and women throughout the CKD spectrum in a cohort representative of the CKD population without baseline CVD of Spain, and to determine whether smoking is a risk factor for hyperkalemia.

MATERIALS AND METHODS

Design and study population

The design of the NEFRONA study has been reported in detail [14, 15]. Briefly, 2445 CKD G3–G5 patients [937 in the CKD category of estimated glomerular filtration rate (eGFR) G3, 820 in category G4-G5, 688 in category G5D, i.e. undergoing chronic dialysis] and 559 controls that had eGFR >60 ml/min/1.73 m^2 were enrolled from 81 Spanish hospitals and nine primary care centers between October 2009 and June 2011. Participants were adults (18–75 years of age) without a history of previous CVD (i.e. without unstable angina, myocardial infarction, transient ischemic attack, stroke, congestive heart failure, arrhythmia, peripheral artery disease, amputation for vascular disease or aortic aneurysm). The present analysis includes patients with data on serum potassium at baseline, which were 96.3% of the original cohort (2408 in the CKD group and 483 in the control group) (Fig. 1). The study protocol was approved by the ethics committee of each hospital and participants were enrolled after signing informed consent. This research followed the principles of the Declaration of Helsinki. The design of the study included a follow-up visit at 24 months for participants with CKD that did not have baseline evidence of subclinical atherosclerosis [i.e. hemodynamically significant stenotic carotid plaque or an ankle-brachial index (ABI) <0.7] and had not developed a cardiovascular event. Overall, 1555 CKD patients were reassessed at 2 years for subclinical atherosclerosis, blood tests and medication changes. Of them, 1510 had data on baseline serum potassium levels. Additionally, all participants were followed for 4 years to record incident cardiovascular events defined as unstable angina, myocardial infarction, transient ischemic attack, stroke, congestive heart failure, arrhythmia, peripheral artery disease, amputation for vascular disease, aortic aneurysm, or cardiovascular death (i.e. caused by myocardial infarction,

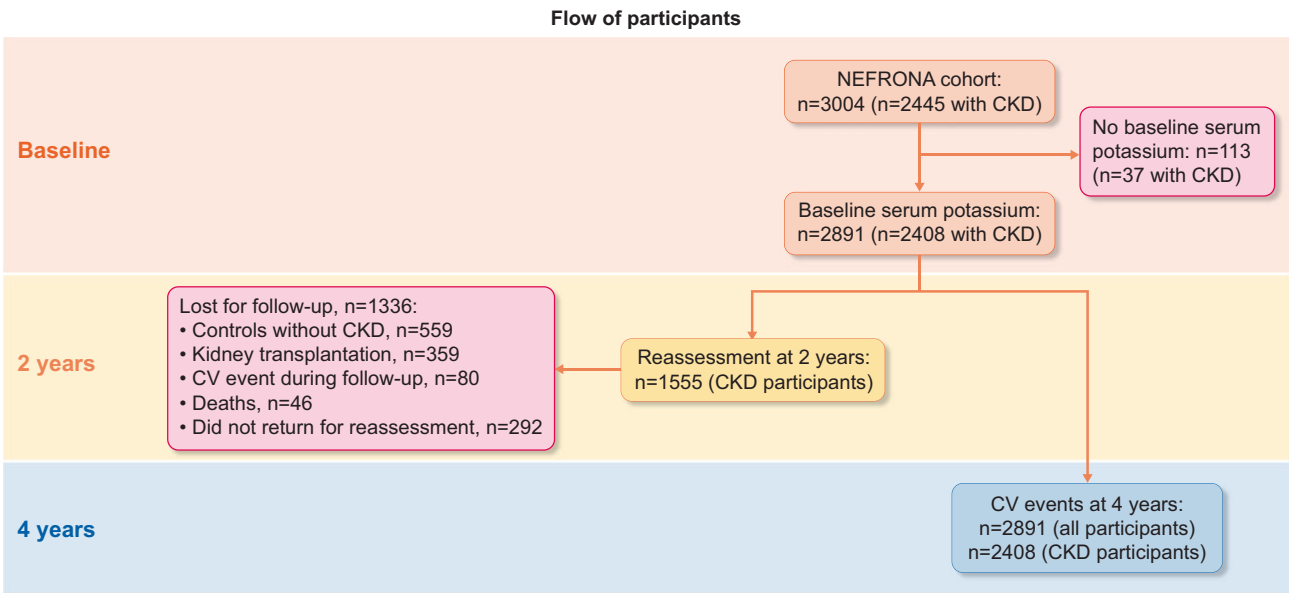


Figure 1: Participants flow chart.

arrhythmia, congestive heart failure, stroke, aneurysm, mesenteric infarction, or sudden death).

Clinical data and laboratory examinations

Health status, medical history, cardiovascular risk factors, and drug use information was obtained at baseline. A physical examination consisted of office blood pressure, anthropometric measures, standard vital tests, and ABI measurements as previously described [16]. ABI was considered pathological when ≤0.9 or ≥1.4. Biochemical data were obtained from a routine fasting blood test within three months from the vascular study. Current smokers were classified as smokers, except when indicated. Dyslipidemia was diagnosed from the clinical history. GFR was estimated from serum creatinine using the Modification of Diet in Renal Disease Study formula (MDRD-4). Hyperkalemia was defined as serum K >5.0 mEq/L unless otherwise indicated.

Statistical analysis

Univariable relationships were analysed by Student's *t* test for normally distributed variables, and Mann–Whitney's test for non-parametric analysis. Chi squared test was used to compare two categorical variables and the Kruskal–Wallis test for independent samples to compare more than two categories. One-way ANOVA was used to compare multiple independent groups and Bonferroni *post hoc* test was used. To determine whether smoking was a risk factor for hyperkalemia, significant variables in bivariate analyses and potential confounders were included to develop aetiological multivariable logistic regression models for men and women to carefully check the criteria for confounding for this specific exposure-outcome relationship [17, 18]. Imputation was not used. Prognostic multivariate logistic models were built to determine variables associated with RAASi discontinuation. Kaplan–Meier curves were built to show the estimated survival function of time free from cardiovascular events, depending on potassium levels. Proportional Cox hazards modelling was used to determine the association of hyperkalemia with cardiovascular events after 4 years of follow-up. A statistical significance level of 0.05 was used. Analyses were made on SPSS 24.0.

RESULTS

Participant characteristics

A total of 2891 adult participants with baseline serum potassium values but no baseline CVD were evaluated, 483 were controls (226, 47% women) and 2408 were CKD patients (924, 38% women). Baseline characteristics are described in Table 1. CKD patients were older and more frequently male than controls. Hypertension, dyslipidemia, diabetes, and cardiovascular events during follow-up were more common among CKD patients, as were the use of RAASi and other anti-hypertensive drugs. Systolic and diastolic blood pressure, pulse pressure, and serum triglyceride, glucose, phosphate, urea, and C reactive protein (CRP) levels were significantly higher in CKD patients, while total, LDL and HDL cholesterol, calcium, sodium, and 25-OH vitamin D levels were lower in CKD patients than in controls. Overall, the characteristics of CKD patients and their differences from controls are in line with expectations. Of note, office blood pressure control was suboptimal in CKD patients.

Serum potassium in CKD

Median potassium levels were higher in CKD patients than in controls, but the spread of serum potassium values was also wider in CKD patients (Fig. S1A, see online supplementary material) and prevalence of both hypo and hyperkalemia was higher in CKD patients, independently of the definition of hyperkalemia used ($P < 0.001$) (Table 1). Around one-third of CKD participants with hyperkalemia had serum potassium values ranging from 5.01 to 5.20 mEq/L and one third from 5.21 to 5.50 mEq/L (Fig. S2, see online supplementary material). Patients in all individual CKD GFR G categories had higher serum potassium levels than controls ($P < 0.001$), except for PD patients (Fig. 2A). Serum potassium levels increased as eGFR decreased and peaked in hemodialysis patients (Fig. 2A). Of note, serum potassium levels were higher in patients on hemodialysis than in PD patients (Fig. 2A; Fig. S1B, see online supplementary material). Consistently, the prevalence of hyperkalemia increased as eGFR decreased and was higher in patients on hemodialysis than in PD patients, the latter having a prevalence of hyperkalemia similar to participants with CKD G3 (Fig. 2B). The prevalence of severe hyperkalemia (serum potassium >6.0 mEq/L) was highest in hemodialysis patients: 49/472 (10.38%) (Fig. 2C). By contrast, PD patients had the highest prevalence of hypokalemia (18/235, 7.6%).

Among all patients with CKD, there were no differences in the prevalence of hyperkalemia between participants treated or not with RAASi for any definition of hyperkalemia (Table 2A). However, among participants with CKD G3–G5, hyperkalemia was more common in participants on RAASi and severe hyperkalemia was only observed in among participants on RAASi (Table 2B). Additionally, serum potassium was higher in CKD G3–G5 patients on RAASi with or without diuretics than in those with only diuretics (Fig. 2D). Thus, the association of RAASi with high serum potassium levels was limited to participants not on dialysis.

Association of smoking with hyperkalemia in CKD patients

Table 3 shows the differences between current smokers and non-smokers in the CKD population. The bivariate analysis shows that CKD patients that smoke are younger, mostly male, with lower BMI, SBP and HDL cholesterol, and higher triglycerides. Furthermore, the percentage of patients with hyperkalemia (defined as K >5.0 mEq/L) was higher among current smokers, despite lower mean serum K levels.

In multivariate analysis, smoking was consistently associated with hyperkalemia in the crude regression (Model 1), when corrected by age and sex (Model 2) or in the full regression model (Model 3) adjusted by potential confounders identified in the previous bivariate analysis or in the literature (Table 4).

Gender differences in baseline characteristics among CKD patients

Male and female CKD patients differed in multiple baseline characteristics. The prevalence of smoking history, diabetes, CVD, and use of RAASi and other antihypertensive drugs, BMI, and triglycerides and 25-OH-vitamin D levels were higher in men than in women (Table S1, see online supplementary material). By contrast, total, HDL and LDL cholesterol, total calcium and

Table 1: Baseline: characteristics and cardiovascular outcomes of the NEFRONA cohort.

	Control ($n = 483$)	CKD ($n = 2408$)	*P*
Age (years)	56 (47–63)	61 (50–68)	**<0.001**
Men, *n* (%)	257 (53.2)	1484 (61.6)	**0.001**
Smoking			0.094
Ex-smoker, *n* (%)	228 (40.8)	881 (36.0)	
Current smoker, *n* (%)	109 (19.5)	490 (20.0)	
BMI (kg/m^2)	27.73 (24.89–30.59)	27.77 (24.69–31.34)	0.676
Diabetes, *n* (%)	63 (13.0)	692 (28.7)	**<0.001**
Hypertension, *n* (%)	271 (56.1)	2304 (95.7)	**<0.001**
Dyslipidemia, *n* (%)	169 (35.0)	1593 (66.2)	**<0.001**
Cardiovascular events during follow-up, *n* (%)	12 (2.5)	201 (8.3)	**<0.001**
Family history of premature CV event, *n* (%)	53 (11.0)	199 (8.3)	0.054
Anti-hypertensive drugs, *n* (%)	177 (36.6)	2123 (88.2)	**<0.001**
RAASi, *n* (%)	143 (29.6)	1669 (69.3)	**<0.001**
Diuretics, *n* (%)	46 (9.5)	1102 (45.8)	**<0.001**
RAASi plus diuretics, *n* (%)	40 (8.3)	884 (36.7)	**<0.001**
Beta-blockers	21 (4.3)	390 (16.2)	**<0.001**
Potassium (mEq/L)	4.47 (4.2–4.7)	4.80 (4.4–5.2)	**<0.001**
Hypokalemia, *n* (%)	4 (0.8)	57 (2.4)	**0.032**
Hyperkalemia, *n* (%)			
K > 5.0, *n* (%)	43 (8.9%)	808 (33.6%)	**<0.001**
K > 5.2, *n* (%)	25 (5.2%)	546 (22.7%)	**<0.001**
K > 5.5, *n* (%)	10 (2.1%)	259 (10.8%)	**<0.001**
K > 6.0, *n* (%)	0 (0.0%)	77 (3.2%)	**<0.001**
Systolic blood pressure (mmHg)	133 (122–144)	141 (128–157)	**<0.001**
Diastolic blood pressure mmHg	80 (73–87)	81 (74–69)	**0.041**
Total cholesterol (mg/dl)	200 (179–223)	175 (151–202)	**<0.001**
HDL cholesterol (mg/dl)	51 (43–62)	47 (38–58)	**<0.001**
LDL cholesterol (mg/dl)	125 (105–146)	100 (78–121)	**<0.001**
Triglycerides (mg/dl)	96 (71–141)	125 (91–174)	**<0.001**
Glucose (mg/dl)	97 (88–106)	97 (87–113)	**0.001**
Total calcium (mg/dl)	9.40 (9.10–9.70)	9.30 (8.91–9.70)	**0.002**
Phosphate (mg/dl)	3.50 (3.05–3.90)	3.83 (3.30–4.60)	**<0.001**
Urea (mg/dl)	36 (31–43)	96 (64–131)	**<0.001**
Sodium (mEq/L)	141 (139–142.50)	140 (139–142)	**<0.001**
CRP (mg/dl)	1.57 (0.78–3.08)	2.00 (0.95–4.54)	**0.001**
25-OH vitamin D (ng/ml)	18.67 (14.53–23.86)	14.81 (11.04–19.23)	**<0.001**

Quantitative data expressed as median (IQR). BMI: body mass index;CKD: chronic kidney disease; CRP: C reactive protein; CV: cardiovascular; HD: hemodialysis; K: potassium; PD: peritoneal dialysis; RAASi: Renin angiotensin aldosterone system inhibitors. Statistically significant *P* values are highlighted in bold.

phosphate levels were lower in men than in women. However, there were no overall differences in serum potassium levels or the prevalence of hypokalemia or hyperkalemia between men and women (Table S1, Fig. S1C, see online supplementary material).

Only a few of the baseline differences between men and women with CKD were consistent across all CKD categories (Table S2, see online supplementary material). In men, smoking was more frequent and total and HDL-cholesterol were lower in all categories of CKD.

Gender differences in serum potassium according to CKD category

Fig. S3 (see online supplementary material) shows serum potassium levels in men and women according to CKD category and dialysis modality (Fig. S3A and B, see online supplementary material) or according to the use of RAASi and diuretics (Fig. S3C and D, see online supplementary material), and the prevalence of hyperkalemia and hypokalemia (Fig. S3E–H, see online supplementary material). In men, serum potassium and the prevalence of hyperkalemia peaked in CKD G4/G5, while in women they peaked in hemodialysis. (Fig. S3A, B, E–H, see online supplementary material). In this regard, serum potassium levels were higher in men with non-dialysis CKD (G3–G5) than in women, but differences were not observed in dialysis CKD (hemodialysis or PD) (Table S2, see online supplementary material). In line with this observation, severe hyperkalemia was observed in men (1.3%) but not in women with G3 CKD, and hyperkalemia (any definition) was more prevalent in men with CKD G4/G5 than in women (Table S2, see online supplementary material). By contrast, severe hyperkalemia was more prevalent among women (15.3%) than among men (8.2%) in hemodialysis.

As done for the whole population, we next explored a potential etiological association between current smoking and hyperkalemia in males and in females with CKD.

Association of smoking with hyperkalemia in CKD patients stratified by sex

Bivariate analysis of differences between current smokers and non-smokers in males was similar to observations in the whole population. However, in males, average serum K levels were

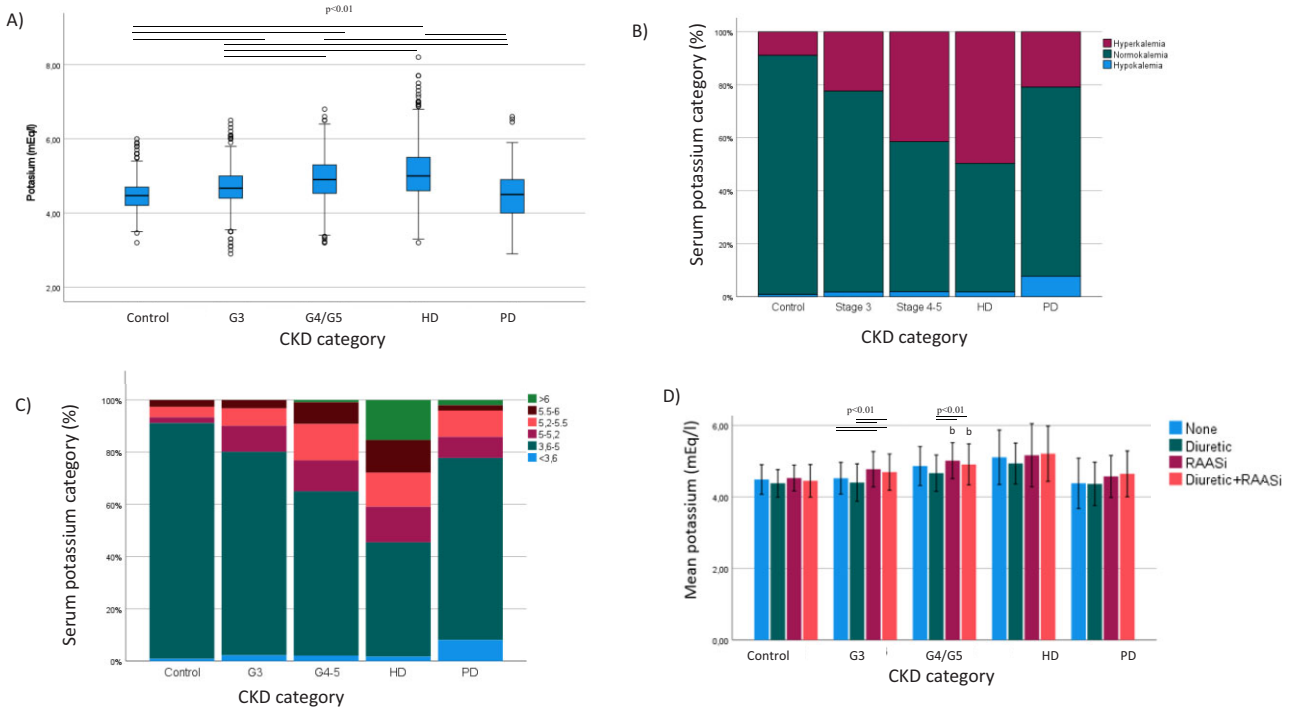


Figure 2: Potassium levels according to CKD category. (**A**) Boxplot of serum potassium values according to CKD category. Circles represent outliers. One Way ANOVA. (**B**) Histogram presenting the distribution of serum potassium levels into hypokalemia (serum potassium <3.6 mEq/l), normokalemia (3.6–5.0 mEq/l), and hyperkalemia (>5.0 mEq/l, purple) potassium levels for different CKD categories. (**C**) Histogram representing five serum potassium categories for different CKD categories. Kruskal–Wallis for independent samples. Bar chart of potassium values according to CKD stage and medication (ACEi and diuretics). (**D**) Bar chart of serum potassium values according to CKD category and medication (ACEi and diuretics). One-way ANOVA.

Table 2: Prevalence: of hyperkalemia in NEFRONA participants with CKD according to different definitions and RAASi treatment. Data expressed as *n* (%).

Definition of hyperkalemia	No RAASi	RAASi	*P*
A) All participants with CKD			
>5.0 mEq/L	234 (31.7)	574 (34.4)	0.191
>5.2 mEq/L	164 (22.2)	382 (22.9)	0.707
>5.5 mEq/L	84 (11.4)	175 (10.5)	0.520
>6.0 mEq/L	29 (3.9)	48 (2.9)	0.178
B) Participants with CKD G3–G5			
>5.0 mEq/L	76 (21.2)	462 (33.7)	<0.001
>5.2 mEq/L	43 (12)	298 (21.8)	<0.001
>5.5 mEq/L	14 (3.9)	125 (9.1)	0.001
>6.0 mEq/L	0 (0)	25 (1.8)	0.01

higher in smokers (Table 5A). Female smokers were also younger, with a lower BMI and SBP (Table 5B). In addition, a lower percentage of diabetics and reduced levels of urea and hsCRP were associated with being a female current smoker.

Multivariate analysis showed an association of smoking with the prevalence of hyperkalemia in males in the crude (Model 1) and in the adjusted models (Models 2 and 3, Table 6A). However, no association was found in females (Table 6B).

Serum potassium levels and RAASi discontinuation or diuretic addition

Overall, 155 (13.5%) CKD participants on RAASi at baseline discontinued them and 98 (8.5%) CKD participants initiated diuretics during a 2-year follow-up, while 253 (22%) reached the combined endpoint of stopping RAASi or initiating diuretics, i.e. participant who either discontinued RAASi or initiated diuretics, two maneuvers that may decrease serum potassium.

RAASi were discontinued in 119 (11.5% of participants with both RAASi at baseline and follow-up data at 2 years) participants with CKD G3–G5, 27 (44.3%) on HD and 9 (17.3%) on PD. By gender, 84 (11.7%) men and 71 (16.5%) women stopped RAASi ($P = 0.0218$).

Diuretics were initiated in 85 (8.1%) participants with CKD G3–G5, 4 (6.6%) on HD and 9 (17.3%) on PD. Overall, 66 (9.1%) of men and 32 (7.4%) of women initiated diuretics ($P = 0.095$).

The combined endpoint of RAASi discontinuation or diuretic initiation was reached in 150 (20.8%) men and 103 (24.0%) women. This included 204 (19.7%) participants with CKD G3–G5, 31 (50.8%) on HD and 18 (34.6%) on PD.

Multivariate analysis of factors associated with RAASi discontinuation within 2 years in participants with CKD G3–G5 (i.e. non-dialysis CKD) showed that hyperkalemia (potassium levels >5.0 mg/dl) was significantly associated in the crude analysis (OR: 1.526, 95% CI: 1.031–2.259, $P = 0.034$), when adjusted by age and sex (OR: 1.573, 95% CI: 1.061–2.332, $P = 0.024$) and with further adjustment by other comorbidities like the diagnosis of hypertension, diabetes, heart failure, and dyslipidemia (OR: 1.517, 95% CI:1.020–2.256, $P = 0.039$). In stratified analysis by sex, hyperkalemia was not associated with RAASi discontinuation, probably due to the smaller number of participants analysed.

In multivariate analysis, hyperkalemia was not associated with diuretic initiation or with the combined endpoint (RAASi discontinuation or diuretic initiation) (not shown).

Table 3: Bivariate: analysis of factors associated with being a current smoker.

	Non-smoker ($n = 1925$)	Current smoker ($n = 480$)	P
Age (years)	63 (51–69)	55 (45–63.25)	**0.000**
Male, *n* (%)	1124 (58.3)	360 (75)	**0.000**
BMI (kg/m^2)	27.89 (24.98–31.53)	26.99 (23.56–30.45)	**0.000**
Diabetes, *n* (%)	557 (28.9)	135 (28.1)	0.664
Hypertension, *n* (%)	1845 (95.7)	459 (95.6)	0.811
Dyslipidemia, *n* (%)	1274 (66.1)	319 (66.5)	0.706
CKD stage			0.651
CKD G3	753 (39)	182 (38)	
CKD G4/G5	636 (33)	157 (33)	
HD	347 (18)	98 (20)	
PD	192 (10)	43 (9)	
Cardiovascular events during follow-up, *n* (%)	156 (8.1)	45 (9.4)	0.330
Family history of premature CV event, *n* (%)	168 (8.7)	31 (6.5)	0.120
Anti-hypertensive treatment			
RAASi, *n* (%)	1335 (69.2)	334 (69.6)	0.921
Diuretics, *n* (%)	896 (46.5)	206 (42.9)	0.122
Combination RAASi + Diuretics			0.198
None, *n* (%)	421 (21.8)	100 (20.8)	
Diuretic, *n* (%)	172 (8.9)	46 (9.6)	
RAASi, *n* (%)	611 (31.7)	174 (36.3)	
Diuretic + RAASi, *n* (%)	724 (37.6)	160 (33.3)	
Beta-blockers	328 (17.0)	62 (12.9)	**0.032**
Potassium (mEq/L)	4.80 (4.40–5.20)	4.51 (4.90–5.30)	**0.001**
Hyperkalemia (>5), *n* (%)	624 (32.4)	184 (39.3)	**0.013**
Hypokalemia, *n* (%)	47 (2.4)	10 (2.1)	0.648
Systolic blood pressure (mmHg)	142 (129–158)	137 (125–153)	**0.000**
Diastolic blood pressure mmHg	81 (73–89)	81 (74.75–89)	0.503
Total cholesterol (mg/dl)	175 (151–202)	175 (151–205)	0.717
HDL cholesterol (mg/dl)	48 (39–59)	45 (36–53)	**0.000**
LDL cholesterol (mg/dl)	100 (78–120.95)	101 (77–124)	0.864
Triglycerides (mg/dl)	123 (90.6–169)	139 (95–189)	**0.000**
Glucose (mg/dl)	97 (87–113)	95.24 (86–112.25)	0.555
Total calcium (mg/dl)	9.32 (8.98–9.70)	9.30 (8.90–9.70)	0.190
Phosphate (mg/dl)	3.80 (3.30–4.60)	3.90 (3.40–4.70)	0.053
Urea (mg/dl)	95 (63.02–133)	95 (66–122)	**0.039**
Sodium (mEq/L)	140 (139–142)	140 (138–142)	0.239
CRP (mg/dl)	1.96 (0.94–4.54)	2.14 (1.01–4.57)	0.955
25-OH vitamin D (ng/ml)	14.90 (11.16–19.40)	14.89 (10.76–18.99)	0.543

Quantitative data expressed as median (IQR). BMI: body mass index; CKD: chronic kidney disease; CRP: C reactive protein; CV: cardiovascular; HD: hemodialysis; K: potassium; PD: peritoneal dialysis; RAASi: Renin angiotensin aldosterone system inhibitors. Statistically significant P values are highlighted in bold.

Table 4: Multivariate: analysis of the effect of current smoking on the risk of hyperkalemia.

	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Smoking	1.3 (1.05–1.6)	0.017	1.3 (1.05–1.6)	0.02	1.4 (1.1–1.8)	0.003

Model 1: Crude analysis. Model 2 adjusted by age and sex. Model 3 further adjusted by body mass index, systolic blood pressure, sodium, HDL cholesterol, triglycerides, urea, treatment with RAASI and diuretics and treatment with beta blockers.

Serum potassium levels and incidence of cardiovascular events

Cardiovascular events were assessed over 4 years of follow-up for CKD and control participants. Overall, 213 of 2481 participants (7.1%) developed a cardiovascular event during a 4-year follow-up. This included 148 (8.5%) men and 65 (5.7%) women ($P = 0.004$). Among CKD participants, 211 of 2408 (8.8%) suffered a cardiovascular event during a 4-year follow-up, including 142 (9.6%) men and 59 (6.4%) women ($P = 0.006$).

The incidence of cardiovascular events was higher in patients with hyperkalemia both in the whole population (Fig. 3A) or when stratified by sex (Fig. 3B and C). The risk of cardiovascular events was higher in participants with hyperkalemia >5.0 mg/dl in the full (CKD and control) cohort either in unadjusted analysis (OR: 1.998, 95% CI: 1.523–2.620)

Table 5: Bivariate: analysis of factors associated with being a current smoker stratified by sex.

A) Males

	Non-smoker ($n = 802$)	Current smoker ($n = 120$)	P
Age (years)	63 (52–69)	58 (46.25–65)	**0.000**
BMI (kg/m^2)	27.97 (25.25–31.05)	27.39 (24.22–30.49)	**0.007**
Diabetes, *n* (%)	338 (30.1)	118 (32.8)	0.398
Hypertension, *n* (%)	1083 (96.4)	346 (96.1)	0.672
Dyslipidemia, *n* (%)	758 (67.4)	244 (67.8)	0.768
CKD stage			0.270
CKD G3	480 (42.7)	143 (39.7)	
CKD G4/G5	340 (30.2)	116 (32.2)	
HD	195 (17.3)	74 (20.6)	
PD	109 (9.7)	27 (7.5)	
Cardiovascular events during follow-up, *n* (%)	103 (9.2)	39 (10.8)	0.296
Family history of premature CV event, *n* (%)	91 (8.1)	20 (5.6)	0.122
Anti-hypertensive drugs			
RAASi, *n* (%)	807 (71.8)	248 (68.9)	0.315
Diuretics, *n* (%)	502 (44.7)	153 (42.5)	0.429
Combination RAASi + diuretics			0.571
None, *n* (%)	232 (20.6)	79 (21.9)	
Diuretic, *n* (%)	85 (7.6)	33 (9.2)	
RAASi, *n* (%)	390 (34.7)	128 (35.6)	
Diuretic + RAASi, *n* (%)	417 (37.1)	120 (33.3)	
Beta-blockers	190 (16.9)	46 (12.8)	0.068
Potassium (mEq/L)	4.79 (4.40–5.20)	4.96 (4.60–5.30)	**0.000**
Hyperkalemia (K > 5.0), *n* (%)	363 (32.3)	147 (40.8)	**0.003**
Hypokalemia, *n* (%)	27 (2.4)	5 (1.4)	0.249
Systolic blood pressure (mmHg)	142 (130–158)	139 (126.25–153.75)	**0.003**
Diastolic blood pressure mmHg	81 (74–89)	80 (74–89)	0.883
Total cholesterol (mg/dl)	168 (144–194)	171 (148.2–201)	0.088
HDL cholesterol (mg/dl)	43 (36–52.6)	43 (34–50)	**0.036**
LDL cholesterol (mg/dl)	96.7 (75–117)	99 (74–122)	0.753
Triglycerides (mg/dl)	123 (92–173)	145 (101–199)	**0.000**
Glucose (mg/dl)	99 (89–115)	97.3 (88–116)	0.280
Total calcium (mg/dl)	9.30 (8.97–9.70)	9.30 (8.90–9.60)	0.631
Phosphate (mg/dl)	3.70 (3.20–4.50)	3.90 (3.36–4.70)	**0.009**
Urea (mg/dl)	93 (63–134)	95.2 (65–126)	0.352
Sodium (mEq/L)	140.30 (139–142)	140 (138.17–142)	0.226
CRP (mg/dl)	1.92 (0.94–4.33)	2.25 (1.16–4.83)	0.344
25-OH vitamin D (ng/ml)	15.64 (11.78–19.96)	14.81 (10.74–18.88)	0.085

B) Females

	Non-smoker ($n = 802$)	Current smoker ($n = 120$)	P
Age (years)	62 (50–69)	51 (42.75–57.25)	**0.000**
BMI (kg/m^2)	27.83 (24.35–32.44)	25.55 (21.93–30.48)	**0.000**
Diabetes, *n* (%)	219 (27.2)	17 (14.2)	**0.002**
Hypertension, *n* (%)	762 (94.8)	113 (94.2)	0.787
Dyslipidemia, *n* (%)	516 (64.2)	75 (62.5)	0.841
CKD stage			0.801
CKD G3	273 (34)	39 (32.5)	
CKD G4/G5	296 (36.8)	41 (34.2)	
HD	152 (18.9)	24 (20)	
PD	83 (10.3)	16 (13.3)	
Cardiovascular events during follow-up, *n* (%)	53 (6.6)	6 (5)	0.472
Family history of premature CV event, *n* (%)	77 (9.6)	11 (9.2)	0.879
Anti-hypertensive drugs			
RAASi, *n* (%)	528 (65.7)	86 (71.7)	0.236
Diuretics, *n* (%)	394 (49)	53 (44.2)	0.256
Combination RAASi + Diuretics			0.095
None	189 (23.5)	21 (17.5)	
Diuretic	87 (10.8)	13 (10.8)	

Table 5: Continued

	Non-smoker ($n = 1123$)	Current smoker ($n = 360$)	P
RAASi	221 (27.5)	46 (38.3)	
Diuretic + RAASi	307 (38.2)	40 (33.3)	
Beta-blockers	138 (17.2)	16 (13.3)	0.358
Potassium (mEq/L)	4.8 (4.37–5.2)	4.70 (4.40–5.20)	0.925
Hyperkalemia (K > 5.0), *n* (%)	261 (32.5)	37 (30.8)	0.722
Hypokalemia *n* (%)	20 (2.5)	5 (4.2)	0.290
Systolic blood pressure (mmHg)	140 (126–159)	133.5 (122.75–150)	**0.008**
Diastolic blood pressure mmHg	81 (73–89)	82 (75–90)	0.264
Total cholesterol (mg/dl)	186 (163.5–212)	189.5 (162.5–216.5)	0.685
HDL cholesterol (mg/dl)	53 (45–66)	50.5 (42.5–60)	0.120
LDL cholesterol (mg/dl)	104 (82–124)	109.5 (85–132.6)	0.252
Triglycerides (mg/dl)	122 (90–164)	121.5 (91.2–167)	0.850
Glucose (mg/dl)	95 (85–110)	91.2 (83–102)	0.156
Total calcium (mg/dl)	9.40 (9.00–9.70)	9.30 (8.92–9.70)	0.225
Phosphate (mg/dl)	4.00 (3.50–4.70)	4.10 (3.40–4.80)	0.693
Urea (mg/dl)	99 (65–132)	94.5 (67.2–113.7)	**0.007**
Sodium (mEq/L)	140 (138–142)	140 (138–142)	0.717
CRP (mg/dl)	2.06 (0.92–4.88)	1.70 (0.88–3.88)	**0.043**
25-OH vitamin D (ng/ml)	13.91 (10.44–18.37)	15.39 (10.77–19.42)	0.449

Quantitative data expressed as median (IQR). BMI: body mass index; CKD: chronic kidney disease; CRP: C reactive protein; CV: cardiovascular; HD: hemodialysis; K: potassium; PD: peritoneal dialysis; RAASi: Renin angiotensin aldosterone system inhibitors. Statistically significant P values are highlighted in bold.

Table 6: Multivariate: analysis of the effect of current smoking on the risk of hyperkalemia stratified by sex.

	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
A) Males*						
Smoking	1.5 (1.2–2.0)	0.002	1.5 (1.2–2.0)	0.02	1.5 (1.2–2.0)	0.003
B) Females**						
Smoking	0.9 (0.6–1.4)	0.9	0.9 (0.6–1.4)	0.9	1.1 (0.7–1.7)	0.7

*Model 1: Crude analysis. Model 2 adjusted by age. Model 3 further adjusted by body mass index, systolic blood pressure, sodium, HDL cholesterol, triglycerides, phosphate, treatment with RAASI and diuretics and treatment with beta blockers.
**Model 1: Crude analysis. Model 2 adjusted by age. Model 3 further adjusted by body mass index, diabetes, systolic blood pressure, Urea, usCRP, treatment with RAASI and diuretics and treatment with beta blockers.

or following adjustment by age and sex (OR: 1.932, 95% CI: 1.473–2.535) or full adjustment by other comorbidities (smoking status, diabetes, hypertension, dyslipidemia, CKD category or presence of atheroma plaque. OR: 1.414, 95% CI: 1.069–1.871) In sensitivity analyses, among participants with CKD, hyperkalemia (serum potassium >5.0 mEq/L) was also associated with a higher risk of a cardiovascular event (Table S3, see online supplementary material).

The association between hyperkalemia and cardiovascular events was stronger in men than in women. In men from the full cohort, hyperkalemia was associated with cardiovascular events in the crude analysis (OR: 1.988, 95% CI: 1.437–2.750, $P < 0.01$), after adjusting by age (OR: 1.971, 95% CI: 1.425–2.726, $P < 0.01$) and in fully adjusted models (adjusted for age, smoking, diabetes, hypertension, dyslipidemia, CKD stage, atheroma plaque. OR: 1.458, 95% CI 1.045–2.035; $P = 0.027$). However, in women the association between hyperkalemia and cardiovascular events was significant in the crude (OR: 1.926, 95% CI: 1.172–3.164, $P = 0.01$) analysis and following adjustment by age (OR:1.847, 95% CI: 1.124–3.036, $P = 0.016$) but not in the fully adjusted model [OR: 1.279 (0.757–2.160), $P = 0.357$]. The sensitivity analysis in participants with CKD yielded similar results (Table S3, see online supplementary material).

DISCUSSION

The main findings are that in a cohort of CKD patients selected for the absence of baseline CVD and thus, devoid of this confounding factor, hyperkalemia is common among men and women, but the prevalence and outcomes may differ by gender. Thus, serum potassium levels were higher and hyperkalemia and severe hyperkalemia more prevalent in men than in women in non-dialysis CKD (G3–G5). However, RAASi discontinuation was more common in women as was severe hyperkalemia among hemodialysis patients. In multivariate etiological models, current smoking was an independent risk factor for hyperkalemia in men but not in women. The association of hyperkalemia with cardiovascular events within 4 years was stronger in men.

Overall, participants with CKD displayed an increased prevalence of disturbances of potassium homeostasis. However, the

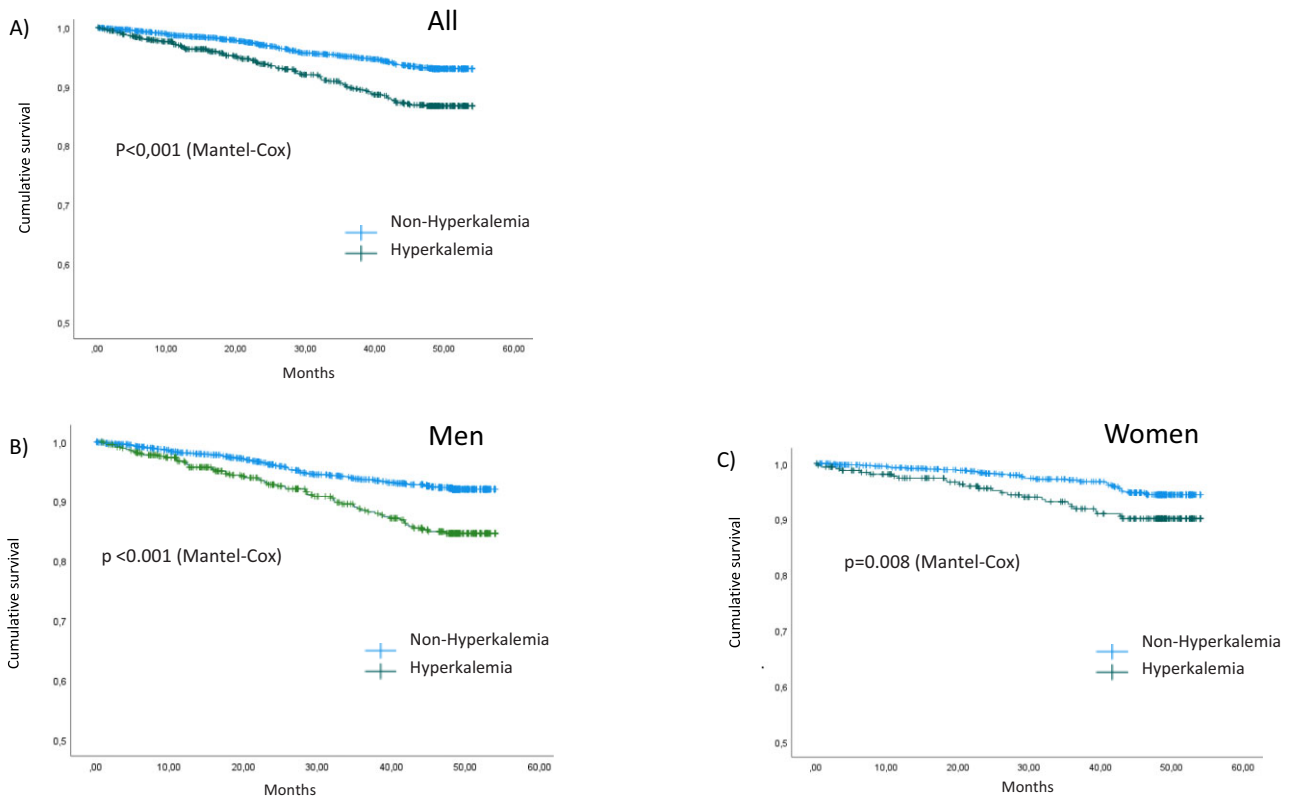


Figure 3: Incidence of cardiovascular events (CVE) during a 4-year follow-up according to the baseline presence of hyperkalemia in the whole study population. (**A**) Overall CVE-free survival curves (*$P < 0.001$ vs non-hyperkalemia, Mantel-Cox). (**B**) CVE-free survival in men (*$P < 0.001$ vs non-hyperkalemia, Mantel-Cox). (**C**) CVE-free survival in women ($P = 0.008$ vs non-hyperkalemia). Proportional COX hazards model was used to determine the association of hyperkalemia with cardiovascular events. Hyperkalemia was defined as serum potassium >5.0 mEq/L.

epidemiology of potassium abnormalities differed for CKD category, dialysis modality and gender. The prevalence of hyperkalemia increased with decreasing eGFR and was higher in individuals on hemodialysis than in those on PD. In this regard, reports of serum potassium in dialysis patients should always report hemodialysis and PD separately, as in the latter the prevalence of hyperkalemia was similar to CKD G3, but they had the highest prevalence of hypokalemia. In non-dialysis CKD, serum potassium levels were higher and hyperkalemia more prevalent in men than in women. Among the multiple baseline differences between men and women, smoking emerged as both more common in men and associated with hyperkalemia only in men, as discussed below. Thus, smoking could contribute to gender differences regarding hyperkalemia in CKD. The epidemiology of severe hyperkalemia also shifted from pre-dialysis (more common in men) to hemodialysis (more common in women). However, the bulk of severe hyperkalemia was observed in hemodialysis patients. In this regard, PD appears to offer the best serum potassium control in terms of preventing hyperkalemia and this may be an advantage especially for women because of their higher prevalence of severe hyperkalemia while on hemodialysis.

The association of RAASi with hyperkalemia differed for participants with CKD according to dialysis status. RAASi were associated with hyperkalemia in participants with CKD not on dialysis (CKD G3–G5), but there was no association in dialysis patients. This may be related to the additional potassium excretion pathways, beyond the urine, in dialysis patients, such as hemodialysate or PD effluents. By contrast, diuretics were associated with lower serum potassium. In this regard, both stopping RAASi and initiating diuretics may contribute to lower serum potassium levels, potentially having opposite impact on outcomes: discontinuation of RAASi may deprive patients of their beneficial effects [19]. By contrast, adding diuretics may decrease serum potassium as well as improve blood pressure control [20], which was suboptimal in the present cohort. In fact, clinical guidelines for the management of hypertension recommend starting with dual therapy, for example, with the RAASi-diuretic combination [21]. Furthermore, adding a diuretic, instead of stopping RAASi may magnify rather than decrease the positive impact on albuminuria [20]. However, stopping RAASi was more common that initiating diuretics in the present cohort and hyperkalemia was a variable independently associated with stopping RAASi in participants not on dialysis, i.e. those that could benefit from their kidney protective effects, but not for initiating diuretics. Moreover, women were more likely to have RAASi stopped, despite the lower prevalence of hyperkalemia, illustrating potential gender differences in overall care and/or in hyperkalemia management.

Smoking has been associated with hyperkalemia previously but its different impact in men and women had not been described. In a US cohort of 1 208 815 primary care users, smoking was one of the strongest predictors of hyperkalemia, together with kidney failure, mineralocorticoid receptor antagonists and diabetes [22]. Among 180 type-2 diabetes and 180 non-diabetic patients with CKD followed in a nephrology

outpatient clinic, in multivariate analysis, CKD G4 (OR 4.53), use of angiotensin-converting enzyme inhibitors (ACEIs; OR 2.23) and smoking (OR 2.25) were independently associated with hyperkalemia [23]. Current smoking was also associated with predialysis serum potassium variability in hemodialysis patients [24]. Although etiological models suggested a potential causative role of current smoking on hyperkalemia, to our knowledge, the molecular determinants of hyperkalemia in smoking men are unknown. Smoking was associated with higher odds of low serum bicarbonate in patients with CKD, independently of eGFR, and metabolic acidosis promotes potassium exit from cells into the extracellular space [25]. Why this would be specific for men remains unclear. Different possibilities include a higher potassium ingestion in men, observed in some studies of 24 h urinary potassium excretion [26], a higher prevalence of current smoking in men or the number of cigarettes smoked (a 'dose' effect), as women tend to smoke a lower number of daily cigarettes [27]. Of note, former smokers did not have an increased risk of hyperkalemia in our study, suggesting that the impact of smoking in serum potassium is reversible. In this regard, classical studies already described a rapid, transient and dose-dependent increase in serum potassium, (around 67% over baseline) following the parenteral administration of nicotine to dogs, consistent with release of potassium from cells [28]. Additionally, the smoking-induced increase of catecholamines and the effect of catecholamines on serum potassium levels over time has also been suggested to potentially play a role [23].

The association of smoking and hyperkalemia may be clinically significant. Thus, among 434 027 RAASi users, smoking was independently associated with the risk of the first occurrence of death or cardiovascular events, together with increasing age, CKD, diabetes, and heart failure [29]. In a prospective study of 7636 middle-aged British men followed for 11.5 years, hyperkalemia (≥5.2 mEq/L) was independently associated with increased mortality, particularly non-cardiovascular deaths only among current smokers [30]. Indeed, among factors leading to discontinuation of ACEIs because of adverse drug events, history of smoking was a risk factor for hyperkalemia (HR: 5.4; 95% CI: 1.3–23.2) [31].

Despite the association of smoking with hyperkalemia and with the adverse outcomes of hyperkalemia, current textbooks do not mention smoking in chapters devoted to hyperkalemia nor in a recent KDIGO controversies conference of the topic [32, 33]. We propose that smoking should be addressed in men with CKD and hyperkalemia before considering alternatives such as stopping RAASi.

In this cohort free of CVD at baseline, hyperkalemia was independently associated with incident cardiovascular events. The association was stronger for men than for women. Various factors may have contributed to this observation, including the higher number of men and of cardiovascular events in men. These results are original as prior reports on the association of hyperkalemia with CV events in participants with CKD did not exclude those with baseline CVD.

Certain limitations should be acknowledged, including those inherent to observational studies that do not allow to draw definitive cause-and-effect conclusions. The risk factor analysis was centered around baseline risk factors. Additionally, neither the RAASi dose nor dietary information nor diuretic subclasses were collected. Spain is considered a low CVD risk (<100 CVD deaths per 100 000) country, together with France, the United Kingdom, Norway, Switzerland, Denmark, Belgium, and The Netherlands in Europe [34, 35]. Thus, results may not be extrapolated to higher CVD risk countries. However, the present study also has strengths. It reports on a large well-characterized cohort of CKD patients that expand the whole CKD G3 to G5D spectrum and encompasses both hemodialysis and PD patients. Furthermore, contrary to prior studies, it allows the dissociation between factors related to CKD and to CVD, as participants with baseline clinical or subclinical evidence of CVD were excluded from the cohort. Finally, it addresses gender-specific differences in risk facts and outcomes of hyperkalemia, identifying a clinically actionable and gender-specific risk factor for hyperkalemia, i.e. smoking. However, putative causal relationships should be validated in interventional studies.

In conclusion, hyperkalemia is common among men and women with CKD, but the prevalence and outcomes differ, potentially leading to actionable items of care. While the association observed in the present does not conclusively prove causality, etiological multivariate models suggest a potentially causal role of current smoking on hyperkalemia in men which is further supported by biological plausibility for a cause-and-effect relationship. Stopping smoking should be emphasized in all CKD patients, but especially in men with hyperkalemia given the intrinsic benefits of stopping smoking and the potential relationship with hyperkalemia, especially if stopping RAASi is being considered. In this regard, hyperkalemia was more clearly associated with adverse cardiovascular outcomes in men than in women with CKD. However, RAASi were more likely to be stopped in women with non-dialysis CKD despite a lower prevalence of hyperkalemia than men, pointing to gender differences in care that should be better characterized and addressed.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

APPENDIX

Aladrén Regidor, Mª José Hospital Comarcal Ernest Lluch (Calatayud); Almirall, Jaume; Ponz, Esther, Corporació Parc Taulí (Barcelona); Arteaga Coloma, Jesús Hospital de Navarra (Pamplona); Bajo Rubio, Mª Auxiliadora; Díaz, Raquel Hospital La Paz (Madrid); Belart Rodríguez, Montserrat, Sistemes Renals (Lleida); Gascón, Antonio, Hospital Obispo Polanco (Teruel); Bover Sanjuan, Jordi, Fundació Puigvert, IIB Sant Pau (Barcelona); Bronsoms Artero, Josep, Clínica Girona (Girona); Cabezuelo Romero, Juan B; Muray Cases, Salomé, Hospital Reina Sofía (Murcia); Calviño Varela, Jesús, Hospital Universitario Lugus Augusti (Lugo); Caro Acevedo, Pilar, Clínica Ruber (Madrid); Carreras Bassa, Jordi, Diaverum Baix Llobregat (Barcelona); Cases Amenós, Aleix; Massó Jiménez, Elisabet, Hospital Clínic (Barcelona); Moreno López, Rosario, Hospital de la Defensa (Zaragoza); Cigarrán Guldris, Secundino; López Prieto, Saray, Hospital Da Costa (Lugo); Comas Mongay, Lourdes, Hospital General de Vic (Barcelona); Comerma, Isabel, Hospital General de Manresa (Barcelona); Compte Jové, Mª Teresa, Hospital Santa Creu Jesús (Tarragona); Cuberes Izquierdo, Marta, Hospital Reina Sofía (Navarra); de Álvaro, Fernando; Hevia Ojanguren, Covadonga, Hospital Infanta Sofía (Madrid); de Arriba de la Fuente, Gabriel, Hospital Universitario Guadalajara (Guadalajara); del Pino y Pino, Mª Dolores, Complejo Hospitalario Universitario Torrecardenas (Almería); Diaz-Tejeiro Izquierdo, Rafael; Ahijado Hormigos, Francisco Hospital Virgen de la Salud (Toledo); Dotori, Marta. USP Marbella (Málaga); Duarte, Verónica, Hospital de Terrassa (Barcelona); Estupiñan Torres, Sara, Hospital Universitario Canarias (Santa Cruz de Tenerife); Fernández Reyes, Mª José, Hospital de Segovia (Segovia); Fernández Rodríguez, Mª Loreto, Hospital Príncipe de Asturias (Madrid); Fernández, Guillermina, Clínica Santa Isabel (Sevilla); Galán Serrano, Antonio, Hospital General Universitario de Valencia (Valencia); García Cantón, Cesar, Hospital Universitario Insular de Gran Canaria (Las Palmas); García Herrera, Antonio L, Hospital Universitario Puerto Real (Cádiz); García Mena, Mercedes, Hospital San Juan de Dios (Zaragoza); Gil Sacaluga, Luis; Aguilar, Maria, Hospital Virgen del Rocío (Sevilla); Górriz, José Luis, Hospital Universitario Doctor Peset (Valencia); Huarte Loza, Emma, Hospital San Pedro (Logroño); Lerma, José Luis, Hospital Universitario Salamanca (Salamanca); Liebana Cañada, Antonio, Hospital de Jaén (Jaén); Marín Álvarez, Jesús Pedro, Hospital San Pedro de Alcántara (Cáceres); Martín Alemany, Nàdia, Hospital Jose p Trueta (Girona); Martín García, Jesús, Hospital Nuestra Señora de Sonsoles (Ávila); Martínez Castelao, Alberto, Hospital Universitari de Bellvitge (Barcelona); Martínez Villaescusa, María, Complejo Hospitalario Universitario de Albacete (Albacete); Martínez, Isabel, Hospital Galdakao (Bilbao); Moina Eguren, Iñigo, Hospital Basurto (Bilbao); Moreno Los Huertos, Silvia, Hospital Santa Bárbara (Soria); Mouzo Mirco, Ricardo, Hospital El Bierzo, Ponferrada (León); Munar Vila, Antonia, Hospital Universitari Son Espases (Palma de Mallorca); Muñoz Díaz, Ana Beatriz, Hospital Virgen del Consuelo (Valencia); Navarro González, Juan F, Hospital Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife); Nieto, Javier; Carreño, Agustín, Hospital General Universitario de Ciudad Real (Ciudad Real); Novoa Fernández, Enrique, Complexo Hospitalario de Ourense (Ourense); Ortiz, Alberto; Fernandez, Beatriz, IIS-Fundación Jiménez Díaz (Madrid); Paraíso, Vicente, Hospital Universitario del Henares (Madrid); Pérez Fontán, Miguel, Complejo Hospitalario Universitario A Coruña (A Coruña); Peris Domingo, Ana, Hospital Francesc de Borja (Valencia); Piñera Haces, Celestino, Hospital Universitario Marqués de Valdecilla (Santander); Prados Garrido, Mª Dolores, Hospital Universitario San Cecilio (Granada); Prieto Velasco, Mario, Hospital de León (León); Puig Marí, Carmina, Hospital d'Igualada (Barcelona); Rivera Gorrín, Maite, Hospital Universitario Ramón y Cajal (Madrid); Rubio, Esther, Hospital Puerta del Hierro (Madrid); Ruiz, Pilar, Hospital Sant Joan Despí Moisès Broggi (Barcelona); Salgueira Lazo, Mercedes; Martínez Puerto, Ana Isabel, Hospital Virgen Macarena (Sevilla); Sánchez Tomero, José Antonio, Hospital Universitario de la Princesa (Madrid); Sánchez, José Emilio, Hospital Universitario Central de Asturias (Oviedo); Sans Lorman, Ramon, Hospital de Figueres (Girona); Saracho, Ramon, Hospital de Santiago (Vitoria); Sarrias, Maria; Serón, Daniel, Hospital Universitari Vall d'Hebron (Barcelona); Soler, María José; Barrios, Clara, Hospital del Mar (Barcelona); Sousa, Fernando. Hospital Rio Carrión (Palencia); Toran, Daniel, Hospital General de Jerez (Cadiz); Tornero Molina, Fernando, Hospital de Sureste (Arganda del Rey); Usón Carrasco, José Javier, Hospital Virgen de la Luz (Cuenca); Valera Cortes, Ildefonso, Hospital Virgen de la Victoria (Málaga); Vilaprinyo del Perugia, Mª Merce, Institut Catala d'Urologia i Nefrologia (Barcelona); Virto Ruiz, Rafael C, Hospital San Jorge (Huesca); Vicente Pallarés Carratalá Clinica MEDEFIS (Vila-real. Castellón), Carlos Santos Altozano CS Azuqueca de Henares (Guadalajara); Miguel Artigao Ródenas CS Zona III (Albacete); Inés Gil Gil Área Básica Sanitaria de Arán, CAP Viella (Lleida); Francisco Adan Gil CS Alfaro (La Rioja); Emilio García Criado Centro de Salud del Carpio (Córdoba.); Rafael Durá Belinchón CS Godella (Valencia); Jose Mª Fernández Toro CS Zona Centro (Cáceres); Juan Antonio Divisón Garrote Centro de Salud de Casas Ibáñez. Consultorio de Fuentealbilla (Albacete).

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