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Impact of hyperuricemia on CKD risk beyond genetic predisposition in a population-based cohort study

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The bidirectional effect of hyperuricemia on chronic kidney disease (CKD) underscores the importance of hyperuricemia as a risk factor for CKD. We evaluated the effect of hyperuricemia on the presence and development of CKD after considering genetic background by calculating polygenic risk scores (PRSs). We employed genome-wide association study summary statistics—excluding the United Kingdom Biobank (UKB) datasets among published CKD Gen Consortium papers—to calculate the PRSs for CKD in white background subjects. To validate PRS performance, we divided the UKB into two datasets to validate and test the data. We used logistic regression analysis to evaluate the association between hyperuricemia and CKD, and performed Kaplan–Meier survival analysis exclusively for subjects with available follow-up data. In total, 438,253 clinical data and 4,307,940 single nucleotide polymorphisms from 459,155 samples were included. We observed a significant positive association between PRS and CKD and the presence and development of CKD. Hyperuricemia significantly increased CKD risk (adjusted odds ratio 1.55, 95% confidence interval 1.48–1.61). The impact of hyperuricemia on CKD was maintained irrespective of PRS range. In addition, negative interaction between hyperuricemia and PRS for CKD was found. Survival analysis indicates that the presence of hyperuricemia significantly increased the risk of CKD development. The PRS for CKD thoroughly reflects the risk of CKD development. Hyperuricemia is a significant indicator of CKD risk, even after incorporating the genetic risk score for CKD. Irrespective of genetic risk, patients with a prospective risk of developing CKD require uric acid monitoring and management.

Keywords Polygenic risk score, Uric acid, Hyperuricemia, Chronic kidney disease

Chronic kidney disease (CKD) is a significant public health issue with an increasing prevalence[1,2]. As a progressive condition, identifying risk factors and prognostic factors, particularly those that can be modified, could significantly reduce the disease burden. Hyperuricemia is an emerging non-traditional risk factor for the development and progression of CKD[3,4]. Although epidemiological studies have shown that hyperuricemia increases the risk of kidney dysfunction,[5,6] the role of hyperuricemia in CKD is not yet fully established.

Uric acid functions as an antioxidant in the extracellular environment, and plays a protective role in neurological diseases such as multiple sclerosis[7,8]. However, intracellular uric acid acts as a pro-oxidant, reducing endothelial nitric oxide activity and inhibiting cellular proliferation and migration[9,10]. Hyperuricemia can trigger hypertension and accelerate the progression of CKD as a result of long-term activation of the renin–angiotensin–aldosterone system, oxidative stress, and the loss of endothelial nitric oxide[11–13]. In addition, a high level

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of serum uric acid has been found to be independently associated with CKD, metabolic syndrome, and cardiovascular disease[14,15].

Since the development of uric acid-lowering agents, may experimental and clinical studies have been conducted to demonstrate their disease-preventive effects[16,17]. Randomized trials have shown that allopurinol or febuxostat, which reduce uric acid levels, have a positive impact on systolic blood pressure, estimated glomerular filtration, and albuminuria[18–20]. Based on these results, several studies have attempted to identify genetic polymorphisms that affect serum uric acid levels and increase the risk of CKD[21,22]. However, the association between a genetic urate score and CKD has not yet been confirmed.

Recently, it was shown that polygenic risk scores (PRSs) calculated based on large-scale genome-wide association studies (GWAS) can estimate the effect of genetic variants on the risk of the disease of interest. Considering the complexity of the risk factors contributing to CKD development, the PRS for CKD was calculated to evaluate the genetic effects on CKD and their interactions with other risk factors of interest. We aimed to evaluate whether hyperuricemia has an additional effect on the risk of CKD, in addition to the genetic risk assessed by the PRS, given its nature as a modifiable risk factor.

Methods

Study populations and data acquisition

We utilized the United Kingdom Biobank (UKB) prospective cohort data (https://www.ukbiobank.ac.uk)[23]. The UKB is a large-scale database which comprises the data of 502,413 individuals aged between 40 and 69 years. For the phenotype dataset, we excluded subjects with non-white background, without data for serum creatinine, cystatin C, without applicable data for CKD or ESKD based on the ICD-10 code. We focused on non-Hispanic white subjects, who contributed to 94% of the UKB cohort, resulting in sample of 438,253 subjects for our final analysis. For the sensitivity analysis with longitudinal data set, we collected the second time repeated measurements of date of attending assessment center, which includes kidney-related phenotypes such as serum creatinine, cystatin C, ICD-10 code for CKD or ESKD.

Definition of clinical outcome and exposures

CKD was considered the main outcome, and we defined CKD as the presence of one or more of the following conditions in the baseline or second stage cohort of the UKB database: 1) estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 by creatinine (field 30,700) or cystatin C (field 30,720) based on the CKD Epidemiology Collaboration (CKD-EPI) equation; 2) a diagnostic code for CKD stage 3–5 (N18.3–N18.5) or end-stage kidney disease (ESKD) (N18.6, Z94.0) based on the International Classification of Disease 10th revision (ICD-10) code (field 41,270); or 3) a record of ESKD diagnosis (field 42,026 or 42,027).

As the main exposure, uric acid was used as a continuous and categorical variable, defining hyperuricemia as urate levels > 420 μmol/L in males and > 360 μmol/L in females.

Genotyping, quality control, and imputation

Among the 502,413 subjects in the UKB, 50,000 were genotyped using the UK Biobank Lung Exome Variant Evaluation (UK BiLEVE) Axiom Array by Affymetrix and the remaining subjects were genotyped using the UK Biobank Axiom Array. Pre-phasing was carried out with SHAPEIT3[24] with 1000 Genome phase 3,[25] and imputation of untyped single nucleotide polymorphisms (SNPs) was performed with IMPUTE4 (https://jmarchini.org/software/)[26] using UK10K, 1000 Genome phase 3, and the HRC panel,[27] resulting in 93,095,623 autosomal SNPs. The imputed dataset was downloaded and quality control was performed. SNPs were filtered out if the missing genotype rates were ≥ 0.01, Hardy–Weinberg Equilibrium P values were < 10^{-6}, or minor allele frequencies (MAF) were < 0.01. Subjects were excluded if the they were not from a White background. The detailed procedure is illustrated in Fig. 1. All data management was performed using PLINK,[28] PLINK2,[29] GCTA,[30] and ONETOOL[31].

GWAS and heritability analyses

We estimated SNP heritability and genetic correlations using linkage disequilibrium (LD) score regression[32]. LD score regression requires summary statistics from GWASs, and GWASs were conducted with the UKB dataset using logistic regressions for CKD and hyperuricemia after adjusting for the effects of baseline age, sex, and ten principal components (PC) corresponding to the top 10 largest eigenvalues.

PRS calculation and its evaluation

PRS derivation requires GWAS summary statistics and we considered the following GWAS summary data which did not include UKB dataset among the published CKD Gen Consortium papers (https://ckdgen.imbi.uni-freiburg.de/)[33]. Results from SNPs with MAF ≥ 0.005 were utilized for PRS. PRSs were calculated with clumping + thresholding (CT),[34] LDpred with infinitesimal, grid and auto models,[35,36] lassosum,[37] and PRS continuous shrinkage (CS)[38]. For CT, we set the clumping at $P = 10^{-5}$ and pruning at $r^2 = 0.2$. For the LDpred grid model, the proportions of causal variants ρ were set at 0.03, 0.01, 0.3, 0.1, and 1. A 1000 Genomes Phase 3 European subpopulation was used as the linkage disequilibrium (LD) reference panel. For the other hyperparameters, we used the default values. To examine the prevalence of CKD as an increase in PRS, the calculated PRSs for CKD were categorized into deciles. In addition, for logistic regression, we re-defined PRS groups as tertile ranges, and 2nd tertile range was regarded as a reference in the logistic regression model for evaluating the effect of PRS on prevalent CKD.

To validate the PRS performance, we separated the UKB into two datasets of a white background group to validate and test the data. For validation and testing, we used 47,611 subjects genotyped using the UK BiLEVE array chip, and 390,642 subjects genotyped using the Axiom chip. Validation data was used to fit the logistic

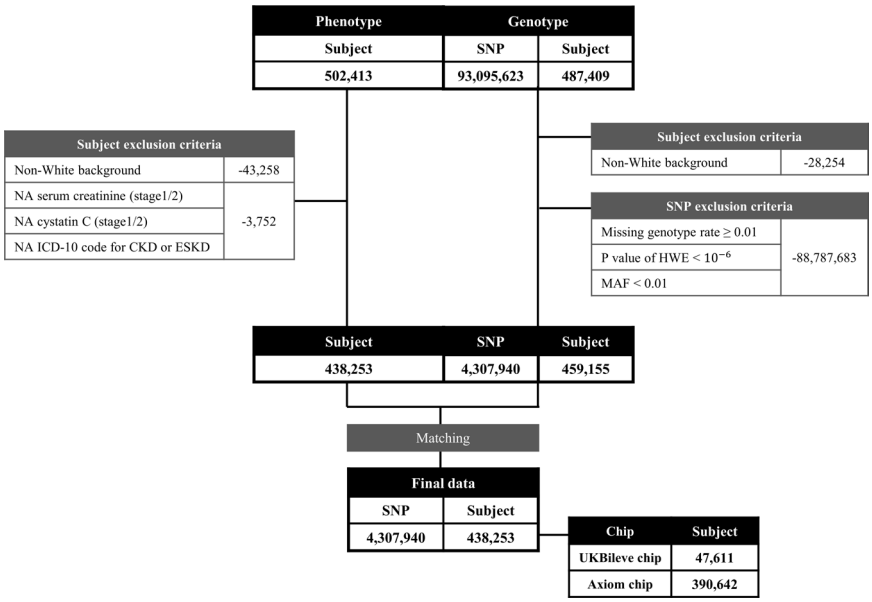

Figure 1. Flow diagram of the study from clinical phenotype and genotype data.

regression of PRS on CKD after adjusting for baseline age, sex, PRS, and PC 1–10 on CKD outcome. Akaike information criterion (AIC) was used to choose the best PRS method.

The PRS significance was evaluated by applying logistic regression to the test data. We included baseline age, sex, eGFR, body mass index (BMI), smoking status, physical activity, comorbidities (type 2 diabetes mellitus [T2DM], hypertension [HTN], cardiovascular diseases [CVD]), hemoglobin, glucose, albumin, calcium, cholesterol and PC 1–10 as covariates. We also conducted survival analyses using the test data. The age at CKD onset was considered the main outcome, and the same covariates as in the logistic regression were used. Survival analyses were conducted using the survival package[39] (version 3.4.0) and ggsurvfit package[40] (version 0.2.0) of R (version 4.5.0).

PRS analysis results for different models are shown in Supplementary Table S1. Among SNPs with GWAS results from Wuttke et al.[33], genotypes for 3,898,527 SNPs were observed in UKB, and they were used for PRS analyses. LDpred grid1 ($P = 0.03$) had the best performance ($P = 1.18 \times 10^{-43}$ and of model AIC = 25,199.84), and was used for subsequent analysis.

Statistical analysis

The baseline characteristics of subjects with and without hyperuricemia were compared using the Student's t-test and the chi-square test. Logistic regression analysis was used to evaluate the association between hyperuricemia and CKD, adjusting for covariates such as age, sex, BMI, smoking status, comorbidities (HTN, T2DM, and CVD), physical activity, blood laboratory findings (hemoglobin, glucose, albumin, calcium, and cholesterol), PRS, and PC 1–10. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated for incident CKD outcomes based on the PRSs. To rigorously investigate the interaction between hyperuricemia and PRS for CKD, we incorporated an interaction term as a covariate in the logistic regression analysis. In addition, we categorized the participants into six groups for analysis based on the tertile range of PRS and hyperuricemia status: PRS for CKD 1st tertile & hyperuricemia (−), PRS for CKD 1st tertile & hyperuricemia (+), PRS for CKD 2nd tertile & hyperuricemia (−), PRS for CKD 2nd tertile & hyperuricemia (+), PRS for CKD 3rd tertile & hyperuricemia (−), and PRS for CKD 3rd tertile & hyperuricemia (+). The group PRS for CKD 1st tertile & hyperuricemia (−) was used as the reference. Furthermore, we assessed the impact of hyperuricemia on CKD development based on sex (male and female), baseline age (age < 60 and age ≥ 60), and T2DM (control and T2DM).

We performed Kaplan–Meier survival analysis to access the risk of CKD development among subjects without underlying CKD who were sequentially followed up in the UKB database. We used hyperuricemia status and PRS grade as independent variables, and the newly diagnosed CKD as the outcome. All analyses were performed using R software, version 3.6.3 (R Foundation) and Rex. All Two-sided P values were two-sided reported, and $P < 0.05$ was considered to indicate statistical significance[41].

Ethical considerations

This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Seoul National University Boramae Medical Center (IRB No. 07-2022-45). The usage of the UK Biobank data was approved by the UK Biobank consortium (application No. 53799). Acquisition of informed consent was not required, as the study investigated anonymous public databases and genetic summary statistics.

Results

Study populations

A total of 438,253 subjects with available clinical data were included in the study, of which 28,970 (6.6%) had CKD and 57,656 (13.2%) had hyperuricemia. Subjects with hyperuricemia were more likely to be male, older, have a higher BMI, and more likely to have HTN, T2DM, and CVD (Table 1). In addition, subjects with hyperuricemia showed a lower eGFR and a higher incidence of CKD, greater albuminuria, higher serum glucose, lower high-density lipoprotein cholesterol, higher low-density lipoprotein cholesterol, and higher triglyceride levels (Table 1).

Heritability analyses and genetic correlation

The estimated heritability from the summary statistics of GWAS on CKD and hyperuricemia were 0.0292 (SE = 0.0021, $P = 5.93 \times 10^{-44}$) and 0.0709 (SE = 0.009, $P = 3.33 \times 10^{-15}$), respectively. Their genetic correlation was 0.5076 (SE = 0.0505, $P = 9.55 \times 10^{-24}$).

Association between PRSs and the risk of CKD

The prevalence of CKD increased from 1645 (4.23%) to 3624 (9.28%) between the 1st decile and the 10th decile (Supplementary Table S2). Different PRS densities in subjects with and without CKD are shown in Supplementary Figure S1.

According to the PRSs, subjects within the 1st tertile of PRSs showed a significantly decreased risk of the development of CKD (OR 0.78), and it was maintained after adjustment of covariates (aOR 0.93, 95% CI 0.89–0.97). On the contrary, subjects within the 3rd tertile showed a significantly increased risk for the development of CKD (OR 1.31), and it was also maintained after adjustment of covariates (aOR 1.12, 95% CI 1.08–1.17) (Table 2).

In the stratified analysis using the tertile ranges of PRS, there was a decreased risk of CKD in the 1st tertile of PRS and an increased risk of CKD in the 3rd tertile of PRS in females and in subjects without T2DM. The impact of PRS was significant irrespective of age groups stratified by a cut-off age of 60 years (Supplementary Table S3).

	Total (n = 438,253)	Hyperuricemia (−) (n = 380,597)	Hyperuricemia (+) (n = 57,656)	Statistic	*P*-value
Age, mean (SD)	56.8 (8.0)	56.5 (8.1)	58.2 (7.7)	−48.13	< 0.001
Male, n (%)	200,531 (45.8)	165,280 (43.4)	35,251 (61.1)	6329.27	< 0.001
Body mass index, mean (SD)	27.39 (4.8)	26.9 (4.5)	30.6 (5.2)	−161.92	< 0.001
< 18.5 kg/m^2	1249 (0.3)	1223 (0.3)	26 (0.1)	26,224.53	< 0.001
18.5–25 kg/m^2	143,992 (33.0)	138,103 (36.4)	5889 (10.3)		
25–30 kg/m^2	186,102 (42.6)	162,235 (42.8)	23,867 (41.6)		
≥ 30 kg/m^2	105,503 (24.2)	77,870 (20.5)	27,633 (48.1)		
Physical Activity	3.4 (2.5)	3.4 (2.5)	3.2 (2.5)	23.12	< 0.001
Smoking status					
Current smoker, n (%)	45,641 (10.5)	40,296 (10.6)	5345 (9.3)	1975.76	< 0.001
Ex-smoker, n (%)	155,503 (35.6)	130,311 (34.4)	25,192 (43.9)		
Non-smoker, n (%)	235,548 (53.9)	208,676 (55.0)	26,872 (46.8)		
Comorbidities					
Hypertension	229,343 (52.7)	188,546 (49.9)	40,797 (71.2)	9009.05	< 0.001
Diabetes	30,127 (7.2)	23,087 (6.4)	7040 (12.8)	2981.76	< 0.001
Cardiovascular disease	45,169 (12.5)	35,504 (11.4)	9665 (19.6)	2623.00	< 0.001
Chronic kidney disease	28,970 (6.6)	18,861 (5.0)	10,109 (17.5)	12,829.03	< 0.001
Laboratory results					
Hemoglobin, g/dL	14.2 (1.2)	14.1 (1.2)	14.5 (1.2)	−70.52	< 0.001
Calcium, mmol/L	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	−45.50	< 0.001
Albumin, g/L	45.2 (2.6)	45.2 (2.6)	45.3 (2.7)	−7.15	< 0.001
Glucose, mmol/L	5.1 (1.2)	5.1 (1.2)	5.3 (1.2)	−32.09	< 0.001
Cholesterol, mmol/L	5.7 (1.1)	5.7 (1.1)	5.7 (1.2)	−0.75	0.454
Uric acid, μmol/L	309.1 (80.4)	289.1 (62.9)	441.2 (54.0)	−615.68	< 0.001
Creatinine based eGFR, mL/min/1.73 m^2	94.3 (11.2)	95.3 (10.3)	87.6 (14.5)	123.44	< 0.001
Cystatin C based eGFR, mL/min/1.73 m^2	90.8 (12.8)	92.1 (11.7)	82.5 (16.1)	136.96	< 0.001
chip = Axiom	390,642 (89.1)	340,093 (89.4)	50,549 (87.7)	146.52	< 0.001
chip = UK BiLEVE	47,611 (10.9)	40,504 (10.6)	7107 (12.3)		

Table 1. Baseline characteristics. SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rates.

Group	Model 1		Model 2	
	OR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
PRS 1st tertile	0.78 (0.76, 0.81)	< 0.001	0.93 (0.89, 0.97)	< 0.001
PRS 2nd tertile	Reference		Reference	
PRS 3rd tertile	1.31 (1.27, 1.35)	< 0.001	1.12 (1.08, 1.17)	< 0.001

Table 2. Impact of PRS on the risk of CKD. Model 1. Non-adjusted. Model 2. Adjusted with age, sex, body mass index, smoking status, comorbidities (hypertension, diabetes, cardiovascular disease), physical activity, laboratory findings (hemoglobin, serum glucose, albumin, calcium, cholesterol, estimated glomerular filtration rate), hyperuricemia, PC1 ~ 10. CKD, chronic kidney disease; PRS, polygenic risk score; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

Association between hyperuricemia and prevalent CKD

As a continuous variable, high uric acid levels increased the risk of CKD (Fig. 2). The presence of hyperuricemia (aOR 1.55, 95% CI 1.48–1.61) and higher PRS (aOR 1.12, 95% CI 1.09–1.14) increased risk of CKD, respectively. Additionally, there were a significant negative interaction between hyperuricemia and PRS for CKD (Table 3).

To enhance intuitive comprehension, we conducted an integrated grouping analysis based on the PRS for CKD and the presence of hyperuricemia. Compared to subjects within the 1st tertile of PRS without hyperuricemia, there was a trend of increasing risk of CKD in subjects within the 2nd and 3rd tertile of PRS; additionally, the risk of CKD was particularly prominent among the subjects with hyperuricemia (Fig. 3).

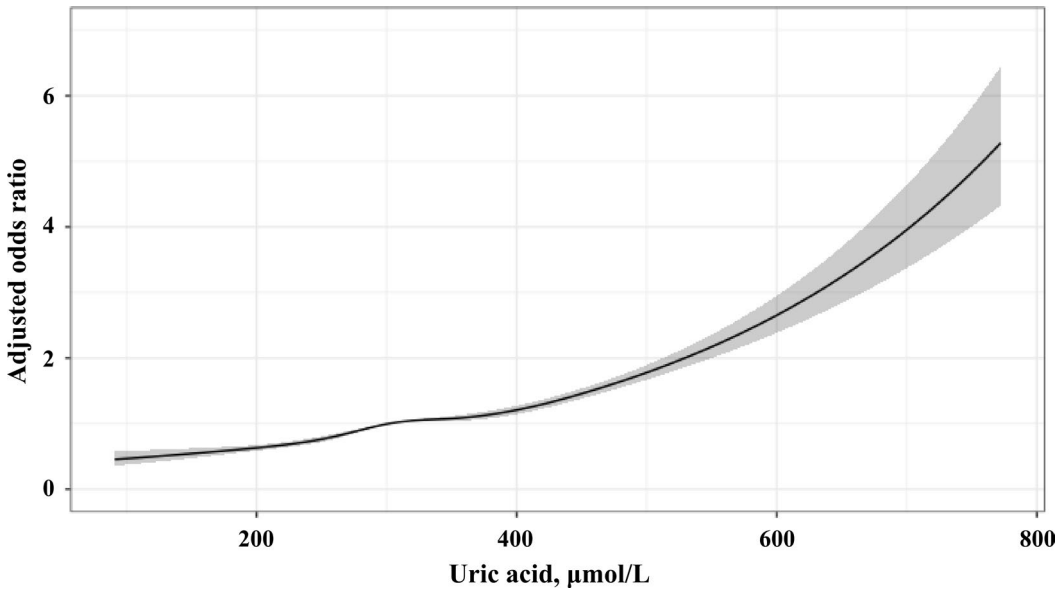

Figure 2. Spline curve for the risk of CKD based on the level of uric acid. Multivariable logistic regression included covariates including age, sex, body mass index, smoking status, comorbidities (hypertension, diabetes, cardiovascular disease), physical activity, laboratory findings (hemoglobin, serum glucose, albumin, calcium, cholesterol, estimated glomerular filtration rate), PC1 ~ 10, PRS for CKD, interaction between urate and PRS for CKD. CKD, chronic kidney disease.

	Hyperuricemia			PRS for CKD			*Interaction		
	β	aOR (95% CI)	*P*-value	*β*	aOR (95% CI)	*P*-value	*β*	aOR (95% CI)	*P*-value
Whole populations	0.44	1.55 (1.48, 1.61)	< 0.001	0.11	1.12 (1.09, 1.14)	< 0.001	− 0.05	0.95 (0.92, 0.99)	0.016

Table 3. Significance of hyperuricemia, PRS for CKD, and their interaction for the risk of CKD. Adjusted variables: age, sex, body mass index, smoking status, comorbidities (hypertension, diabetes, cardiovascular disease), physical activity, laboratory findings (hemoglobin, serum glucose, albumin, calcium, cholesterol, estimated glomerular filtration rate), hyperuricemia, PRS for CKD, PC1 ~ 10, interaction between hyperuricemia and PRS for CKD. CKD, chronic kidney disease; PRS, polygenic risk score; aOR, adjusted odds ratio; CI, confidence interval. *Interaction between hyperuricemia and PRS for CKD.

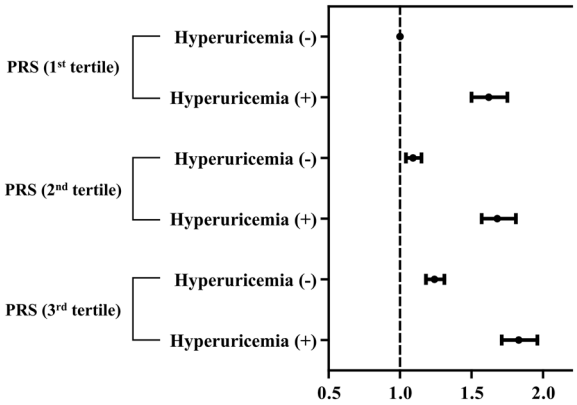

Figure 3. Effect of hyperuricemia on CKD according to the PRS group. PRS group was divided into tertile ranges, and subjects included 1st terile of PRS without hyperuricemia was regarded as a reference group. The X-axis represents the adjusted odds ratio, and the covariates are as follows. Multivariable logistic regression included covariates including age, sex, body mass index, smoking status, comorbidities (hypertension, diabetes, cardiovascular disease), physical activity, laboratory findings (hemoglobin, serum glucose, albumin, calcium, cholesterol, estimated glomerular filtration rate), PC1 ~ 10. CKD, chronic kidney disease; PRS, polygenic risk score.

In the stratified analysis based on sex, the significance of hyperuricemia was higher in females (aOR 1.88, 95% CI 1.69–2.08) than males (aOR 1.29, 95% CI 1.17–1.42) after adjustment for CKD. In addition, the significance of hyperuricemia in CKD was maintained irrespective of age and the presence of T2DM (Supplementary Table S4).

Risk of the development of CKD

A total of 14,699 subjects with follow-up data were included in the survival analysis. During the 51.9 ± 11.0 months of follow-up period, 114 patients (0.8%) were newly diagnosed with CKD. According to the PRS grade, 34 (0.7%), 27 (0.6%), and 53 (1.1%) patients had newly developed CKD in the 1st tertile, 2nd tertile, and 3rd tertile of the PRS grade, respectively. The different baseline characteristics according to PRS grades are shown in Supplementary Table S5. Except for kidney function-related indicators, there were no significant differences in characteristics according to PRS grade. In the survival analysis for CKD development according to the tertile grades of PRS, subjects within the 3rd tertile of PRS showed the highest risk of incident CKD (Supplementary Figure S2).

A total of 2382 (16.2%) patients had hyperuricemia. Participants with hyperuricemia were older, had a higher prevalence of obesity, and engaged in less physical activity. Although there were statistically significant differences in laboratory results between the two groups, these differences were found to be subtle (Supplementary Table S6). Hyperuricemia also significantly increased the risk of developing CKD (Supplementary Figure S3).

Discussion

As a significant modifiable risk factor, we investigated the effect of hyperuricemia on the development of CKD, adding to the genetic risk of CKD, which was estimated based on the PRS. PRSs for CKD were significantly associated with the presence and development of CKD. Considering these genetic risk factors for CKD with PRSs, hyperuricemia was found to play a major role in both the development and presence of CKD. Regardless of the genetic risk of CKD, hyperuricemia may be a significant factor that needs to be managed.

CKD involves complex disease entities including genetic and environmental factors. Significant progress has been made in human genetics in recent decades, leading to improvements in high-throughput genotyping, sequencing technologies, statistical genetics, and bioinformatics. Currently, 600 genes are implicated in monogenic kidney diseases, and GWASs have suggested that hundreds of genes contribute to complex kidney diseases[33,42–44]. The development of GWASs with large-scale population-based data significantly facilitates the risk stratification of CKD using PRS. In this study, we also found that the PRS for CKD showed a positive association with the risk of CKD, even after adjusting for well-known risk factors.

Uric acid is usually generated in the liver and intestine as a byproduct of the purine metabolic pathway, and the kidney has responsible for excreting two-thirds of the uric acid[45]. Although uric acids have a potent role as an antioxidant that can neutralize superoxide, hydroxyl radicals, and singlet oxygen,[46] it has been widely accepted that hyperuricemia with hyperuricosuria causes kidney disease by depositing intraluminal crystal in the collecting duct of the nephron, similar to how gout does with the joints[47,48]. In addition, epidemiological studies have demonstrated that higher levels of uric acid are significantly related to an increased risk of CKD[4,49,50]. Nevertheless, the causal relationship between hyperuricemia and CKD is not clearly understood because of the bidirectional effects between uric acid and kidney function and the abundance of confounding factors.

Similar to attempts to determine the genetic effect on CKD, GWASs have uncovered roughly 30 loci that regulate serum uric acid, including uric acid transporters and regulatory transporter-associated proteins[51,52]. Moreover, among 50 loci associated with eGFR and CKD, nine were identified that are commonly associated with serum uric acid concentration[53]. Although a causal relationship between hyperuricemia and CKD has not

been established yet, we found that there is a relative genetic correlation between CKD and hyperuricemia in this study. Nevertheless, the relationship between uric acid and CKD cannot be easily understood because of the uncontrollable and complex pathway that involves genetic factors related to the regulation of uric acid levels and such target diseases, as well as environmental and/or dietary factors. Therefore, using the PRS for CKD, we evaluated the additional impact of hyperuricemia on CKD. Finally, we found that hyperuricemia played a significant role in increasing the risk of CKD, regardless of the genetic risk score for CKD.

Our findings demonstrate that the effect of hyperuricemia on CKD supports those of previously reported randomized clinical trials demonstrating the efficacy of uric acid-lowering agents in preserving kidney function[18–20]. Recent research involving advanced CKD patients with a high risk of progression found no statistically significant differences between allopurinol and the control group regarding eGFR decline[54]. Another clinical trial using febuxostat also showed an insignificant effect on preserving kidney function in advanced CKD patients[55]. These findings may be related to an attenuation of the effectiveness of pharmacological management due to confounding factors that expand as CKD progresses. Despite the negative results of pharmacological interventions for uric acid control, it is undeniable that uric acid plays a crucial role as a marker, correlate, or representative of metabolic syndrome, cardiovascular disease, and CKD. Our findings, along with those of other studies, indicate that uric acid may be a useful prognostic marker in clinical practice.

This study demonstrates that hyperuricemia has a significant impact on CKD, even after considering the genetic risk score for CKD. We calculated the PRS based on large-population cohort data and validated these scores using an independent data set. However, this study has several limitations. Firstly, while our analysis demonstrates that PRS significantly impact CKD development, the ability to predict individual disease risk based on PRS alone is limited. This is because CKD is influenced by a multitude of factors beyond genetic predisposition. Although we adjusted for certain clinical variables to focus on the pure genetic effect, our study does not fully capture the complexity of CKD etiology, including various environmental and lifestyle factors, which are known to contribute to CKD risk. Ancestry is the parameter that varies the most when calculating the PRS; therefore, it should be a requirement that individuals of the same ancestry be treated as a single population group when calculating scores. In this regard, we included only non-Hispanic whites and the results could not be adjusted for overall ancestry.

Although we performed survival analysis in subpopulations with follow-up data, we could not conduct a Cox proportional hazard analysis that considers various covariates due to the insufficient number of subjects and the limited duration of follow-up. We used the UKB data, which consists of healthy general populations, therefore, healthy volunteer bias should be considered. Despite the genetic correlation between hyperuricemia and CKD, we could not consider share effects in the PRS analysis. Lastly, we could not evaluate medication history, including the use of uric acid lowering agents. To generalize the findings, further research that restricts the analysis to other ethnic populations and considers more comprehensive factors, including drug implications, is needed. Furthermore, given the significant interaction between hyperuricemia and PRS on CKD risk, identifying dietary, life-style, environmental, and genetic risks of hyperuricemia, which are not included in the CKD PRS, may be beneficial for CKD prevention and treatment.

This study demonstrates that hyperuricemia is a significant risk factor representing the risk of CKD, even after considering the genetic risk score for CKD. Monitoring and managing uric acid levels are warranted, especially in patients with a potential risk for CKD, regardless of genetic risk.

Data availability

All data used in the present study were provided by the UK biobank and could be downloaded at https://www.ukbiobank.ac.uk.

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Author contributions

The principal investigator was JL. The study proposal and design were conducted by YK and JL. Acquisition, analysis, or interpretation of data were performed by JJ, YJ, EB, KL, and SW. The study protocol was reviewed by JHP, KJ, SH, JPL, DKK, CHSL, SW and JL. Material and technical supports were provided by YJ, KL, and SW. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Competing interests

The authors declare no competing interests.

Additional information

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