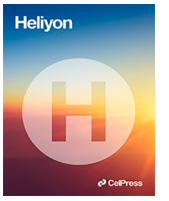
Heliyon 9 (2023) e21108

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Ethnic disparities in bidirectional causal effects between serum uric acid concentrations and kidney function: *Trans*-ethnic Mendelian randomization study

Shijie Wu [1], Minghao Kong [1], Yaxiang Song, Ai Peng [*]

Center for Nephrology and Clinical Metabolomics and Division of Nephrology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, 200072, China

A R T I C L E I N F O

Keywords:
Uric acid
chronic kidney disease
Mendelian randomization study

A B S T R A C T

Introduction: Researchers have investigated the causal effect between serum uric acid (SUA) concentrations and kidney function for decades, but studies produced inconsistent results. This study aimed to clarify the bidirectional causal effects between SUA concentrations and kidney function and to explore the potential ethnic disparities by conducting a *trans*-ethnic Mendelian randomization study in European, African, and Asian ancestries.

Materials and methods: The summary-level data for this study were obtained from the Global Urate Genetics Consortium, CKDGen Consortium, UK Biobank, and Japan Biobank for different outcomes and exposures, respectively. The traits of kidney function were estimated glomerular filtration rate from serum creatinine (eGFRcr), estimated glomerular filtration rate from cystatin C (eGFRcys), and blood urea nitrogen (BUN). Using the multiplicative random-effects inverse variance weighting mode, our primary analysis produced robust results despite heterogeneity. Additionally, we performed the Mendelian randomization pleiotropy residual sum and outlier test to eliminate the horizontal pleiotropy and obtain accurate results.

Results: Our findings revealed that elevated SUA concentrations had causal effects on declined eGFRcys, BUN, and a diagnosis of chronic kidney disease in European ancestries and eGFRcr in Asian ancestries. Additionally, the causal effects of declined eGFRcr and elevated BUN concentrations on elevated SUA concentrations were observed in both European and Asian ancestries. However, no bidirectional causal effect was found between SUA concentrations and eGFRcr among African ancestries.

Conclusions: This *trans*-ethnic Mendelian randomization study confirmed the bidirectional causal effects between SUA concentrations and kidney function and highlighted the importance of considering ethnic disparities in clinical treatments.

1. Introduction

In purine metabolism, uric acid is the final product [1,2]. In the United States, hyperuricemia is prevalent among adults, with a rate of 20.2 % for men and 20.0 % for women in 2015–2016 [3]. Chronic kidney disease (CKD) is a significant global health concern,

* Corresponding author.
E-mail address: pengai@tongji.edu.cn (A. Peng).
[1] Contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e21108
Received 22 March 2023; Received in revised form 12 September 2023; Accepted 16 October 2023
Available online 19 October 2023

causing 697.5 million cases and 1.2 million deaths worldwide in 2017 [4]. Given the association between hyperuricemia and CKD, managing patients of different ethnicities with elevated serum uric acid (SUA) concentrations and CKD is crucial in preventing the progression of CKD [5,6].

The bidirectional causal relationship between SUA concentrations and CKD has been extensively investigated over several decades [7]. Despite the commonly observed association, there remains ongoing debate regarding the impact of SUA concentrations on the progression of CKD. Observational studies have long regarded elevated serum uric acid concentrations as a risk factor for declining kidney function [8,9]. Conversely, several randomized clinical trials failed to provide substantial evidence supporting the clinical benefits of interventions to lower SUA levels [10,11]. The inconsistent findings from these studies posed challenges in drawing definitive conclusions regarding the causal relationship between SUA concentrations and kidney function. Moreover, studies discovered ethnic disparities in the causal effect of SUA levels and coronary artery disease between European and East Asian ancestries [12,13]. Nevertheless, whether there is a bidirectional causal effect between SUA concentrations and kidney function remains unclear.

Mendelian randomization (MR) analysis is a new epidemiological technique that tackles confounding variables commonly found in observational research [14]. As a result, MR analysis is a suitable method for elucidating the common causal effects between SUA and kidney function and whether there are ethnic disparities, with the increasing availability of genetic-wide association studies (GWAS) providing an opportunity. The aim of this study was to clarify the bidirectional causal effects between serum uric acid concentrations and kidney function and to explore the potential ethnic disparities by conducting a *trans*-ethnic Mendelian randomization study in European, African, and Asian ancestries.

2. Materials and Methods

2.1. Study design

We performed this *trans*-ethnic MR study to estimate the bidirectional causal effects between SUA concentrations and kidney function per the STROBE-MR guidelines [15]. The traits of kidney function were estimated glomerular filtration rate from serum creatinine (eGFRcr) and blood urea nitrogen (BUN) [16]. They reflected the level of the renal filtration function. Then, we used these traits above to assess the bidirectional causal effect between SUA concentrations and kidney function in European, Asian, and African ancestries. Additionally, given that most of the clinical trials were carried out in European ancestries, we analyzed the bidirectional causal effect of estimated glomerular filtration rate from serum cystatin C (eGFRcys), urinary albumin creatinine ratio (UACR) and diagnosis of CKD on SUA concentrations to estimate whether different observed endpoints in clinical trials in European ancestries led to bias.

To select instrumental variables (IVs) for SUA concentrations and kidney function, we utilized the summary statistics of the GWAS conducted by the Global Urate Genetics Consortium (GUGC), UK BioBank, and CKDGen Consortium for European ancestries. For African ancestries, the IVs for SUA concentrations and BUN concentrations were picked from the summary statistics of the GWAS from CKDGen Consortium, and the IVs for eGFRcr were picked from the GWAS from UK Biobank. For Asian ancestries, the summary statistics of Japan Biobank were used when picking the IVs for SUA concentrations, eGFRcr, and BUN concentrations.

2.2. Pooled summary statistic of the GWAS

The summary statistics of the GWAS from GUGC included 110,347 European individuals from 48 studies contributing to SUA concentrations. Mean SUA levels ranged from 3.9 to 6.1 mg/dL among detailed studies. The basic characteristics of the GUCC studies' summary data were reported in Köttgen A et al. [17].

For the eGFRcr calculated by the Modification of Diet in Renal Disease (MDRD) Study equation [18], the summary statistics of CKDGen included 133,413 individuals of European ancestries from 49 population-based studies, as well as 16,840 African individuals from 12 different ancestries. Mean eGFRcr ranged from 71.2 to 104.8 ml/min/1.73 m^2 for European ancestries and 76.0 to 111,0 ml/min/1.73 m^2 for African ancestries. Regarding eGFRcys, the summary statistics of CKDGen included 33,152 individuals. Mean eGFRcys in European ancestries ranged from 77.0 to 123.5 ml/min/1.73 m^2. The summary statistics of the GWAS about UACR from the CKDGen included 54,450 participants of European ancestries across the 30 analyses. The 24-hour urine specimens were collected from the early morning hours to calculate UACR for individuals. This ratio was used to assess the amount of albumin in the urine relative to creatinine. The summary statistics included twenty studies with UACR ranging from 2.5 mg/g to 15.6 mg/g. CKD was identified in participants of CKDGen when their eGFR was below 60 mL/min/1.73 m^2. The basic characteristics of the GWAS from CKDGen studies were from the summary data reported by Pattaro C and Teumer A et al. [19,20].

The GWAS of the UK Biobank contained 344,052 participants of BUN concentrations for European ancestries, 6206 participants of SUA concentrations, and 6213 participants of BUN concentrations for African ancestries. The summary statistics of the GWAS from the Japan BioBank included 109,029 participants for SUA concentrations, 143,658 participants for eGFRcr, and 139,818 for BUN concentrations. The mean SUA concentration was 5.3 $\pm$ 1.45 mg/dL, the mean eGFRcr was 73.93 $\pm$ 15.42 ml/min/1.73 m^2, and the mean BUN was 15.44 $\pm$ 4.77 mg/dL. Masahiro Kanai et al. reported the basic characteristics of the GWAS from Japan Biobank [21].

https://gwas.mrcieu.ac.uk/provided all GWAS data used in this *trans*-ethnic MR study.

2.3. MR analyses

To perform this *trans*-ethnic MR Study of bidirectional causal effects, we conducted several MR analyses between different

exposures and outcomes among European, African, and Asian ancestries, respectively.

Three key assumptions underlying the use of IVs in MR analysis exist. Firstly, the single nucleotide polymorphism (SNP) is significantly connected to the exposure. Secondly, the SNP is independent of potential confounders; Thirdly, the direct correlation between an SNP and the result is not found owing to horizontal pleiotropy, only through the exposure [15,22,23]. To ensure that the IVs meet these assumptions, we implemented a selection procedure. The process of selecting IVs was consistent across all MR analyses, as illustrated in Fig. 1. To guarantee the IVs satisfied the first assumption, we chose index SNPs associated with the exposure ($P < 5 \times 10^{-6}$) that were more likely to be related to the exposure of interest. The clumping approach ($r^2 < 0.001$, windows size = 10000 kb) was used to eliminate SNPs in significant linkage disequilibrium. Subsequently, based on the summary statistics of the GWAS from UK Biobank and Japan Biobank, the associations between index SNPs and potential confounders were evaluated in the following traits, respectively: hypertension, diabetes, body mass index (BMI), high-density lipoprotein cholesterol (HDL) concentrations and triglycerides concentrations. To avoid possible covariance problems, we removed the index SNPs with the potential confounders ($P < 5 \times 10^{-6}$). The detailed information on confounders and removed SNP in this step was presented in Supplementary Table S1 and Supplementary Table S2. The match of the effect allele for each SNP of summary statistics between exposure and outcome was checked by the harmonies function from the TwoSampleMR R package. This step involved removing SNPs that exhibited palindromes or potential strand mismatches [24]. Additionally, we employed the Steiger filter method to minimize the influence of reverse causality effects induced by the IVs.

The primary analysis was the multiplicative random-effects inverse variance weighting (mre-IVW) mode. For optimal accuracy, selecting valid IVs and considering heterogeneity is essential. This approach maintains the relative weights of individual SNP estimates, which sets it apart from the additive MR analysis method [25]. Egger, weighted median, and weighted mode were performed in the MR analyses as secondary methods. Notably, Horizontal pleiotropy may occur when a variable affects the outcome in addition to its influence on the exposure under MR analyses. Infringement of the 'no horizontal pleiotropy' assumption led to notable bias in MR analyses. Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test is recommended when horizontal pleiotropy is observed in at least 50 % of the IVs [26]. Hence, we used this test to identify potential horizontal pleiotropy in MR analyses and estimate the corrected results [26]. If the MR-PRESSO test detected significant horizontal pleiotropy, we would remove the IVs ($P < 0.05$) and perform the MR analysis again. Further, we tested the robustness and consistency of the results using a leave-one-out analysis. If a potentially influential SNP were labeled in the 'leave-one-out' sensitivity analysis, conclusions would be drawn cautiously. All analyses were performed with R (R Foundation for Statistical Computing, version 4.4.2).

3. Results

3.1. Summary of population characteristics

To accurately evaluate genetic disparities among ethnic groups, distinct IVs were selected to assess the genetic differences in SUA concentrations and kidney function in European, African, and Asian ancestries. The comprehensive evaluation of kidney function was based on eGFRcr and BUN. Table 1 shows a summary of basic characteristics from the summary statistics of the GWAS chosen for this

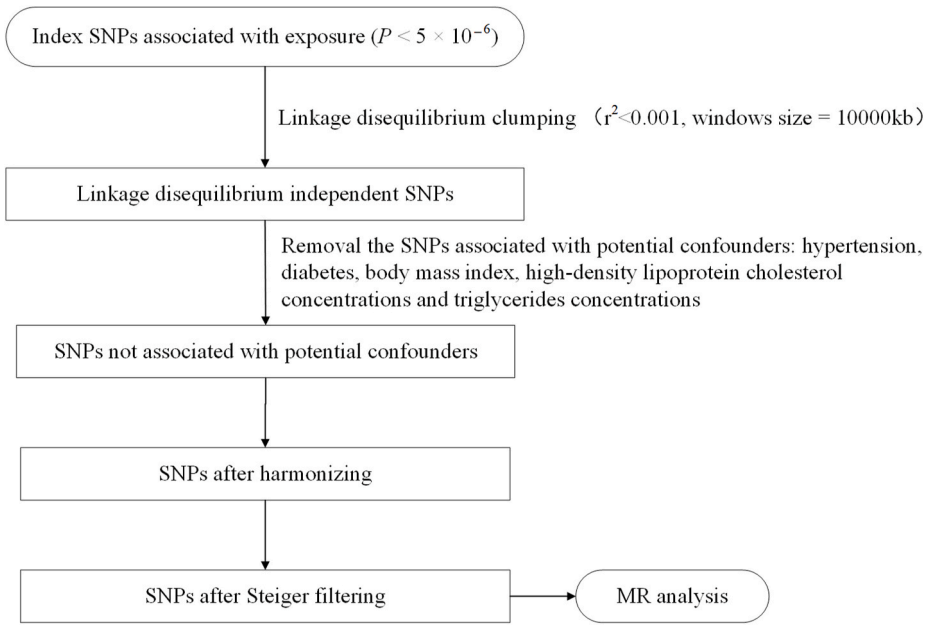


Fig. 1. The flow chart of picking instrumental variables.

study. Additionally, the bidirectional causal effect of eGFRcys, UACR, and diagnosis of CKD on SUA concentrations was estimated to determine whether various observed endpoints in clinical trials in European ancestry led to bias.

3.2. Picking of instrumental variables for SUA concentrations

For European ancestries,3,328 SNPs were associated with SUA in the GWAS from GUGC. After the procedure of picking instrumental variables and MR-PRESSO test, 24 SNPs were eligible when eGFRcr was used as the outcome, 33 SNPs were eligible when eGFRcys was used as the outcome, 27 SNPs were eligible when BUN was used as the outcome, 35 SNPs were eligible when UACR was used as an outcome, and 34 SNPs were eligible when a diagnosis of CKD was used as outcome. For African ancestries, 1399 SNPs were associated with SUA. After picking instrumental variables and MR-PRESSO test, 12 SNPs were eligible when eGFRcr was used as the outcome, and 33 SNPs were eligible when BUN was used. For Asian ancestries, 12,240 SNPs were associated with SUA. After picking instrumental variables and MR-PRESSO test, 65 SNPs were eligible when eGFRcr was used as the outcome, and 68 SNPs were eligible when BUN was used.

The number of SNPs retained after each picking step is presented in Supplementary Table S3 and Supplementary Table S4. The characteristic of SNP used in MR analyses after MR-PRESSO test is presented in Table 2 and Supplementary Table S5.

3.3. Estimates of the causal effect of SUA concentrations on kidney function

Table 2 shows the causal effect estimates of SUA on eGFRcr, eGFRcys, BUN, UACR, and diagnosis of CKD in MR analyses after the MR-PRESSPO test. As assessed by the mre-IVW MR analysis among different ethnicities, the causal effect of SUA concentrations on kidney function showed ethnic disparities. Specifically, the β of eGFRcr for SUA was −0.011 (95%CI: from −0.023 to 0.002, $P = 0.099$) in European ancestries, 0.007 (95%CI: from −0.016 to 0.029, $P = 0.552$) in African ancestries and −0.112 (95%CI: from −0.169 to −0.055, $P < 0.001$) in Asian ancestries. Furthermore, the significant causal effect of SUA on eGFRcys was discovered in European ancestries. For BUN, the β for SUA was 0.036 (95%CI: from 0.003 to 0.070, $P = 0.032$) in European ancestries, 0.223 (95%CI: from 0.147 to 0.299, $P < 0.001$) in African ancestries while −0.015 (95%CI: from −0.042 to 0.012, $P = 0.275$) in Asian ancestries. Additionally, the MR analysis of European ancestries also found that the estimates of the causal effect of CKD ($P = 0.019$) were generally significant. Fig. 2 shows forest plots of the estimates for a causal effect of SUA on kidney function using the mre-IVW analysis. Scatter plots of the SNP-SUA associations against the SNP-kidney function associations were presented in Supplementary Fig. S1 to Supplementary Fig. S9, visualizing the causal effect of estimate for single SNP on eGFRcr, eGFRcys, BUN, UACR, and diagnosis of CKD. Based on the MR-Egger test and 'leave-one-out' analysis presented in Supplementary Fig. S1 to Supplementary Fig. S9, there was no evidence of directional pleiotropy, and no single SNP produced the result. Funnel plots and radial plots are presented in Supplementary Fig. S1 to Supplementary Fig. S9.

3.4. Picking of instrumental variables for kidney function

Using similar picking procedures, the IVs of kidney function on SUA were picked. 3650 SNPs were associated with eGFRcr for European ancestries, and 72 SNPs were eligible when SUA was used as an outcome after MR-PRESSO test. 47,298 SNPs were associated with BUN, 97 of which were eligible when SUA was used as an outcome after MR-PRESSO test. 67 SNPs were associated with UACR, 8 of which were eligible when SUA was used as an outcome after MR-PRESSO test. 681 SNPs were associated with a diagnosis of CKD, 16 SNPs of which were eligible when SUA was used as the outcome after MR-PRESSO test. For African ancestries, 55 SNPs were associated with eGFRcr, 209 SNPs were associated with BUN, 16 SNPs and 18 SNPs of which were eligible when SUA was used as outcome after MR-PRESSO test. For Asian ancestries, 10,961 SNPs were associated with eGFRcr, and 7245 SNPs were associated with BUN. 135 SNPs and 97 SNPs were eligible when SUA was used as the outcome after MR-PRESSO test. Table 3, Supplementary Tables S3–S5 contains

Table 1
The summary of basic characteristics of the summary statistics of the GWAS.

Trait	Source	Ethnicity	Sample size	Unit
Uric acid	GUCC	European	110347	mg/dL
eGFRcr	CKDGen	European	133814	log mL/min/1.73 m^2
eGFRcys	CKDGen	European	33152	log mL/min/1.73 m^2
BUN	UK Biobank	European	344052	mg/dL
UACR	CKDGen	European	54450	log mg/g
CKD[a]	CKDGen	European	12385 cases, 104780 controls	log odds
Uric acid	UK BioBank	African	6206	umol/L
eGFRcr	CKDGen	African	16474	log mL/min/1.73 m^2
BUN	UK BioBank	African	6213	mmol/L
Uric acid	Japan Biobank	Asian	109029	mg/dL
eGFRcr	Japan Biobank	Asian	143658	mL/min/1.73 m^2
BUN	Japan Biobank	Asian	139818	mg/dL

Abbreviations: eGFRcr estimated glomerular filtration rate from serum creatinine; eGFRcr estimated glomerular filtration rate from cystatin C; BUN blood urea nitrogen; UACR urinary albumin creatinine ratio; GUGC Global Urate Genetics Consortium.

[a] A diagnosis of chronic kidney disease.

Table 2
The MR analyses of causal effect of SUA concentrations on kidney function after MR-PRESSO test.

Outcome	Ethnicity	The number of SNPs	mre-IVW		Egger		Weighted Median		Weighted Mode	
			β or OR	*P*	β or OR	*P*	β or OR	*P*	β or OR	*P*
eGFRcr[a]	European	24	−0.011 (-0.023,0.002)	0.099	−0.006 (-0.025,0.036)	0.723	−0.016 (-0.029, −0.002)	0.023	−0.014 (-0.032,0.005)	0.156
eGFRcys[a]	European	33	−0.024 (-0.046, −0.003)	0.028	0.014 (-0.018,0.047)	0.396	−0.005 (-0.021,0.012)	0.573	−0.007 (-0.023,0.009)	0.391
BUN[a]	European	27	0.036 (0.003,0.070)	0.032	−0.010 (-0.069,0.048)	0.73	0.015 (-0.019,0.050)	0.382	0.011 (-0.029,0.052)	0.585
UACR[a]	European	35	−0.003 (-0.051,0.045)	0.898	0.041 (-0.037,0.119)	0.307	0.052 (-0.005,0.108)	0.307	−0.053 (0.000,0.105)	0.06
CKD[b]	European	34	1.181 (1.028,1.355)	0.019	1.013 (0.806,1.275)	0.238	1.150 (1.009,1.311)	0.036	1.119 (0.981,1.275)	0.102
eGFRcr[a]	African	12	0.007 (-0.016,0.029)	0.552	0.041 (-0.009,0.092)	0.909	0.021 (-0.007,0.049)	0.136	0.014 (-0.016,0.044)	0.375
BUN[a]	African	33	0.223 (0.147,0.299)	<0.001	0.053 (-0.132,0.238)	0.58	0.143 (0.026,0.260)	0.016	0.042 (-0.097,0.180)	0.559
eGFRcr[a]	Asian	65	−0.112 (-0.169, −0.055)	<0.001	−0.012 (-0.100,0.075)	0.782	−0.058 (-0.098, −0.017)	0.005	−0.070 (-0.104, −0.036)	<0.001
BUN[a]	Asian	68	−0.015 (-0.042,0.012)	0.275	−0.041 (-0.082, −0.001)	0.051	−0.015 (-0.046,0.017)	0.36	−0.024 (-0.051,0.003)	0.081

Abbreviations: MR, mendelian randomization; IVW, inverse variance weighted; OR, odds ratio; eGFRcr, estimated glomerular filtration from serum creatinine.
eGFRcys, estimated glomerular filtration from cystatin C; BUN, blood urea nitrogen; UACR, urinary albumin creatinine ratio; CKD, a diagnosis of chronic kidney disease.
[a] continues outcome.
[b] categorical outcome.

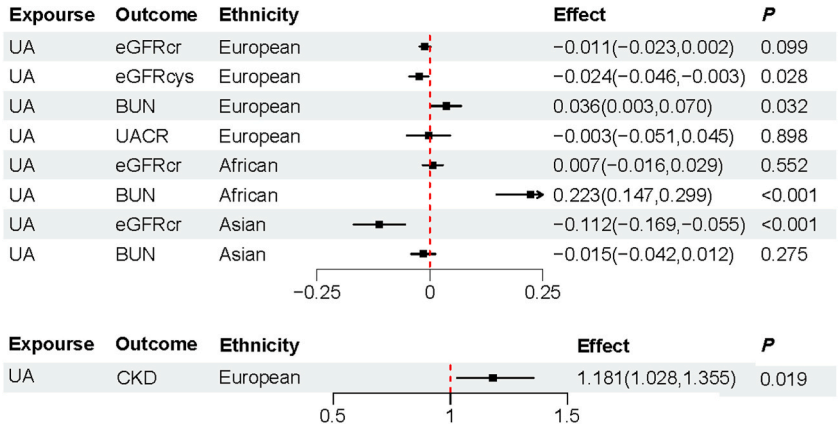


Fig. 2. The forest plot of causal effect of SUA concentrations on kidney function from mre-IVW analyses.

information about the number and characteristics of SNPs retained at each picking stage and MR-PRESSO test.

3.5. *Estimates of causal effect of kidney function on SUA concentrations*

Table 3 demonstrats the causal-effect estimates of eGFRcr, BUN, UACR, and diagnosis of CKD on SUA concentrations from the MR analyses after the MR-PRESSPO test.

The results of the mre-IVW study revealed that the impact of kidney function on SUA was not statistically significant across various ethnicities. In particular, the β of SUA for eGFRcr was −0.166 (95%CI: from −0.285 to −0.046, $P = 0.007$) in European ancestries, −0.200 (95%CI: from −0.638 to 0.237, $P = 0.369$) in African ancestries and −0.329 (95%CI: from −0.374 to −0.294, $P < 0.001$) in Asian ancestries. For BUN, the β for SUA was 0.280 (95%CI: from 0.161 to 0.339, $P < 0.001$) in European ancestries, 0.202 (95 % CI: from 0.116 to 0.289, $P < 0.001$) in African ancestries and 0.243 (95%CI: from 0.181 to 0.305, $P < 0.001$) in Asian ancestries. Furthermore, the mre-IVW MR analysis revealed that the causal effects of the diagnosis of CKD were generally significant among European ancestries. Fig. 3 illustrates the forest plots of the estimates of kidney function traits on the mre-IVW MR analysis. approaches. Scatter plots of the SNP-kidney function associated with the SNP-SUA presents in Supplementary Fig. S10 to Supplementary Fig. S18. The MR-Egger test revealed no directional pleiotropy, and the 'leave-one-out' analysis given in Supplementary Fig. S10 to Supplementary Fig. S18 suggests that the MR analysis result was not produced from a single SNP. Funnel and radial plots are presented in Supplementary Fig. S10 to Supplementary Fig. S18.

4. Discussion

This study conducted *trans*-ethnic Mendelian randomization analyses involving individuals of European, African, and Asian ancestries to investigate the relationship between SUA levels and kidney function. Comparing the MR results across different ancestries, we identified bidirectional causal effects between SUA concentrations and kidney function, shedding light on ethnic disparities genetically for the first time. Additionally, the inconsistent genetic causal effects of SUA concentrations on different kidney function traits suggested that different observed endpoints in clinical trials in European ancestries may lead to bias.

The high prevalence of CKD has sparked an ongoing search for treatable risk factors for kidney disease. A large cohort study based on German populations showed that the overall prevalence of gout in patients with CKD was 24.3 % [27]. The co-occurrence of hyperuricemia and CKD presented a significant challenge in treating these patients [5,6,28]. While elevated SUA concentrations has been identified as a potential contributing factor to CKD, it is still debatable whether hyperuricemia results from impaired renal excretion of SUA or contributes to kidney disease [7,29,30]. Some research supported that hyperuricemia was a risk factor for CKD. For instance, a meta-analysis with 99,205 individuals and 3492 incident CKD presented that the relative risk of CKD was 1.22 per 1 mg/dL SUA level increment [31]. Several potential mechanisms for impaired kidney function caused by uric acid, including adverse physiological effects such as vascular smooth muscle cell proliferation, endothelial dysfunction, and oxidative stress [32–35]. However, recent randomized clinical controlled trials have shown conflicting results, with some indicating that ULT (urate-lowering treatment) with allopurinol or febuxostat did not prevent the decline in eGFR in population with high risk of CKD progression [10,11,36,37]. The cohort study included patients with CKD and no albuminuria treated from 2004 to 2019, indicating ULT was associated with a higher risk of both incident eGFR less than 60 mL/min/1.73 m^2 and incident albuminuria [37]. Clinicians and researchers can gain more accurate insights into the causal relationship between SUA concentrations and kidney function by examining it in both directions.

The observed differences in ethnic disparities may arise from genetic, environmental, and lifestyle factors. Ethnic disparities due to genetic factors were observed in the MR analysis of SUA on coronary artery disease and cardiometabolic factors in European and East Asian ancestries [12,13]. The SUA level was observed to increase the risk of CAD in East Asians ($P = 3.27 \times 10^{-5}$) but not in Europeans ($P = 0.658$). Consistent with our result, previous MR analyses conducted among populations of European ancestry have failed to

Table 3
The MR analyses of causal effect of kidney function on SUA concentations after MR-PRESSO test.

Exposure	Ethnicity	The number of SNPs	mre-IVW		Egger		Weighted Median		Weighted Mode	
			β	*P*	β	*P*	β	*P*	β	*P*
eGFRcr	European	72	−0.166 (-0.285, −0.046)	0.007	0.017 (-0.318,0.351)	0.922	−0.070 (-0.190, −0.051)	0.257	−0.036 (-0.190,0.117)	0.645
eGFRcys	European	10	−0.394 (-0.744, −0.043)	0.028	−0.478 (-1.592,0.636)	0.372	−0.224 (-0.717,0.268)	0.372	−0.049 (-0.864,0.766)	0.909
BUN	European	97	0.280 (0.161,0.339)	<0.001	0.548 (0.175,0.922)	0.005	0.23 (0.088,0.372)	0.001	0.666 (0.1011.232)	0.023
UACR	European	8	−0.011 (-0.186,0.164)	0.901	0.552 (0.027,1.077)	0.085	−0.065 (-0.097,0.227)	0.901	0.085 (-0.113,0.282)	0.429
CKD	European	16	0.122 (0.08,0.163)	<0.001	0.149 (0.022,0.275)	0.037	0.090 (0.04,0.139)	<0.001	0.096 (0.036,0.156)	0.007
eGFRcr	African	16	−0.2 (-0.638,0.237)	0.369	−0.392 (-1.961,1.177)	0.632	−0.148 (-0.740,0.443)	0.623	−0.244 (-1.038,0.551)	0.557
BUN	African	18	0.202 (0.116,0.289)	<0.001	0.202 (-0.122,0.525)	0.239	0.193 (0.078,0.309)	0.001	0.181 (-0.013,0.375)	0.085
eGFRcr	Asian	135	−0.329 (-0.374, −0.284)	<0.001	−0.358 (-0.492, −0.225)	<0.001	−0.333 (-0.393, −0.273)	<0.001	−0.375 (-0.488, −0.261)	<0.001
BUN	Asian	97	0.243 (0.181,0.305)	<0.001	0.257 (0.078,0.436)	0.006	0.159 (0.084,0.234)	<0.001	0.063 (-0.092,0.219)	0.427

Abbreviations: MR, mendelian randomization; IVW, inverse variance weighted; eGFRcr, estimated glomerular filtration rate from serum creatinine; eGFRcys, estimated glomerular filtration rate from cystatin C; BUN, blood urea nitrogen; UACR, urinary albumin creatinine ratio; CKD, a diagnosis of chronic kidney disease.

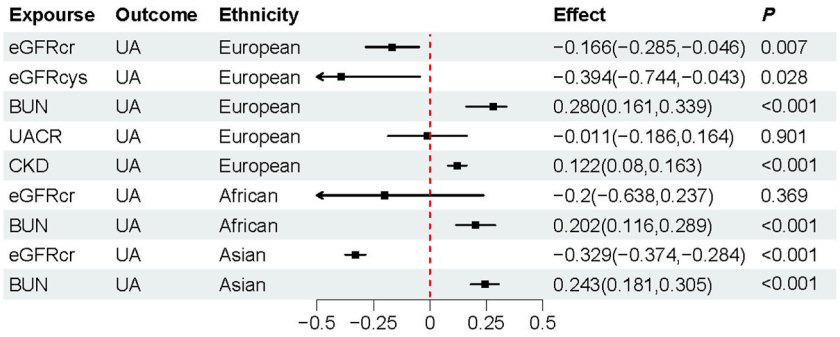


Fig. 3. The forest plot of causal effect of kidney function on SUA concentrations from mre-IVW analyses.

support a causal relationship between serum uric acid levels and eGFR [38]. Our study revealed potential ethnic differences in the causal effect of SUA on declined eGFR, as compared to MR analyses of Asian and African ancestries. There may be variations in genetic variants related to uric acid levels and kidney function among ethnic groups, resulting in diverse outcomes. In addition to genetics, environmental and lifestyle factors contribute to the observed disparities. The cross-sectional study presented that the current racial disparities may be explained by differences in the frequencies or levels of critical social or lifestyle and clinical factors [39].

Recognizing and comprehending the existing disparities among different ethnic groups is crucial in enhancing healthcare outcomes as it helps tailor medical interventions to address individual patient requirements. Notably, various ethnicities exhibit differential susceptibility and response to specific ailments or treatments, such as the development and progression of CKD. Consequently, healthcare providers can provide more precise and effective care by acknowledging and considering these differences. More extensive randomized clinical trials among different ethnicities are required to study the ethnic difference in the causal effect of SUA concentrations on kidney function and improve racial inequity in clinical trials of ULT.

Additionally, given that most clinical trials were carried out in Europeans, we analyzed different kidney traits to estimate whether different observed endpoints in clinical trials in European ancestries led to bias. Previous studies have investigated the potential causal relationship between SUA levels and albuminuria [40,41]. For instance, a cross-sectional study involving 83 patients with type 2 diabetes mellitus demonstrated that an increase in SUA concentrations by one μmol/L led to a 1.5 % increase in the likelihood of albuminuria [42]. Our MR analysis did not support the causal effect of SUA levels on the UACR. Thus, hyperuricemia may be unlikely to induce albuminuria genetically. Nevertheless, our analysis found a causal effect of elevated SUA concentrations on eGFRcys and CKD in individuals of European ancestry. The inconsistent causal effects of SUA concentrations on different kidney function traits suggested that varying clinical endpoints in trials in European ancestries may introduce bias. More clinical trials or meta-analyses based on different clinical endpoints need to further validate this.

We also conducted MR analyses on the causal effect of kidney function on SUA concentrations. The mre-IVW MR method confirmed significant estimates of the causal effect of decreased eGFRcr and increased BUN concentrations on increased SUA concentrations in European and Asian ancestries. These findings aligned with previous Mendelian randomization studies, which have also reported causal effects of declining kidney function leading to increased SUA levels in individuals of European ancestry [43]. This further supported the evidence suggesting that impaired kidney function can influence the regulation of SUA levels. Notably, we found no causal effect between eGFRcr and SUA in individuals of African ancestry. This suggested that the causal effect of decreased kidney function on increased SUA may also have ethnic disparities. Furthermore, the causal effect of UACR on SUA in European ancestries was not discovered. It indicated that the presence of albuminuria does not promote elevated SUA concentrations in European ancestries.

Our study had several strengths. First, this research is the first study using MR analyses to clarify the bidirectional causal effect between SUA concentrations and kidney function and the potential ethnic differences in this causal effect. Furthermore, we used several traits of kidney function, including eGFRcr and BUN, to evaluate kidney function better and the bidirectional causal effect between SUA concentrations and kidney function. And eGFRcys, UACR, and diagnosis of CKD on SUA were used to estimate whether different observed endpoints in clinical trials in European ancestries lead to bias. Third, we used the summary statistics of the GWAS based on European, African, and Asian ancestries to explore whether ethnic disparities existed on bidirectional causal effects. Finally, we used a variety of techniques to decrease the probability of contravention of three MR assumptions, including removing the SNPs associated with possible confounders, using Steiger filtering to decrease the reverse causal effect induced by IVs, picking mre-IVW as a primary method to present results without heterogeneity and directional pleiotropy.

Several limitations should be mentioned. First, due to data limitations, $P < 5 \times 10^{-6}$ instead of $P < 5 \times 10^{-8}$ was chosen as the threshold of genetical significance to balance statistical rigor and practical considerations. Moreover, kidney function in African and Asian ancestries was only evaluated regarding eGFRcr and BUN. We found the causal effect of SUA on eGFRcr in Asian ancestries. However, we could not perform an MR analysis to explore the possible causal effect of SUA concentrations on CKD among Asian ancestries due to data limitations. Besides, the MR analyses performed by the GWAS summary statistics disregarded the nonlinear connection between the exposures and the outcomes. Further confirmation of the relationship between SUA concentrations and CKD is needed based on clinical trials in different ancestries.

Author contribution statement

Shijie Wu, Minghao Kong, Yaxiang Song, Ai Peng: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding

The authors did not receive support from any organization for the submitted work.

Data availability

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank GUCC, CKDGen, UK Biobank, and Japan Biobank for sharing the summary statistics publicly and freely.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21108.

References

[1] L.B. Sorensen, Role of the intestinal tract in the elimination of uric acid, Arthritis Rheum. 8 (5) (1965) 694–706.
[2] J.K. Maesaka, S. Fishbane, Regulation of renal urate excretion: a critical review, Am. J. Kidney Dis. 32 (6) (1998) 917–933.
[3] M. Chen-Xu, et al., Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: the national health and nutrition examination survey, 2007-2016, Arthritis Rheumatol. 71 (6) (2019) 991–999.
[4] GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2020;395(10225):709-733. doi:10.1016/S0140-6736(20)30045-3.
[5] R.J. Johnson, et al., Uric acid and chronic kidney disease: still more to do, Kidney International Reports 8 (2) (2023) 229–239.
[6] A.B. Vargas-Santos, T. Neogi, Management of gout and hyperuricemia in CKD, Am. J. Kidney Dis. 70 (3) (2017) 422–439.
[7] R.J. Johnson, et al., Uric acid and chronic kidney disease: which is chasing which? Nephrol. Dial. Transplant. 28 (9) (2013) 2221–2228.
[8] R.P. Obermayr, et al., Elevated uric acid increases the risk for kidney disease, J. Am. Soc. Nephrol. 19 (12) (2008) 2407–2413.
[9] T. Nakagawa, et al., Unearthing uric acid: an ancient factor with recently found significance in renal and cardiovascular disease, Kidney Int. 69 (10) (2006) 1722–1725.
[10] A. Doria, et al., Serum urate lowering with allopurinol and kidney function in type 1 diabetes, N. Engl. J. Med. 382 (26) (2020) 2493–2503.
[11] S.V. Badve, et al., Effects of allopurinol on the progression of chronic kidney disease, N. Engl. J. Med. 382 (26) (2020) 2504–2513.
[12] J. Zheng, et al., Trans-ethnic Mendelian-randomization study reveals causal relationships between cardiometabolic factors and chronic kidney disease, Int. J. Epidemiol. 50 (6) (2022) 1995–2010.
[13] K. Wang, et al., Mendelian randomization analysis of 37 clinical factors and coronary artery disease in East Asian and European populations, Genome Med. 14 (1) (2022) 63.
[14] N.M. Davies, M.V. Holmes, G. Davey Smith, Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians, Bmj 362 (2018) k601.
[15] V.W. Skrivankova, et al., Strengthening the reporting of observational studies in epidemiology using mendelian randomization: the STROBE-MR statement, JAMA 326 (16) (2021) 1614–1621.
[16] M.A. Ferguson, S.S. Waikar, Established and emerging markers of kidney function, Clin. Chem. 58 (4) (2012) 680–689.
[17] A. Köttgen, et al., Genome-wide association analyses identify 18 new loci associated with serum urate concentrations, Nat. Genet. 45 (2) (2013) 145–154.
[18] A.S. Levey, et al., A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group, Ann. Intern. Med. 130 (6) (1999) 461–470.
[19] C. Pattaro, et al., Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function, Nat. Commun. 7 (2016), 10023.
[20] A. Teumer, et al., Genome-wide association studies identify genetic loci associated with albuminuria in diabetes, Diabetes 65 (3) (2016) 803–817.
[21] M. Kanai, et al., Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases, Nat. Genet. 50 (3) (2018) 390–400.
[22] J. Zheng, et al., Recent developments in mendelian randomization studies, Curr Epidemiol Rep 4 (4) (2017) 330–345.
[23] C.A. Emdin, A.V. Khera, S. Kathiresan, Mendelian Randomization. Jama 318 (19) (2017) 1925–1926.
[24] S. Purcell, et al., PLINK: a tool set for whole-genome association and population-based linkage analyses, Am. J. Hum. Genet. 81 (3) (2007) 559–575.
[25] J. Bowden, et al., A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization, Stat. Med. 36 (11) (2017) 1783–1802.
[26] M. Verbanck, et al., Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases, Nat. Genet. 50 (5) (2018) 693–698.
[27] J Jing, JT Kielstein, UT Schultheiss, et al., Prevalence and correlates of gout in a large cohort of patients with chronic kidney disease: the German Chronic Kidney Disease (GCKD) study, Nephrol Dial Transplant 30 (4) (2015) 613–621, https://doi.org/10.1093/ndt/gfu352.
[28] M Bevis, M Blagojevic-Bucknall, C Mallen, S Hider, E Roddy, Comorbidity clusters in people with gout: an observational cohort study with linked medical record review, Rheumatology (Oxford) 57 (8) (2018) 1358–1363, https://doi.org/10.1093/rheumatology/key096.
[29] S.A. Fathallah-Shaykh, M.T. Cramer, Uric acid and the kidney, Pediatr. Nephrol. 29 (6) (2014) 999–1008.
[30] S.W. Jung, et al., Uric acid and inflammation in kidney disease, Am J Physiol Renal Physiol 318 (6) (2020) F1327–f1340.

[31] P. Zhu, et al., Serum uric acid is associated with incident chronic kidney disease in middle-aged populations: a meta-analysis of 15 cohort studies, PLoS One 9 (6) (2014), e100801.
[32] D.B. Corry, et al., Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system, J. Hypertens. 26 (2) (2008) 269–275.
[33] J.X. Zhang, et al., Uric acid induces oxidative stress via an activation of the renin-angiotensin system in 3T3-L1 adipocytes, Endocrine 48 (1) (2015) 135–142.
[34] U.M. Khosla, et al., Hyperuricemia induces endothelial dysfunction, Kidney Int. 67 (5) (2005) 1739–1742.
[35] M. Sellmayr, et al., Only hyperuricemia with crystalluria, but not asymptomatic hyperuricemia, drives progression of chronic kidney disease, J. Am. Soc. Nephrol. 31 (12) (2020) 2773–2792.
[36] K. Kimura, et al., Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial, Am. J. Kidney Dis. 72 (6) (2018) 798–810.
[37] W. Hassan, et al., Association of uric acid-lowering therapy with incident chronic kidney disease, JAMA Netw. Open 5 (6) (2022), e2215878.
[38] D.M. Jordan, et al., No causal effects of serum urate levels on the risk of chronic kidney disease: a Mendelian randomization study, PLoS Med. 16 (1) (2019), e1002725.
[39] N. McCormick, et al., Racial and sex disparities in gout prevalence among US adults, JAMA Netw. Open 5 (8) (2022), e2226804.
[40] E.S. Kim, et al., Serum uric acid level is associated with metabolic syndrome and microalbuminuria in Korean patients with type 2 diabetes mellitus, J Diabetes Complications 25 (5) (2011) 309–313.
[41] J.E. Lee, et al., Serum uric acid is associated with microalbuminuria in prehypertension, Hypertension 47 (5) (2006) 962–967.
[42] A. Klisic, et al., Xanthine oxidase and uric acid as independent predictors of albuminuria in patients with diabetes mellitus type 2, Clin. Exp. Med. 18 (2) (2018) 283–290.
[43] S. Park, et al., Mendelian randomization reveals causal effects of kidney function on various biochemical parameters, Commun. Biol. 5 (1) (2022) 713.