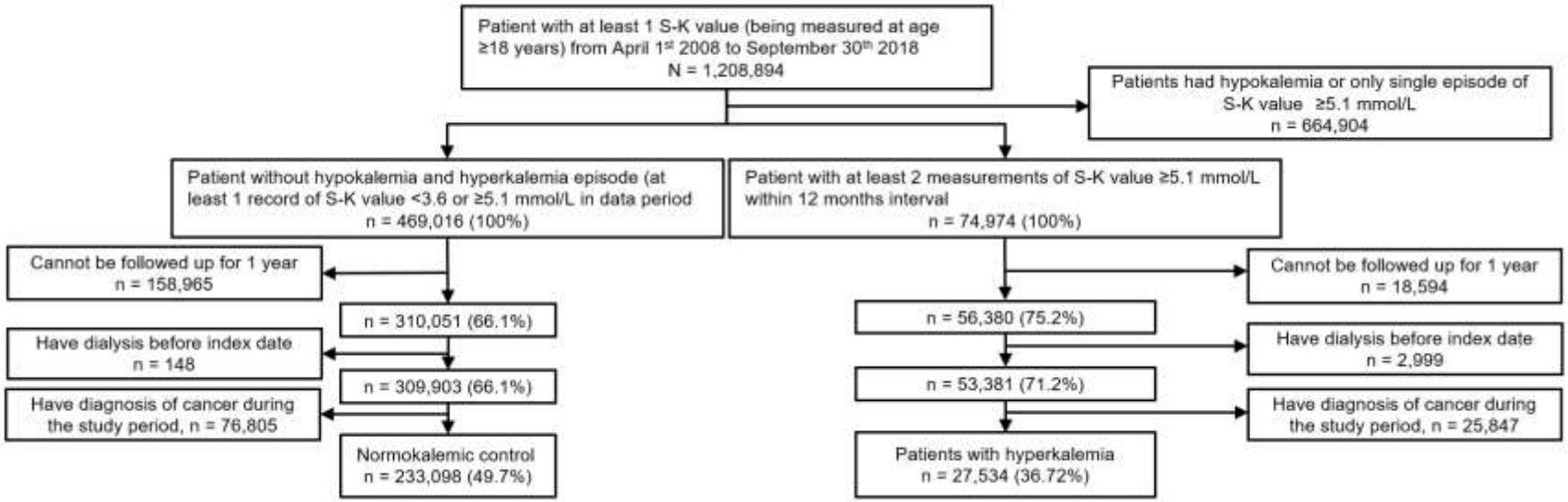
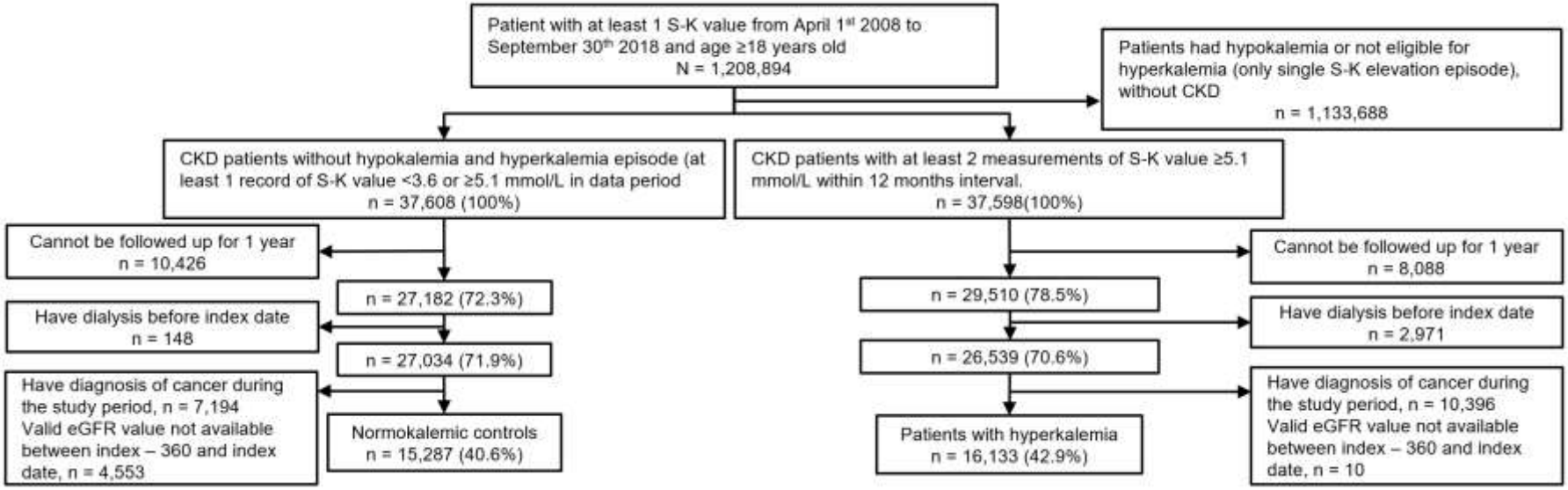
Figure S1. Flow diagram of patient inclusion in the study

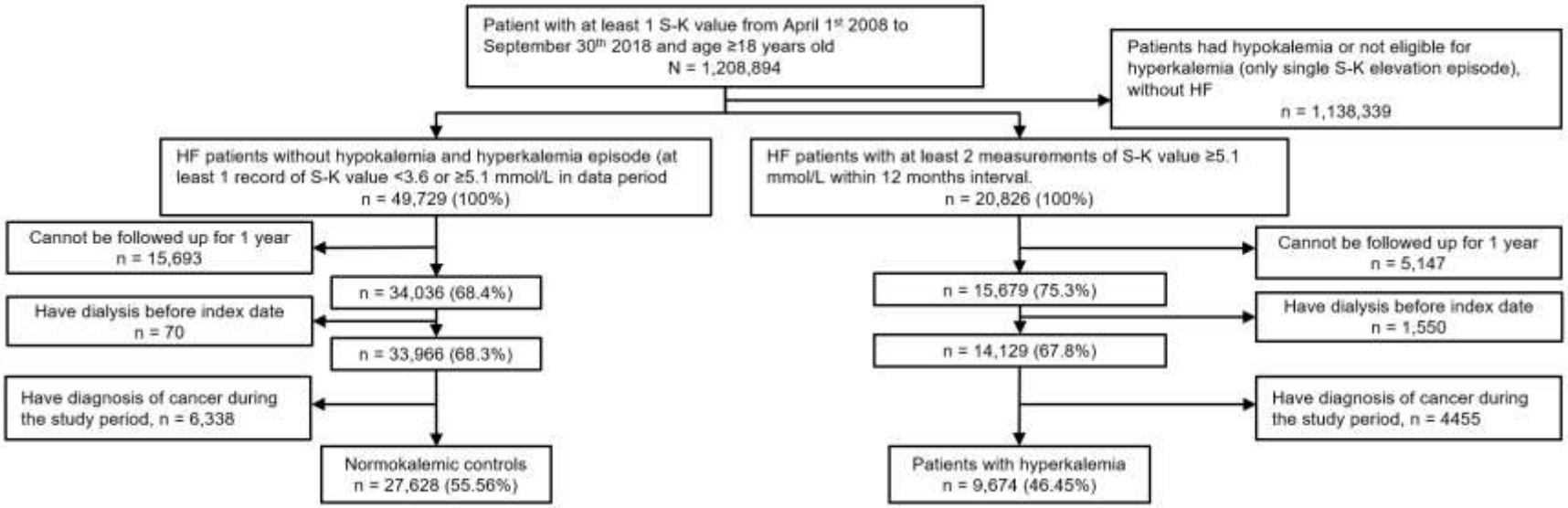
A Overall cohort



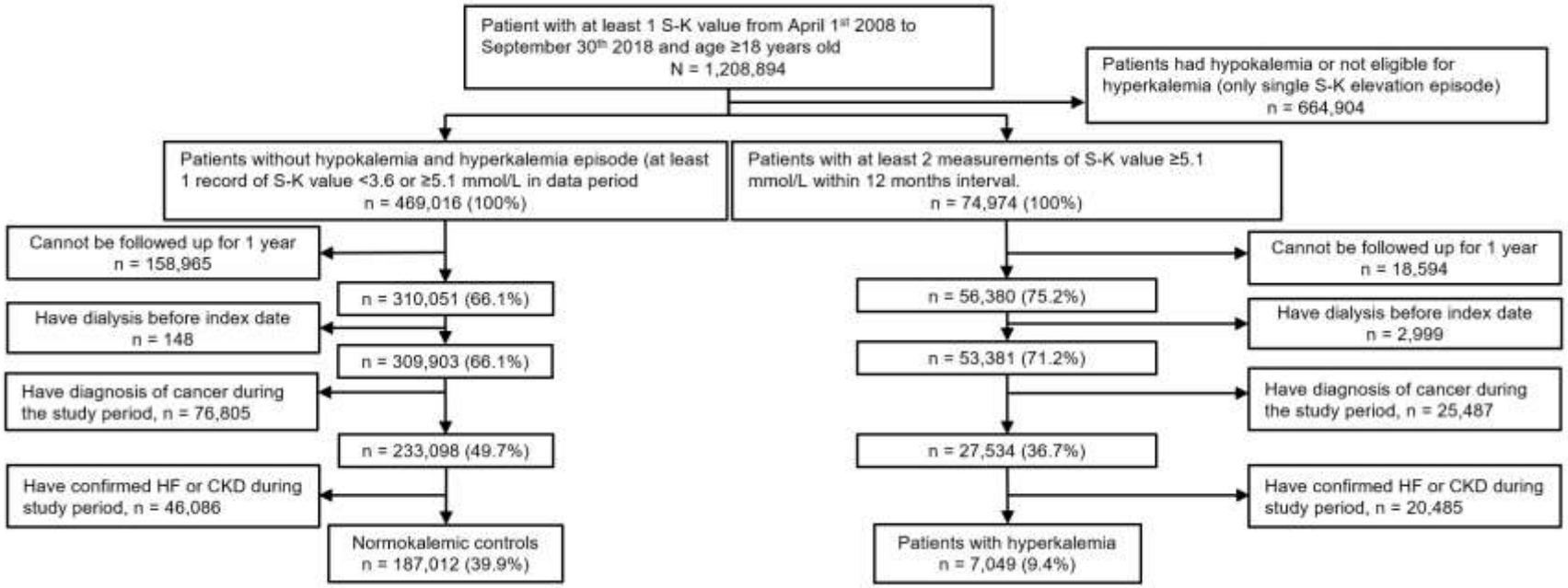
B CKD cohort


Patient with at least 1 S-K value from April 1st 2008 to September 30th 2018 and age ≥18 years old
N = 1,208,894
Patients had hypokalemia or not eligible for hyperkalemia (only single S-K elevation episode), without CKD
n = 1,133,688
CKD patients without hypokalemia and hyperkalemia episode (at least 1 record of S-K value <3.6 or ≥5.1 mmol/L in data period
n = 37,608 (100%)
CKD patients with at least 2 measurements of S-K value ≥5.1 mmol/L within 12 months interval.
n = 37,598(100%)
Cannot be followed up for 1 year
n = 10,426
n = 27,182 (72.3%)
Have dialysis before index date
n = 148
n = 27,034 (71.9%)
Have diagnosis of cancer during the study period, n = 7,194
Valid eGFR value not available between index – 360 and index date, n = 4,553
Normokalemic controls
n = 15,287 (40.6%)
Cannot be followed up for 1 year
n = 8,088
n = 29,510 (78.5%)
Have dialysis before index date
n = 2,971
n = 26,539 (70.6%)
Have diagnosis of cancer during the study period, n = 10,396
Valid eGFR value not available between index – 360 and index date, n = 10
Patients with hyperkalemia
n = 16,133 (42.9%)

C HF cohort

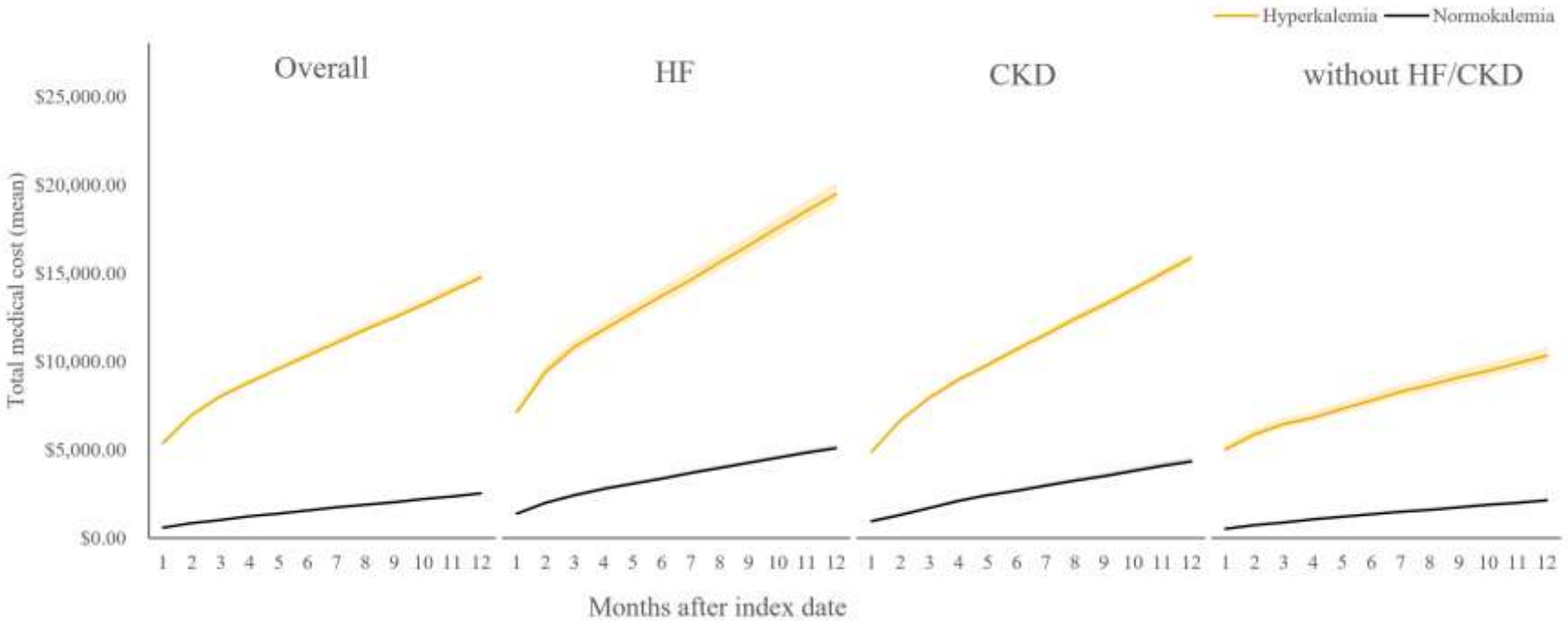

Patient with at least 1 S-K value from April 1st 2008 to September 30th 2018 and age ≥18 years old
N = 1,208,894
Patients had hypokalemia or not eligible for hyperkalemia (only single S-K elevation episode), without HF
n = 1,138,339
HF patients without hypokalemia and hyperkalemia episode (at least 1 record of S-K value <3.6 or ≥5.1 mmol/L in data period
n = 49,729 (100%)
HF patients with at least 2 measurements of S-K value ≥5.1 mmol/L within 12 months interval.
n = 20,826 (100%)
Cannot be followed up for 1 year
n = 15,693
n = 34,036 (68.4%)
Have dialysis before index date
n = 70
n = 33,966 (68.3%)
Have diagnosis of cancer during the study period, n = 6,338
Normokalemic controls
n = 27,628 (55.56%)
Cannot be followed up for 1 year
n = 5,147
n = 15,679 (75.3%)
Have dialysis before index date
n = 1,550
n = 14,129 (67.8%)
Have diagnosis of cancer during the study period, n = 4455
Patients with hyperkalemia
n = 9,674 (46.45%)

D Cohort of patients without CKD or HF



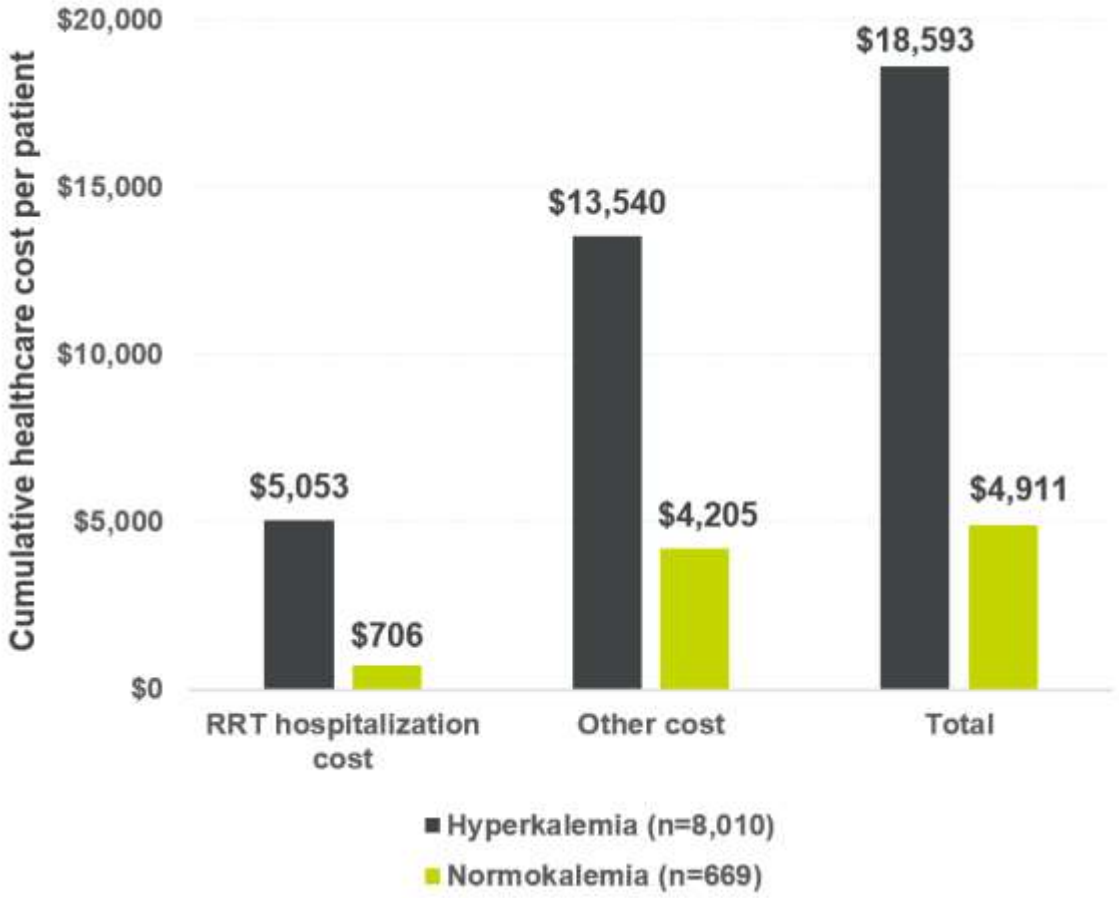
CKD, chronic kidney disease; HF, heart failure; S-K, serum potassium.

Figure S2. Cumulative healthcare cost within 12 months in cohorts with or without CKD or HF.



CKD, chronic kidney disease; HF, heart failure; S-K, serum potassium.

Figure S3. Cumulative healthcare cost per patient within 12 months in patients with CKD stage 4−5.



CKD, chronic kidney disease; RRT, renal replacement therapy.

Item S1. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2	Design: Observational retrospective cohort study…
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Structured abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	4	Line 94: In this study…
Methods				
Study design	4	Present key elements of study design early in the paper	5	Line 112: Study design and patient selection
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	Line 113: This was a retrospective cohort study…
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	Line 113: We extracted patients aged…
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7	Line 161: To measure the differences in healthcare costs…
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	Line 131: Covariates and health economic outcome
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5	Line 104: Data source Line 131: Covariates and health economic outcome
Bias	9	Describe any efforts to address potential sources of bias	7	Line 161: To measure the differences… Line 171: In addition…

Study size	10	Explain how the study size was arrived at	8	Line 186: We identified…

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Line 155: Statistical analysis
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Line 155: Statistical analysis
		(*b*) Describe any methods used to examine subgroups and interactions	7	Line 158: Hyperkalemia patients were stratified…
		(*c*) Explain how missing data were addressed	N.A.	We did not conduct any imputations for missing data. The limitations of using secondary data is described as study limitations in the discussion part.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N.A.	Because this is a retrospective cohort study using secondary data, we did not make effort to address the lost of follow up from database.
		(*e*) Describe any sensitivity analyses	N.A.	We did not conduct sensitivity analysis, instead we conducted stratified analysis and propensity score-matching to adjust the effect of confounders as much as possible.
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	Line 186: We identified…
		(b) Give reasons for non-participation at each stage	8	Line 187: After excluding…
		(c) Consider use of a flow diagram	Figure S1	Study flow diagram is depicted in the supplementary material.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	Line 194: Baseline characteristics of…
		(b) Indicate number of participants with missing data for each variable of interest	N.A.	N.A.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Table 1	Lengths of follow up
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8	Results
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N.A.	N.A.
		Cross-sectional study—Report numbers of outcome events or summary measures	N.A.	N.A.

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8	Described in the results section. For instance, we used 95% confidence intervals to present the estimated values.
		(*b*) Report category boundaries when continuous variables were categorized	8	Described in the results section. For instance, the severity of hyperkalemia was categorized based on the serum potassium values.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8	Described in the results section. For instance, the results were described as X-fold higher as well as absolute cost differences with 95% confidence intervals.

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8	Described in the results section. For instance, we provided subgroup analysis based on the CKD stages and subgroup based on the number of repeated hyperkalemic episodes.
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	Line 253: In this study…
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13	Line 310: Several limitations should…
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14	Line 326: Finally, since this was an observational study…
Generalisability	21	Discuss the generalisability (external validity) of the study results	13	Line 318: Data were collected…
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15	Line 348: Financial disclosure

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table S1. Definitions of high-risk subgroups

Subgroup	Definition
Chronic kidney disease	Defined as either a diagnosis of chronic nephritic syndrome (ICD-10 code: N03), glomerular disease (N05-N08), chronic kidney disease/chronic renal failure (N18-N19), diabetic nephropathy (E102, E112, E122, E132, E142), or hypertension with renal failure (I120, I13), or the presence of an average eGFR of <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ CKD stage 1: eGFR ≥90 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, stage 2: eGFR 60-89 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, stage 3a: eGFR 45-59 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, stage 3b: eGFR 30-44 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, stage 4: eGFR 15-29 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, and stage 5: eGFR <15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$
Diabetes mellitus	Defined as a diagnosis of DM (E10-E14)
Heart failure	Defined as a diagnosis of heart failure (I50, I110)
Hypertension	Defined as a diagnosis of hypertension (I10-I15)

ICD-10, International Classification of Diseases 10th revision; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus

Table S2. List of comorbidities

Condition	ICD-10 code
Myocardial infarction	I21; I22; I23; I24
Peripheral vascular disease	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	I60-I69; G45
Chronic pulmonary disease	J40-J47; J60-J67; J684; J701; J703; J841; J920; J961; J982; J983
Moderate to severe liver disease	B150; B160; B162; B190; K704; K72; K766; I85
Atrial fibrillation or atrial flutter	I48
Valvular heart disease	I00-I02; I05-I09; I34; I35; I36; I37; Q20-Q25;
Alcoholism-related or other substance-abuse related disorders	T36-T65; F10-F19; G312; G612; G721; I426; K292; K860; K70; R780; T51; Z714; Z721
Acute kidney injury	N17
Sepsis	A021, A207, A227, A241, A267, A282, A327, A394, A400-A403, A409-A415, A418-A419, A427, A548, B007, B349, B377, D71, I301, I330, J020, J209, J950, L029, L080, M8699, O080, O753, O85, O883
Gastrointestinal bleeding	K250, K252, K254, K256, K260, K262, K264, K266, K284, K290, K571, K573
Gastrointestinal perforation	K251, K252, K255, K256, K261, K265, K266, K285, K570, K572
Peripheral edema	R600

ICD-10, International Classification of Diseases 10th revision;

Table S3. Drug and non-drug treatment for renal disease stratified by CKD stages

	CKD stage 3a		CKD stage 3b		CKD stage 4		CKD stage 5	
	Hyperkalemia	Normokalemia	Hyperkalemia	Normokalemia	Hyperkalemia	Normokalemia	Hyperkalemia	Normokalemia
Within 12 months								
N	2,655	6,586	4,128	2,345	4,745	430	3,265	239
Erythropoietin stimulating agent, n (%)	69 (3)**	14 (0.2)	337 (8)**	26 (1)	1,365 (29)**	38 (9)	2,047 (63)**	28 (12)
Prescription days per year, Mean±SD	5.4±4.7	5.1±4.0	5.2±4.5	5.2±3.0	6.6±5.0	6.4±4.3	9.3±10.1*	4.9±3.9
Healthcare cost per patient per year, $, Mean±SD	928±1,554	686±429	759±1,021	785±504	942±1,030	888±1,127	1,128±1,144*	701±684
Phosphate binder, n (%)	1 (0.0)	3 (0.1)	9 (0.2)*	0 (0)	86 (2)*	0 (0)	950 (29)**	18 (8)
Prescription days per year, Mean±SD	62	138.3±95.7	135.7±118.7	n/a	121.3±106.0	n/a	139.1±126.4*	36.1±82.2
Healthcare cost per patient per year, $, Mean±SD	115	428±574	435±686	n/a	182±411	n/a	342±783	45±64
Active vitamin D, n (%)	136 (5)	302 (5)	234 (6)*	172 (7)	358 (8)	33 (8)	785 (24)**	18 (8)
Prescription days per patient per year, Mean±SD	228.2±135.0	262.6±120.8	217.7±136.0*	250.5±124.3	187.5±133.9*	264.2±121.4	152.8±130.9	151.3±154.6
Healthcare cost per patient per year, $, Mean±SD	114±108*	155±131	106±109*	144±146	73±90**	146±126	46±112	80±127
Uremic toxin absorbent, n (%)	29 (1)**	16 (0.2)	174 (4)**	28 (1)	800 (17)**	32 (7)	738 (23)**	12 (5)
Prescription days per year, Mean±SD	199.5±130.1	208.4±132.3	226.4±121.2	259.0±131.2	220.6±120.4	254.3±127.0	180.5±124.9*	105.3±129.1
Healthcare cost per patient per year, $, Mean±SD	825±826	783±851	1,136±789	1,136±794	1,110±756	1,311±843	948±784	655±790
Sodium bicarbonate, n (%)	636 (24)**	897 (14)	1,010 (24)**	305 (13)	1,335 (28)**	60 (14.0)	1,847 (57)**	57 (24)
Prescription days per year, Mean±SD	116.4±136.5	99.5±138.0	114.3±137.5	101.4±136.2	106.1±128.6	99.5±136.5	80.9±113.8	61.7±110.7
Healthcare cost per patient per year, $, Mean±SD	22±42**	16±25	22±41*	16±27	27±66	11±21	99±212*	37±69
Potassium binder, n (%)	357 (13)**	2 (0.0)	824 (20)**	8 (0.3)	1,632 (34)**	9 (2)	1,345 (41)**	6 (3)
Prescription days	133.1±128.1	54.5±51.6	137.7±132.5*	268.5±138.6	142.7±130.3*	230.4±129.1	130.8±125.9	72.0±128.3

per year, Mean±SD								
Healthcare cost per patient per year, $, Mean±SD	217±271	49±49	222±267	338±228	241±288	422±280	213±263	141±271
Hospitalization for renal replacement therapy, n (%)	12 (0.5)**	1 (0.0)	33 (1)**	0 (0)	181 (4)**	3 (1)	1,257 (39)**	38 (16)
Number of hospitalizations per year, Mean±SD	1.0±0.0	1	1.1±0.2	n/a	1.2±0.5	1.0±0.0	1.6±1.1	1.3±0.5
Healthcare cost per hospitalization, $, Mean±SD	88,279±83,690	13,653	29,210±33,394	n/a	21,816±25,373	9,761±1,132	14,739±18,436*	8,394±5,804
After 12 months								
N	2,495	6,550	3,735	2,313	4,090	402	2,652	221
Erythropoietin stimulating agent, n (%)	182 (7)**	32 (0.5)	676 (18)**	63 (3)	1,774 (43)**	42 (10)	1,368 (52)**	11 (5)
Prescription days per year, Mean±SD	3.9±5.4	3.8±3.6	4.2±4.9	3.3±3.3	6.0±6.0	5.3±5.0	8.0±10.8	4.8±4.7
Healthcare cost per patient per year, $, Mean±SD	655±1,680	747±1,033	667±1,051	496±597	854±906	832±1,710	898±1,085	899±1,033
Phosphate binder, n (%)	33 (1)**	5 (0.1)	110 (3)**	4 (0.2)	520 (13)**	3 (1)	1,117 (42)**	18 (8)
Prescription days per year, Mean±SD	62.5±67.2	72.7±66.4	68.6±82.3	16.7±17.1	97.8±100.4	73.7±44.5	131.9±132.5**	22.5±52.7
Healthcare cost per patient per year, $, Mean±SD	156±261	161±314	264±761	48±90	280±606	28±28	572±1,097*	25±36
Active vitamin D, n (%)	198 (8)**	387 (6)	373 (10)*	186 (8)	722 (18)*	47 (12)	909 (34)**	24 (11)
Prescription days per patient per year, Mean±SD	166.6±135.4**	206.2±134.9	154.4±131.1**	205.3±137.0	136.3±117.8	170.9±130.9	139.3±129.3	131.8±155.3
Healthcare cost per patient per year, $, Mean±SD	82±101**	124±123	69±90**	116±130	43±63**	85±94	37±95	74±126
Uremic toxin absorbent, n (%)	70 (3)**	31 (0.5)	336 (9)**	58 (3)	922 (23)**	43 (11)	400 (15)**	4 (2)
Prescription days per year, Mean±SD	121.6±118.6	161.9±117.7	156.4±119.6	165.6±126.5	164.9±121.7	187.1±123.7	148.4±120.0	196.8±180.4
Healthcare cost per patient per year, $, Mean±SD	595±607	672±647	711±629	687±658	802±654	951±649	765±675	989±978
Sodium bicarbonate, n	745 (30)**	1,269 (19)	1,212 (32)**	382 (17)	1,727 (42)**	73 (18)	1,397 (53)**	62 (28)

(%)								
Prescription days per year, Mean±SD	83.7±118.0*	71.7±117.7	84.6±116.5	76.2±116.8	80.8±109.0	77.6±122.4	59.8±96.3	54.9±105.2
Healthcare cost per patient per year, $, Mean±SD	19±40**	11±21	22±86*	12±22	43±149	9±19	106±330*	11±22
Potassium binder, n (%)	507 (20)**	8 (0.1)	1,057 (28)**	13 (1)	1,732 (42)**	7 (2)	947 (36)**	2 (0.9)
Prescription days per year, Mean±SD	130.3±122.6*	33.8±31.2	137.9±122.8	175.2±170.3	134.7±121.6	162.6±147.7	108.4±117.0	136.8±191.2
Healthcare cost per patient per year, $, Mean±SD	207±249	63±63	217±241	206±236	222±255	284±297	175±243	314±441
Hospitalization for renal replacement therapy, n (%)	54 (2)**	2 (0.0)	172 (5)**	1 (0.0)	716 (18)**	2 (0.5)	1,252 (47)**	23 (10)
Number of hospitalizations per year, Mean±SD	0.6±0.7	0.3±0.1	0.7±0.8	0.9	0.8±0.7	0.4±0.1	1.0±0.9*	0.6±0.3
Healthcare cost per hospitalization, $, Mean±SD	15,279±21,947	4,372±866	17,420±20,673	13,950	12,776±16,748	5,804±1,561	11,309±13,980	8,983±7,885

*p <0.05, ** p <0.001 vs. Normokalemic control by ANOVA for continuous variables and chi-squared test or Fisher's exact test for categorical variables.
CKD, chronic kidney disease; SD, standard deviation;

Table S4. Patient characteristics of propensity-score matched cohort of hyperkalemia and normokalemic controls

	Hyperkalemia (N=5,859)	Normokalemia (N=5,859)	Standardized Difference
Age			
Mean±SD	71±13	71±12	0.019
Age group, n (%)			
18-64	1,567 (27)	1,504 (26)	
65-79	2,710 (46)	2,786 (48)	0.029
80+	1,582 (27)	1,569 (27)	
Gender, male, n (%)	3,423 (58)	3,398 (58)	0.009
Lengths of follow up (months)			
Mean±SD	43.0±24.4	43.6±22.0	0.023
Serum potassium value at index date			
Mean±SD	5.3±0.3	4.3±0.3	3.462
Serum potassium value group, n (%)			
≥5.1 and <5.5 mmol/L	4,619 (79)	0 (0)	
≥5.5 and <6.0 mmol/L	1,021 (17)	0 (0)	
≥6.0 and <6.5 mmol/L	170 (3)	0 (0)	
≥6.5 and <7.0 mmol/L	30 (0.5)	0 (0)	
≥7.0 mmol/L	19 (0.3)	0 (0)	
CKD, n (%)	5,859 (100)	5,859 (100)	0
Stage 1	195 (3)	194 (3)	
Stage 2	1,091 (19)	1,070 (18)	
Stage 3a	2,264 (39)	2,301 (39)	0.032
Stage 3b	1,745 (30)	1,770 (30)	
Stage 4	394 (7)	379 (6)	
Stage 5	170 (3)	145 (2)	
HF, n (%)	1,548 (26)	1,575 (27)	0.010
Diabetes, n (%)	2,887 (49)	2,876 (49)	0.004
Hypertension, n (%)	4,158 (71)	4,206 (72)	0.018
Dyslipidemia, n (%)	1,970 (34)	2,011 (34)	0.015
Charleson comorbidity index, Mean±SD	1.0±1.1	1.1±1.1	0.019
RAASi treatment, n (%)	2,718 (46)	2,754 (47)	0.012
ACEi	501 (9)	404 (7)	0.062

ARB	2,145 (37)	2,341 (40)	0.069
MRA	586 (10)	297 (5)	0.188
Thiazide diuretics, n (%)	98 (2)	188 (3)	0.010
Loop diuretics, n (%)	563 (10)	475 (8)	0.053

*Standardized difference >0.1 was considered as non-negligible difference. SD, standard deviation; CKD, chronic kidney disease; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitor; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralcorticoid receptor antagonist.