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ORIGINAL RESEARCH

Exploring Bidirectional Causality between Obstructive Sleep Apnea and Chronic Kidney Disease via Mendelian Randomization

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Purpose: It remains unclear about the causal association between obstructive sleep apnea (OSA) and chronic kidney disease (CKD) and renal function. This study aimed to explore the bidirectional causal relationship between OSA and CKD and renal function.

Methods: We used a 2-sample bidirectional Mendelian randomization (MR) method to evaluate the causal relationship between OSA and estimated glomerular filtration rate from creatinine (eGFRcrea), eGFR from cystatin C (eGFRcys), urine albumin to creatinine ratio (UACR), blood urea nitrogen (BUN), and chronic kidney disease (CKD). Inverse variance weighted (IVW), MR-Egger, weighted median, MR-Egger, and pleiotropy residual sum and outlier test (MR-PRESSO) were used to calculate the β or odds ratio [OR] and their 95% CIs.

Results: Genetically predicted OSA was found to be associated with BUN (β=0.040, 95% CI: 0.013–0.067, p = 0.003), but not associated with CKD (OR = 1.075, 95% CI: 0.916–1.263, p = 0.375), eGFRcrea (β=0.007, 95% CI: −0.004–0.017, p = 0.203), eGFRcys (β=−0.012, 95% CI: −0.026–0.002, p = 0.102), or UACR (β=−0.025, 95% CI: −0.058–0.007, p = 0.122). In the reverse analysis, genetically predicted eGFRcys (OR, 0.687; 95% CI, 0.497–0.950, p = 0.023) and BUN (OR, 1.686; 95% CI, 1.299–2.073, p = 0.008) was associated with an increased risk of OSA. The Cochrane's Q test reveals significant heterogeneity between various single nucleotide polymorphisms. MR-Egger indicated no evidence of genetic pleiotropy. Results were robust using other MR methods in sensitivity analyses.

Conclusion: Through the two-sample MR analysis, we identified kidney function may have a causal relationship with OSA, but a causal relationship between OSA and CKD and kidney function remains uncertain. More studies are required to better understand the relationship between OSA and CKD and kidney function.

Keywords: obstructive sleep apnea, chronic kidney disease, renal function, bidirectional, Mendelian randomization

Introduction

Both chronic kidney disease (CKD) and obstructive sleep apnea (OSA) are prevalent diseases and are associated with increased risk of mortality and morbidity.[1,2] Globally, the prevalence of CKD was about 10%[3] and it was estimated there were 697.5 million cases of CKD and 1.2 million people died from CKD in 2017.[4] The prevalence of OSA, a severe sleep disorder with repetitive apneas and hypopneas,[5] ranged from 6% to 17% in the general adult population and reached as high as 49% in the elderly.[6] It has recently garnered interest whether there is a bidirectional relationship between OSA and CKD. A better understanding of the bidirectional relationship is necessary to inform public health policies to reduce disease burden.

OSA-related hypoxia can lead to renal disease and accelerate the progression by oxidative stress, inflammation, the renin-angiotensin-aldosterone system, sympathetic activation, and endothelial dysfunction.[7] Furthermore, CKD can contribute to the development of OSA and increase the severity of sleep apnea by inducing uremic neuropathy and

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myopathy, altered chemoreflex sensitivity, and hypervolemia.[8,9] Some cross-sectional and case-control studies have reported a significant association between OSA and CKD[10–12] or decreased renal function,[13] whereas discordant data were also reported.[14,15] Cohort studies showed an increased risk of CKD incidence associated with OSA, compared to those without OSA.[16,17] Moreover, a high prevalence of OSA has been reported in patients with CKD, reaching about 39.3%.[18] The declined kidney function increases the prevalence of OSA.[19] Therefore, there may be a bidirectional relationship between OSA and CKD. However, the causal relationships between OSA and CKD and kidney function have not been well investigated, partly due to overlapping confounding comorbidities.

Mendelian randomization (MR) uses genetic variants randomly allocated during conception as instrumental variables for exposure to estimate the exposure-outcome causal effect and can avoid potential bias by confounding and reverse causation compared with traditional observational studies.[20] OSA and CKD share many common risk factors, and the study design of observational studies cannot address the question of reverse causality. MR is an ideal study design, mimicking a Randomized Controlled Trial to address these concerns and explore the bidirectional relationship. The causal relationship between sleep traits and CKD and kidney function has been explored via MR design and found that genetically predicted sleeplessness/insomnia increased the risk of CKD.[21] However, MR analysis on the association of OSA and CKD and kidney function is lacking.

To comprehensively evaluate the causal association between OSA and CKD and kidney function, in the present study, we performed a bidirectional 2-sample MR analysis to evaluate the bidirectional causal nature between OSA and CKD and kidney function.

Materials and Methods

Study Design

We implemented 2-sample bidirectional MR analyses to investigate the causal associations between OSA and CKD and kidney function, using summary results from the largest published genome-wide association studies (GWAS). This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) reporting guideline.[22] This study utilized publicly available GWAS summary data and all the information and data involved in this study were anonymized, and all the original studies related to the GWAS involved in the GWAS data had been approved by the relevant review board. Therefore, the ethical statement is not required for this study, which have been approved by the ethical committee in the Shenzhen Qianhai Shekou Free Trade Zone Hospital (2025-KY-006-01K).

Data Sources

We used published genetic variants associated with OSA from the FinnGen project (DATA FREEZE 10, https://www.finngen.fi/en, accessed on 01 Feb 2024). The FinnGen study is a large-scale genomics initiative and the DF10 covered individuals primarily of Finnish ancestry and included total sample size of 412,181 (230,310 females and 181,871 males), with 21,311,942 variants analyzed and 2,408 endpoints.[23] This GWAS included 366,484 controls and 43,901 OSA patients identified using Finland nationwide health registries (Table 1).[24] Data was collected from National Hospital Discharge Registry (available from 1968), Causes of Death Registry (available from 1969), Cancer Registry (available from 1953) and Medication Reimbursement Registry (available from 1995), all these using unique national personal identification codes. Registry data were available from the beginning of the registry until December 31, 2018. OSA was diagnosed according to the International Classification of Diseases, Tenth Revision (ICD10) and Ninth Revision (ICD9) codes (ICD10: G47.3, ICD9: 3472A), following self-reported symptoms, clinical examination, and sleep registration applying apnea-hypopnea index (AHI) or respiratory event index (REI) ≥5/h.[25]

The summary statistics of instrument variables for CKD were derived from a meta-analysis by the Chronic Kidney Diseases Genetics Consortium (CKDGen Consortium),[26] which included 23 European ancestry cohorts (n = 480,698; 41,395 patients and 439,303 controls). Enrolled cohorts were listed in Supplementary Table S1. Information about CKDGen Consortium have been described, including details of participant recruitment and genotyping in the individual studies contributing data.[27,28] More detailed participant characteristics of the CKDGen Consortium studies have been

Table 1 Characteristics of the Used Genome-Wide Association Study in the Study

Phenotypes	Study/Consortium	Cases/Controls	PubMed ID
OSA	FinnGen consortium	43,901/366,484	–
CKD	CKDGen Consortium	41,395/439,303	31152163
eGFRcrea	CKDGen Consortium and UK Biobank	1,001,909	34272381
eGFRcys	CKDGen Consortium and UK Biobank	460,826	34272381
BUN	CKDGen Consortium and UK Biobank	852,678	34272381
UACR	Meta-analysis of 54 studies	547,361	31511532

Abbreviations: BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFRcrea, estimated glomerular filtration rate from creatinine; eGFRcys, eGFR from cystatin C; OSA, obstructive sleep apnea; UACR, urine albumin to creatinine ratio.

reported by Wuttke et al.[1] CKD patients were defined as having an estimated glomerular filtration rate (eGFR) level of <60 mL/min/1.73 m^2. The estimated glomerular filtration rate based on creatinine (eGFRcrea) (n = 1,001,909), estimated glomerular filtration rate based on cystatin C (eGFRcys) (n = 460,826), and blood urea nitrogen (BUN) (n = 852,678) data were used to reflect the kidney function, which were obtained from a meta-analysis of GWAS from the CKDGen Consortium and UK Biobank.[29] GWAS data for urine albumin-creatinine ratio (UACR) (n = 547,361) was also obtained from a meta-analysis[28] (Table 1). All the summary statistics used in the present MR analysis were derived from GWAS that adjusted for age, sex, and principal components of ancestry. The values of eGFR were expressed in mL/min/1.73m² and UACR were expressed in mg/g and eGFR and UACR were log-transformed prior to analysis. There was a low likelihood of sample overlap because FinnGen (for OSA) recruited from Finland, UK Biobank from the UK, and the CKDGen Consortium included multiple international cohorts but FinnGen was not part of the CKDGen Consortium. Our analysis was based on GWAS summary statistics, where missing data had already been handled at the cohort-specific GWAS level.

Selection of Instrument Variables

The genetic instruments, referring to genetic variants (single nucleotide polymorphisms, SNPs) that are used as proxies for an exposure of interest, were selected based on the following criteria: 1) The genetic variant should be strongly associated with the exposure; 2) The genetic instruments are not associated with confounding factors that could bias the causal inference; 3) The genetic instruments should affect the outcome only through the exposure. The qualified instrumental variables were selected using strict selection criteria. We included all SNPs that reach the genome-wide significance level of $P < 5 \times 10^{-8}$ and then pruned SNPs with $R^2 < 0.001$ and clumping distance >10,000 kb to eliminate the linkage disequilibrium and ensure the instrument independence. Instrumental strength for the SNP–exposure association was measured by averaging SNP-specific F-statistics SNP-specific, which was calculated by the square of the beta divided by the variance for the SNP–exposure association. All weak instrumental variables (F-statistic<10) were excluded to ensure instrument reliability.[30]

Mendelian Randomization Analysis

We applied the random-effects inverse variance–weighted (IVW) as the principal analysis.[31] Several sensitivity analyses were performed, including the weighted median,[32] MR-Egger,[33] Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO),[34] to examine the robustness of the effect estimates. The IVW method applies a meta-analysis approach, combining the Wald estimates from each SNP to produce an overall effect estimate.[35] This method provides an unbiased result if horizontal pleiotropy is absent. MR-Egger regression evaluates pleiotropy by using the Instrument Strength Independent of Direct Effect (InSIDE) assumption.[36] We used MR-Egger to identify potential directional pleiotropy, with a P-value for the intercept in MR-Egger analysis of <0.05 showing significant pleiotropy. The weighted median method remains valid even if up to 50% of instrumental variables are invalid. If the InSIDE assumption does not hold, this method demonstrates greater statistical power, reduced bias, and lower type I error rates compared to MR-Egger regression. The weighted median method can generate a consistent estimate if up to half of the weights have been

derived from valid SNPs, so this method can be used to check invalid instrument bias.[37] MR-PRESSO analysis was used to identify and correct the potential horizontal pleiotropic outliers.[34] Horizontal pleiotropy occurred when a genetic variant influenced the outcome through pathways other than the exposure. MR-PRESSO is particularly useful when horizontal pleiotropy biases causal estimates, as it helps refine instrumental variable selection while maintaining statistical power. However, its effectiveness depends on at least 50% of the genetic variants being valid instruments, and it assumes the Instrument Strength Independent of Direct Effect (InSIDE) condition holds. Compared to MR-Egger, MR-PRESSO has been shown to provide more precise estimates when pleiotropy was driven by a subset of outlier SNPs rather than affecting all instruments equally.[34] Cochrane's Q statistics was used to test the heterogeneity of estimates across individual SNPs, with a P value of <0.05 indicating heterogeneity. The leave-one-out method was performed by sequentially excluding each SNP to identify whether any single SNP drove the estimates.

Results were reported as odds ratio (OR) and 95% confidence interval (CI) for binary outcome and β and 95% CIs if the outcome is continuous. We used the Bonferroni correction to control for the false discovery rate (FDR) and reduce the likelihood of type I errors, with the significance threshold was set at p < 0.05/number of tests. The MendelianRandomization, MRPRESSO, TwoSampleMR packages were used in R (version 4.1.2; R Foundation for Statistical Computing).

Results

Association of Genetically Predicted OSA with CKD and Kidney Function

A total of 865 SNPs associated with OSA at genome-wide significance ($P < 5*10^{-8}$) were obtained. After dropping 843 SNPs due to linkage disequilibrium reference panel or high linkage disequilibrium ($r^2 > 0.001$), 22 remained in the main analysis. The median F statistics for the associations of genetic instruments with OSA was 33.46 (range from 30.06 to 130.55) (Supplementary Table 1). The SNPs explained 21.39% of the variance in OSA. The selected SNPs for OSA were biologically relevant as they are associated with key physiological mechanisms underlying the disorder. These include pathways related to upper airway collapsibility (eg, rs1800437), neurocognitive control of breathing (eg, rs76229479), obesity (eg, rs9937052), and inflammation (eg, rs28815269).

Table 2 shows the Mendelian randomization estimates on associations of genetically predicted OSA and CKD and kidney function (eGFRcrea, eGFRcys, UACR, BUN). Genetically predicted OSA was associated with an increase in BUN (β = 0.040, 95% CI: 0.013–0.067, p = 0.003), but not associated with CKD (OR, 1.075; 95% CI, 0.916–1.263, p=0.375), eGFRcrea (β = 0.007, 95% CI: −0.004–0.017, p = 0.203), eGFRcys (β = −0.012, 95% CI: −0.026–0.002, p = 0.102), or UACR (β = −0.025, 95% CI: -0.058–0.007, p = 0.122) using the primary IVW analysis (Table 2.) shows the Scatter plot of the association between OSA and CKD and kidney function. A linear regression line for the positive association between OSA and CKD and kidney function and negative association between OSA and eGFRcys and UACR.

Sensitivity analyses using a weighted median, MR-Egger, and MR-PRESSO showed similar findings, with the exception that the causal association of OSA with eGFRcys (β = −0.051, 95% CI: −0.102–0.001, p = 0.073) and BUN (β = 0.098, 95% CI: −0.005–0.201, p = 0.087) approached borderline statistical significance in the MR-Egger analysis (Table 2). MR-Egger intercept indicated no possible horizontal pleiotropy (P value = 0.678 for CKD, 0.785 for eGFRcrea, 0.143 for eGFRcys, 0.351 for UCAR, and 0.273 for BUN) (Table 2). There was statistical evidence of heterogeneity for all the associations ($P < 0.001$), with an I^2 ranging from 45.72% to 90.12% (Table 2). The leave-one-SNP-out-analysis showed similar results (Supplementary Figure 6).

Association of Genetically Predicted CKD and Kidney Function with OSA

In the reverse MR analyses, we included 25 SNPs for CKD, 550 SNPs for eGFRcrea, 269 SNPs for eGFRcys, 64 SNPs for UACR, and 117 SNPs for BUN. The genetic variants used as instrumental variables for CKD and kidney function in the reverse MR analyses are shown in Supplementary Tables 2–7.

Genetically predicted CKD (OR, 1.035; 95% CI, 0.980–1.093, P = 0.221), eGFRcrea (OR, 0.810; 95% CI, 0.560–1.173, p = 0.265), and UACR (OR, 1.028; 95% CI, 0.854–1.236, p = 0.773) were not associated with OSA,

Table 2 Mendelian Randomization Estimates on Associations of Genetically Predicted Obstructive Sleep Apnea and Chronic Kidney Diseases and Kidney Function

Exposure	Outcome	No. of SNPs	Methods	β	Lower 95% CI	Upper 95% CI	P	MR-Egger Intercept (P value)	Cochran's Q test (I^2)	P	Outliers from MR-PRESSO
OSA	CKD	16	IVW	1.075	0.916	1.263	0.375	0.678	39.37 (64.40%)	<0.001	rs11075985; rs76229479
		16	WM	1.095	0.933	1.286	0.265				
		16	MR-Egger	1.227	0.652	2.312	0.537				
		14	MR-PRESSO	1.034	0.926	1.143	0.553				
OSA	eGFRcrea	15	IVW	0.007	−0.004	0.017	0.203	0.785	131.69 (89.37%)	3.15E-21	rs10986727; rs1800437; rs59333125; rs76229479
		15	WM	0.001	−0.004	0.007	0.626				
		15	MR-Egger	0.001	−0.039	0.041	0.957				
		11	MR-PRESSO	0.003	−0.003	0.009	0.325				
OSA	eGFRcys	14	IVW	−0.012	−0.026	0.002	0.102	0.143	79.93 (83.74%)	1.14E-11	rs11075985; rs1885767; rs76229479
		14	WM	−0.008	−0.019	0.002	0.115				
		14	MR-Egger	−0.051	−0.102	0.001	0.073				
		11	MR-PRESSO	−0.007	−0.017	0.003	0.138				
OSA	UACR	15	IVW	−0.025	−0.058	0.007	0.122	0.351	25.79 (45.72%)	0.028	rs1800437
		15	WM	−0.026	−0.061	0.008	0.137				
		15	MR-Egger	−0.082	−0.202	0.037	0.200				
		14	MR-PRESSO	−0.016	−0.043	0.012	0.291				
OSA	BUN	14	IVW	0.040	0.013	0.067	0.003	0.276	131.64 (90.12%)	9.84E-22	rs11075985; rs1800437; rs1885767
		14	WM	0.015	0.001	0.030	0.039				
		14	MR-Egger	0.098	−0.005	0.201	0.087				
		11	MR-PRESSO	0.014	0.004	0.024	0.018				

Abbreviations: BUN, blood urea nitrogen; CKD, chronic kidney disease; CI, confidence interval; eGFRcrea, estimated glomerular filtration rate from creatinine; eGFRcys, eGFR from cystatin C; IVW, inverse variance weighted; MR, Mendelian Randomization; OSA, obstructive sleep apnea; PRESSO, Pleiotropy Residual Sum and Outlier; UACR, urine albumin to creatinine ratio; WM, weighted median.

whereas the causal association of eGFRcys (OR, 0.687; 95% CI, 0.497–0.950, $p = 0.023$) and BUN (OR, 1.686; 95% CI, 1.299–2.073, $p = 0.008$) with OSA showed suggestive statistical significance (Table 3.) scatter plot of the association between CKD and OSA shows a stable trend of the regression line for the associations between CKD and OSA, which suggests no strong causal association; however, the upward trend was observed for BUN and UACR with OSA and downward trend for eGFRcrea, eGFRcys and OSA (Supplementary Figures 7–11).

MR-Egger indicated no horizontal pleiotropy ($p = 0.426$ for CKD, 0.359 for eGFRcrea, 0.071 for eGFRcys, 0.759 for UCAR, and 0.253 for BUN) (Table 3). Sensitivity analyses using a weighted median, MR-Egger, and MR-PRESSO showed similar findings, with exception that the causal association of eGFRcrea and OSA approached statistical significance in the weighted median analysis (OR = 0.603, 95% CI 0.376–0.968; $p = 0.036$) and the association between eGFRcys and BUN and OSA became non-significant in weighted median and MR-Egger analysis. The leave-one-SNP-out-analysis showed similar results (Supplementary Figure 12).

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Table 3 Mendelian Randomization Estimates between Genetically Predicted Chronic Kidney Diseases and Kidney Function and Obstructive Sleep Apnea

Exposure	Outcome	No. of SNPs	Methods	OR	Lower 95% CI	Upper 95% CI	P	MR-Egger intercept (P value)	Cochran's Q test (I^2)	P	Outliers from MR-PRESSO
CKD	OSA	24	IVW	1.035	0.980	1.093	0.221	0.426	38.07 (44.84%)	0.013	rs10224002; rs2484639
		24	WM	1.010	0.947	1.077	0.766				
		24	MR-Egger	0.983	0.858	1.126	0.805				
		22	MR-PRESSO	1.034	0.989	1.079	0.158				
eGFRcrea	OSA	535	IVW	0.810	0.560	1.173	0.265	0.359	1016.90 (49.00%)	1.24E-34	rs111541038; rs12950549; rs17602729; rs34496616; rs3812036
		535	WM	0.603	0.376	0.968	0.036				
		535	MR-Egger	0.573	0.250	1.311	0.188				
		530	MR-PRESSO	0.782	0.430	1.133	0.170				
eGFR_cys	OSA	262	IVW	0.687	0.497	0.950	0.023	0.071	599.02 (58.60%)	4.65E-31	rs223485; rs6873866; rs728538; rs8038729
		262	WM	0.807	0.550	1.184	0.273				
		262	MR-Egger	1.075	0.601	1.923	0.808				
		257	MR-PRESSO	0.702	0.420	0.985	0.015				
UACR	OSA	62	IVW	1.028	0.854	1.236	0.773				
		62	WM	1.053	0.850	1.303	0.637	0.759	121.07 (50.44%)	5.17E-06	rs838142
		62	MR-Egger	1.114	0.645	1.926	0.699				
		61	MR-PRESSO	1.006	0.828	1.185	0.945				
BUN	OSA	115	IVW	1.686	1.299	2.073	0.008	0.253	353.73 (69.47%)	6.84E-28	rs17730281; rs2978981; rs79575541
		115	WM	1.431	1.053	1.809	0.063				
		115	MR-Egger	1.050	0.154	1.946	0.915				
		112	MR-PRESSO	1.006	0.828	1.185	0.010				

Abbreviations: BUN, blood urea nitrogen; CKD, chronic kidney disease; CI, confidence interval; eGFRcrea, estimated glomerular filtration rate from creatinine; eGFRcys, eGFR from cystatin C; IVW, inverse variance weighted; MR, Mendelian Randomization; OR, odds ratio; OSA, obstructive sleep apnea; PRESSO, Pleiotropy Residual Sum and Outlier; UACR, urine albumin to creatinine ratio; WM, weighted median.

Discussion

This study used bidirectional two-sample MR to comprehensively investigate the causal association between OSA and CKD and kidney function. The study did not find any causal association between genetically predicted OSA and CKD and vice versa but identified that genetically predicted OSA was associated with increased BUN (β: 0.040, 95% CI: 0.013, 0.067, $P = 0.003$) and genetically predicted eGFRcys (OR: 0.687, 95% CI: 0.497, 0.950, $P = 0.023$) and BUN (OR: 1.686, 95% CI: 1.299, 2.073, $P = 0.008$) was associated with risk of OSA.

Previous observational studies have repeatedly explored the association between OSA and CKD,[38,39] but most studies were cross-sectional studies,[19,40,41] with limited cohort studies.[16,17,42] A large cohort of US Veterans (n=3,079,514) found both untreated and treated OSA increased the risk of incident CKD; however, this study did not adjust for some important confounders such as lifestyle and metabolic risk factors.[16] A cross-sectional analysis of the Swiss HypnoLaus cohort study (n = 1760) found an association between objective sleep efficiency and CKD but no association with moderate-severe OSA.[43] Another cross-sectional study found that moderate-to-severe OSA did not increase the risk of CKD

progression.[40] Although the bidirectional relationship may be indicated, potential confounding should be considered because OSA and CKD share many common risk factors, and the study design of observational studies cannot address the issue of reverse causality. The study is the first to adopt a two sample MR to explore the causal relationship between OSA and CKD and we did not find any causal association between genetic predicted OSA and CKD as well as genetic predicted CKD and OSA. The non-significant association in the bidirectional MR may be due to the lack of enough instrumental variables available in the present study. A recent MR study showed non-snoring ($P = 0.049$) was suggestively associated with the risk of end-stage renal disease but the association was not reliable in the sensitivity analyses.[21] These findings further suggest the bidirectional relationship between OSA and CKD remains uncertain and more studies are warranted.

Observational and clinical studies have linked OSA with kidney function.[44,45] Our MR results provided genetically predicted estimates, which complemented these studies by minimizing confounding and strengthening causal inference. Interestingly, we found that genetically OSA was only associated with increased BUN but not eGFRcysC, eGFRcrea, and UCAR. Very limited evidence explored the bidirectional relationship between OSA and BUN. An earlier study showed that the number of OSA events per hour was significantly correlated with BUN ($r = 0.490$, $P < 0.01$).[46] BUN is a biochemical indicator of protein metabolism produced in the liver and excreted by the kidneys,[47] which is commonly used to evaluate renal function and an early marker of kidney dysfunction. The different findings may also because that eGFR and UACR primarily reflect glomerular filtration and structural kidney damage, which may require more prolonged or severe exposure to OSA-related stressors before detectable changes occur. Future studies are warranted to study the effect of duration and severity of OSA on the longitudinal progress of CKD and kidney function. Besides evaluating renal function, evidence from previous experiments suggested that BUN levels were positively associated with the occurrence of diabetes,[48] CVD,[49] and stroke,[50] and can predict the outcome of heart failure,[51] which may partly explain the significant association between genetically predicted OSA and BUN. The genetically predicted OSA and BUN may suggest that OSA may not have a causal effect on kidney function but BUN may play a mediation role in the association between OSA and CVD. One retrospective cohort study showed the significant creatinine serum level reduction after 3 years of fixed continuous positive airway pressure (CPAP) treatment of OSA, which indirectly shows the causal relation between OSA and kidney function.[45] Future more studies are needed to use randomized controlled trials (RCTs) to assess whether OSA treatment (eg, CPAP therapy) or prevention (eg, lifestyle interventions) targeting OSA lead to improvements in kidney function markers.

The eGFRcys may be an even better marker of kidney function than eGFRcrea.[52] This study found that decreased eGFRcys was associated with an increased risk of OSA. A significant association between genetically predicted eGFRcrea and OSA was found in WM analysis, but other MR methods did not find a significant association. In combination of the significantly positive association between genetically predicted BUN and OSA, the findings may indicate the causal relationship between kidney function and risk of OSA. It has been largely reported that patients with CKD have a higher prevalence of OSA. A meta-analysis reported the prevalence (36%) of OSA in non-dialysis CKD was more than two folds of the general population.[53]

The mechanism underpin the bidirectional relationship between OSA and kidney function is unclear. OSA may lead to an accelerated decline in renal function through a variety of direct and indirect mechanisms, including hypoxia, activation of the sympathetic nervous system, hypertension, inflammation, oxidative stress and activation of the renin-angiotensin-aldosterone system (RAAS).[54–57] In a hypoxic environment, the renal tubular epithelium undergoes an inflammatory response, which leads to a series of pathological responses including maladaptive cell repair, metabolic switching, death/senescence, and fibrosis.[58,59] Impaired renal function disrupts the body's water-salt balance, and airway congestion due to fluid overload may play a key role in the pathogenesis of sleep apnea in ESRD patients.[60]

The genetic variants such as rs881858, rs700221, rs9474801, and rs4871907 were associated with key genes involved in kidney function and affect the risk of OSA through different biological mechanisms. For example, rs881858 (SLC34A1) influences renal phosphate handling via sodium-phosphate co-transport, while rs700221 (MXD3) may regulate gene expression patterns relevant to renal physiology. rs9474801 (ATF2) is linked to inflammatory pathways and cellular stress responses that can impact kidney health, and rs4871907 (ABCC10) is involved in molecular transport across renal membranes. These variants contribute to kidney function alterations

and may potentially affect OSA through mechanisms such as fluid retention, electrolyte imbalance, and inflammation.[61] Further research is needed to clarify these genetic associations and their impact on the kidney function-OSA link.

The strength of our study is the first study using the two-sample MR analyses from the large-scale GWAS to evaluate the bidirectional relationship between OSA and CKD and kidney function, which has the advantage of being less vulnerable to residual confounders and enabled us to provide a valid appraisal of reverse causation. A better understanding of the relationship between OSA and CKD and kidney function is helpful to facilitating a clearer perception of the underlying pathophysiology and the potential biomarker of CKD, kidney function, and OSA. The findings in the present study have important clinical implications that kidney function biomarkers especially eGFRcys may serve as an early biomarker for OSA susceptibility, and managing OSA in CKD patients may help mitigate further kidney function decline.

However, our study has several limitations. First, the generalizability should be cautioned because participants of the included studies were of European ancestry, so our findings may not apply to non-European ancestry. Second, bias may be introduced due to the definition of CKD, where CKD used by CKDGen was defined as eGFRcrea <60 mL/min/1.73 m^2 but was not verified by a nephrologist or ICD-codes. Third, the relationship between the severity of OSA and clinical features cannot be explored due to the absence of GWAS data for severe OSA. Forth, selection bias especially OSA cannot be avoided possibly because of underdiagnosis, and exclusive restriction bias due to data limitation. Given these limitations, future GWAS databases of population diversity should be constructed and larger MR Studies should be conducted to better confirm the current results. Fifth, the direct biological mechanism mediating the causal link between OSA and kidney function could not be investigated in this MR study. Hence, future studies are warranted to investigate whether the link between OSA and kidney function can be modified.

Conclusions

In conclusion, our study suggests that kidney function may causally affect OSA, but a causal relationship between OSA and CKD and kidney function remains uncertain. More studies are required to better understand the relationship between OSA and CKD and kidney function.

Data Sharing Statement

The data of the current study are available from the corresponding author on reasonable request.

Ethics Statement

This study utilized publicly available GWAS summary data, and all the information and data involved in this study were anonymized, so the ethical statement is not required for this study, which have been approved by the ethical committee in the Shenzhen Qianhai Shekou Free Trade Zone Hospital (2025-KY-006-01K).

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Author Contributions

Pei Qin and Xiaoning Liu contributed to conceptualization, writing–review & editing, supervision, writing – original draft, and project administration. Xiaoning Liu was involved in conceptualization, writing–original draft, methodology, and investigation. Mengna Liu, Bijuan Zhong, Xinxin He, Zheng Zhou, and Yalai Xu, as the subsequent authors, all participated in formal analysis, investigation, and writing–review & editing. All author shave drafted or written, or substantially revised or critically reviewed the article and agreed on the journal to which the article will be submitted; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for

publication, and any significant changes introduced at the proofing stage; and agreed to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors declare no competing interests.

References

1. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet*. 2018;392:2052–2090. doi:10.1016/s0140-6736(18)31694-5
2. Chen W, Li Y, Guo L, Zhang C, Tang S. An umbrella review of systematic reviews and meta-analyses of observational investigations of obstructive sleep apnea and health outcomes. *Sleep Breath*. 2022;26:167–188. doi:10.1007/s11325-021-02384-2
3. Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int*. 2015;88:950–957. doi:10.1038/ki.2015.230
4. Bikbov B, Purcell CA, Levey AS, Global. regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395:709–733. doi:10.1016/s0140-6736(20)30045-3
5. The report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep*. 1999;22:667–689. doi:10.1093/sleep/22.5.667
6. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev*. 2017;34:70–81. doi:10.1016/j.smrv.2016.07.002
7. Adeseun GA, Rosas SE. The impact of obstructive sleep apnea on chronic kidney disease. *Curr Hypertens Rep*. 2010;12:378–383. doi:10.1007/s11906-010-0135-1
8. Chiu K-L, Ryan CM, Shiota S, et al. Fluid shift by lower body positive pressure increases pharyngeal resistance in healthy subjects. *Am J Respir Crit Care Med*. 2006;174:1378–1383. doi:10.1164/rccm.200607-927OC
9. Hui L, Benca R. The bidirectional relationship between obstructive sleep apnea and chronic kidney disease. *J Stroke Cerebrovasc Dis*. 2021;30:105652. doi:10.1016/j.jstrokecerebrovasdis.2021.105652
10. Yayan J, Rasche K, Vlachou A. Obstructive sleep apnea and chronic kidney disease. *Adv Exp Med Biol*. 2017;1022:11–18. doi:10.1007/5584_2017_35
11. Jung SM, Lee MR, Kushwaha PP. Association between obstructive sleep apnea and chronic kidney disease according to sex, long working hours: the Korean National Health and Nutrition Examination Survey (2019–2020). *Life*. 2023;14:13. doi:10.3390/life13081625
12. Beaudin AE, Raneri JK, Ahmed SB, et al. Risk of chronic kidney disease in patients with obstructive sleep apnea. *Sleep*. 2022;45. doi:10.1093/sleep/zsab267
13. Faulx MD, Storfer-Isser A, Kirchner HL, Jenny NS, Tracy RP, Redline S. Obstructive sleep apnea is associated with increased urinary albumin excretion. *Sleep*. 2007;30:923–929. doi:10.1093/sleep/30.7.923
14. Chou YT, Lee PH, Yang CT, et al. Obstructive sleep apnea: a stand-alone risk factor for chronic kidney disease. *Nephrol Dial Transplant*. 2011;26:2244–2250. doi:10.1093/ndt/gfq821
15. Liu T, Zhan Y, Wang Y, Li Q, Mao H. Obstructive sleep apnea syndrome and risk of renal impairment: a systematic review and meta-analysis with trial sequential analysis. *Sleep Breath*. 2021;25:17–27. doi:10.1007/s11325-020-02090-5
16. Molnar MZ, Mucsi I, Novak M, et al. Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax*. 2015;70:888–895. doi:10.1136/thoraxjnl-2015-206970
17. Liu M, Heizhati M, Li N, et al. The relationship between obstructive sleep apnea and risk of renal impairment in patients with hypertension, a longitudinal study. *Sleep Med*. 2023;109:18–24. doi:10.1016/j.sleep.2023.05.020
18. Zhang F, Huang X, Wang H, et al. Prevalence of obstructive sleep apnea in whole spectrum chronic kidney disease patients: a systematic review and meta-analysis. *Sleep Med*. 2024;119:526–534. doi:10.1016/j.sleep.2024.05.047
19. Nicholl DDM, Ahmed SB, Loewen AHS, et al. Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. *Chest*. 2012;141:1422–1430. doi:10.1378/chest.11-1809
20. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37:658–665. doi:10.1002/gepi.21758
21. Li K, Zhao J, Yang W, Ye Z. Sleep traits and risk of end-stage renal disease: a Mendelian randomization study. *BMC Med Genomics*. 2023;16:76. doi:10.1186/s12920-023-01497-9
22. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomisation (STROBE-MR): explanation and elaboration. *BMJ*. 2021;375:n2233. doi:10.1136/bmj.n2233
23. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613:508–518. doi:10.1038/s41586-022-05473-8

24. Strausz S, Ruotsalainen S, Ollila HM, et al. Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health. *Eur Respir J*. 2021;57(5):2003091. doi:10.1183/13993003.03091-2020
25. Li Y, Leng Y, Tang H, et al. Assessment of the causal effects of obstructive sleep apnea on atrial fibrillation: a Mendelian randomization study. *Front Cardiovasc Med*. 2022;9:843681. doi:10.3389/fcvm.2022.843681
26. Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet*. 2019;51:957–972. doi:10.1038/s41588-019-0407-x
27. Pattaro C, Teumer A, Gorski M, et al. Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. *Nat Commun*. 2016;7:10023. doi:10.1038/ncomms10023
28. Teumer A, Li Y, Ghasemi S, et al. Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria. *Nat Commun*. 2019;10:4130. doi:10.1038/s41467-019-11576-0
29. Stanzick KJ, Li Y, Schlosser P, et al. Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals. *Nat Commun*. 2021;12:4350. doi:10.1038/s41467-021-24491-0
30. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601. doi:10.1136/bmj.k601
31. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27:1133–1163. doi:10.1002/sim.3034
32. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Gen Epidemiol*. 2016;40:304–314. doi:10.1002/gepi.21965
33. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44:512–525. doi:10.1093/ije/dyv080
34. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature Genetics*. 2018;50:693–698. doi:10.1038/s41588-018-0099-7
35. Burgess S, Dudbridge F, Thompson SG. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods. *Stat Med*. 2016;35:1880–1906. doi:10.1002/sim.6835
36. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol*. 2017;32:377–389. doi:10.1007/s10654-017-0255-x
37. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol*. 2017;46:1985–1998. doi:10.1093/ije/dyx102
38. Hansrivijit P, Puthenpura MM, Ghahramani N, Thongprayoon C, Cheungpasitporn W. Bidirectional association between chronic kidney disease and sleep apnea: a systematic review and meta-analysis. *Int Urol Nephrol*. 2021;53:1209–1222. doi:10.1007/s11255-020-02699-1
39. Hwu DW, Lin KD, Lin KC, Lee YJ, Chang YH. The association of obstructive sleep apnea and renal outcomes-a systematic review and meta-analysis. *BMC Nephrol*. 2017;18:313. doi:10.1186/s12882-017-0731-2
40. Beaudin AE, Raneri JK, Ahmed S, et al. Association of insomnia and short sleep duration, alone or with comorbid obstructive sleep apnea, and the risk of chronic kidney disease. *Sleep*. 2022;45. doi:10.1093/sleep/zsac088
41. Adams RJ, Appleton SL, Vakulin A, et al. Chronic kidney disease and sleep apnea association of kidney disease with obstructive sleep apnea in a population study of men. *Sleep*. 2017:40. doi:10.1093/sleep/zsw015
42. Lee YC, Hung SY, Wang HK, et al. Sleep apnea and the risk of chronic kidney disease: a nationwide population-based cohort study. *Sleep*. 2015;38:213–221. doi:10.5665/sleep.4400
43. Ogna A, Forni Ogna V, Haba Rubio J, et al. Sleep characteristics in early stages of chronic kidney disease in the hypnolaus cohort. *Sleep*. 2016;39:945–953. doi:10.5665/sleep.5660
44. Zamarrón E, Jaureguizar A, García-Sánchez A, et al. Obstructive sleep apnea is associated with impaired renal function in patients with diabetic kidney disease. *Sci Rep*. 2021;11:5675. doi:10.1038/s41598-021-85023-w
45. Pochetti P, Azzolina D, Ragnoli B, Tillio PA, Cantaluppi V, Malerba M. Interrelationship among obstructive sleep apnea, renal function and survival: a cohort study. *Int J Environ Res Public Health*. 2020;18:17. doi:10.3390/ijerph17144922
46. Tada T, Kusano KF, Ogawa A, et al. The predictors of central and obstructive sleep apnoea in haemodialysis patients. *Nephrol Dial Transplant*. 2007;22:1190–1197. doi:10.1093/ndt/gfl748
47. Van veldhuisen DJ, Ruilope LM, Maisel AS, Damman K. Biomarkers of renal injury and function: diagnostic, prognostic and therapeutic implications in heart failure. *Eur Heart J*. 2016;37:2577–2585. doi:10.1093/eurheartj/ehv588
48. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Higher blood urea nitrogen is associated with increased risk of incident diabetes mellitus. *Kidney Int*. 2018;93:741–752. doi:10.1016/j.kint.2017.08.033
49. Hong C, Zhu H, Zhou X, et al. Association of blood urea nitrogen with cardiovascular diseases and all-cause mortality in USA adults: results from NHANES 1999–2006. *Nutrients*. 2023;16:15. doi:10.3390/nu15020461
50. Peng R, Liu K, Li W, et al. Blood urea nitrogen, blood urea nitrogen to creatinine ratio and incident stroke: the Dongfeng-Tongji cohort. *Atherosclerosis*. 2021;333:1–8. doi:10.1016/j.atherosclerosis.2021.08.011
51. Yano M, Nishino M, Ukita K, et al. Clinical impact of blood urea nitrogen, regardless of renal function, in heart failure with preserved ejection fraction. *Int J Cardiol*. 2022;363:94–101. doi:10.1016/j.ijcard.2022.06.061
52. Aldenbratt A, Lindberg C, Johannesson E, Hammarsten O, Svensson MK. Estimation of kidney function in patients with primary neuromuscular diseases: is serum cystatin C a better marker of kidney function than creatinine? *J Nephrol*. 2022;35:493–503. doi:10.1007/s40620-021-01122-x
53. Huang Z, Tang X, Zhang T, Qiu S, Xia Z, Fu P. Prevalence of sleep apnoea in non-dialysis chronic kidney disease patients: a systematic review and meta-analysis. *Nephrology*. 2019;24:1041–1049. doi:10.1111/nep.13546
54. Sun W, Yin X, Wang Y, et al. Intermittent hypoxia-induced renal antioxidants and oxidative damage in male mice: hormetic dose response. *Dose Response*. 2012;11:385–400. doi:10.2203/dose-response.12-027.Cai
55. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest*. 1997;99:106–109. doi:10.1172/jci119120
56. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96:1897–1904. doi:10.1172/jci118235

57. Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation*. 2005;112:2660–2667. doi:10.1161/circulationaha.105.556746
58. Wang B, Li ZL, Zhang YL, Wen Y, Gao YM, Liu BC. Hypoxia and chronic kidney disease. *EBioMedicine*. 2022;77:103942. doi:10.1016/j.ebiom.2022.103942
59. Shu S, Wang Y, Zheng M, et al. Hypoxia and hypoxia-inducible factors in kidney injury and repair. *Cells*. 2019;8:207. doi:10.3390/cells8030207
60. Tang SC, Lam B, Lai AS, et al. Improvement in sleep apnea during nocturnal peritoneal dialysis is associated with reduced airway congestion and better uremic clearance. *Clin J Am Soc Nephrol*. 2009;4:410–418. doi:10.2215/cjn.03520708
61. Abuyassin B, Sharma K, Ayas NT, Laher I. Obstructive sleep apnea and kidney disease: a potential bidirectional relationship? *J Clin Sleep Med*. 2015;11:915–924. doi:10.5664/jcsm.4946