Sleep disorders and renal failure: exploring the role of creatinine and sleep apnea syndrome through cross-sectional studies and Mendelian randomization analysis

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Abstract

Introduction: The aim of the study was to explore potential factors affecting the emergence of sleep disorders in patients with renal failure.
Material and methods: A cross-sectional study approach was employed in order to evaluate the relationship between renal failure and sleep disorders, and to validate the findings through Mendelian randomization (MR) analysis. Furthermore, we utilized a two-stage MR methodology to quantify the specific contribution of creatinine, mediated by sleep apnea syndrome, to the development of renal failure.
Results: In the multivariate adjusted logistic regression analysis, compared to non-renal failure patients, time to fall asleep in minutes (OR = 0.01, 95% CI: 0.00–0.40, p = 0.022) was significantly reduced, while waking up during the night (OR = 0.73, 95% CI: 0.62–0.86, p = 0.003), feeling unrested during the day (OR = 0.65, 95% CI: 0.48–0.89, p = 0.015), and feeling overly sleepy during the day (OR = 0.67, 95% CI: 0.50–0.89, p = 0.014) were also decreased. In the study of sleep-related factors and renal failure, it was found that sleep apnea syndrome could serve as a mediating factor in mediating creatinine levels for the occurrence of chronic kidney failure (proportion mediated: 2.6%; 95% CI = 0.5–4.7%) and renal failure (proportion mediated: 4.3%; 95% CI = 0.2–8.3%).
Conclusions: Compared to non-renal failure patients, patients with renal failure exhibit significantly reduced sleep onset time and sleep stability. Sleep apnea syndrome may act as a mediator, promoting creatinine-induced damage to the kidneys.

Key words: sleep disorder, renal failure, creatinine, Mendelian randomization, National Health and Nutrition Examination Survey.

Introduction

Renal failure is a global public health concern. Data from the Global Kidney Disease Epidemiology Collaboration (GKDEC) illustrate an increasing

trend in the global prevalence of chronic kidney disease (CKD). It is estimated that more than 800 million people worldwide suffer from CKD, with many progressing to renal failure, which necessitates treatments such as dialysis or kidney transplantation [1]. Epidemiological research has revealed significant disparities in the incidence of CKD and renal failure among different regions and populations. Studies indicate that the risk of CKD and renal failure is significantly elevated in elderly individuals with concomitant diabetes and hypertension [2]. Furthermore, African and Hispanic ethnicities are at a relatively high risk for kidney diseases and renal failure. Socioeconomic factors also play a role, as low-income groups and those with less education are more susceptible to kidney diseases [3].

Sleep plays a crucial role in the clearance of creatinine, a waste product of muscle metabolism. During normal sleep behavior, physiological functions are in a state of regulation and repair. In this process, renal blood flow increases and the glomerular filtration rate improves, enhancing the kidneys' ability to clear waste and metabolic by-products. Some studies suggest that sleep disorders may impact renal function [4], slowing the waste clearance process and leading to the accumulation of metabolic products within the body [5]. This can even accelerate the deterioration of kidney function. Existing research indicates that patients with renal failure may experience abnormalities in metabolic homeostasis [6], cognitive disorders [7] and respiratory control dysfunction [8], and some may develop sleep disorders [9]. This phenomenon is also considered to be a result of the accumulation of toxins in the body [10].

Multiple studies have highlighted sleep as a potential risk factor for the development and progression of CKD, with sleep disorders emerging as one of the most common symptoms in renal failure patients. The prevalence of sleep disorders among patients with chronic kidney disease has been well documented as significant, with approximately 50% of patients experiencing poor sleep quality or insomnia [11]. Similarly, 44% of patients with end-stage renal disease have been identified as suffering from sleep disturbances [12]. Furthermore, 52–67% of patients with renal failure consistently demonstrate excessive daytime sleepiness in various research studies, indicating widespread occurrence of this condition [13].

The pathophysiological causes of sleep disorders in patients with renal failure are complex, mainly including the accumulation of toxins and metabolic abnormalities in the body [14], and the two major aspects of nervous system disorders. Toxin accumulation and metabolic abnormalities directly affect the function of the nervous system, leading to changes in nerve excitability, which in turn triggers sleep disorders. Meanwhile, uremic encephalopathy, as a serious complication of renal failure, can also trigger insomnia and other symptoms [15]. In addition, nerve dysfunction is another important cause of sleep disorder, affecting the sleep-wake cycle of patients [16]. In summary, sleep disorders in patients with renal failure are the result of a combination of pathophysiological factors, and comprehensive treatment is needed to improve sleep quality.

To assess the interplay between sleep disorders and renal failure, this study utilized data on sleep, biochemical markers, and renal conditions from the NHANES database. Employing a cross-sectional study design and adjusting for multiple models, we found that creatinine may be a key factor affecting the relationship between the two. Subsequently, a two-step Mendelian randomization analysis was conducted to examine the relationship among creatinine levels, sleep disorders and their subtypes, and renal failure. This identified potential mechanisms by which sleep disorders manifest in patients with renal failure and analyzed possible mediating factors within the subtypes of sleep disorders.

Material and methods

Study population in NHANES

The NHANES database grew out of a series of surveys on a variety of health issues called the NHANES Program implemented by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) in the early 1960s [17]. The NHANES Program is a cross-sectional survey that has been updated and released with new data every two years since 1999, with the ability to make adjustments each year based on the previous cycle. Adjustments are made to the research project for the new year as well as minor adjustments to previous data [18]. The NHANES program consists of both an interview survey and a physical examination. The interview survey portion is conducted in the participant's home, and all questionnaires have trained personnel to report the information. This was followed by a standardized physical examination and laboratory tests [19]. This study explored sleep disorders and renal failure, and relevant data from the 2005–2006 and 2007–2008 cycles were selected for this study based on data stability and completeness. The NHANES protocols were approved by the National Center for Health Statistics Ethics Review Board, and all participants signed consent forms. A total of 9,765 participants were enrolled after screening for further analysis. The specific screening process is shown in Figure 1.

Research variables and covariates

Questions on sleep (SLQ) were first published in the NHANES database in the 2005–2006 cycle,

including sleep habits and sleep disorders, and were significantly reduced in the 2009–2010 cycle.

The assessment of kidney function is primarily based on the following criteria: Have you ever been informed by a healthcare provider about having weak or failing kidneys? (excluding conditions such as kidney stones, bladder infections, or incontinence). Patients who had cancer during the study were excluded (Have you ever been told you had cancer or malignancy?).

The creatinine indicator (in μmol/l) was obtained from the Standard Biochemistry Profile (BIOPRO) module, and its measurement was performed using the Jaffe rate method as described in Laboratory Methodology 9. Sleep apnea syndrome is characterized by a combination of symptoms such as pauses in breathing, snoring, daytime sleepiness and nocturnal awakenings. The intake of relevant medications was obtained from the "RXDDRUG – Generic drug name" section within the "Prescription Medications" part. The presence of all four of these sleep abnormalities confirms the diagnosis of sleep apnea syndrome.

The following variables were used as covariates to create multivariate models: age (years), gender, race, education level, marital status, body mass index (BMI, kg/m^2), smoking status (previously smoked no less than 100 cigarettes), diabetes, hypertension; anemia was defined as hemoglobin levels below 13 g/dl for males, below 12 g/dl for non-pregnant females, and below 11 g/dl for pregnant females. Hyperlipidemia was determined by the presence of total cholesterol exceeding 200 mg/dl, triglycerides exceeding 150 mg/dl, high-density lipoprotein (HDL) levels below 40 mg/dl in males or below 50 mg/dl in females, low-density lipoprotein (LDL) levels above 130 mg/dl, or the use of lipid-lowering medications. Drinking (Had at least 12 alcohol drinks/1 year?), physical activity (Over the past 30 days do moderate activities for at least 10 min) [20], drug taking (As depicted in Table I).

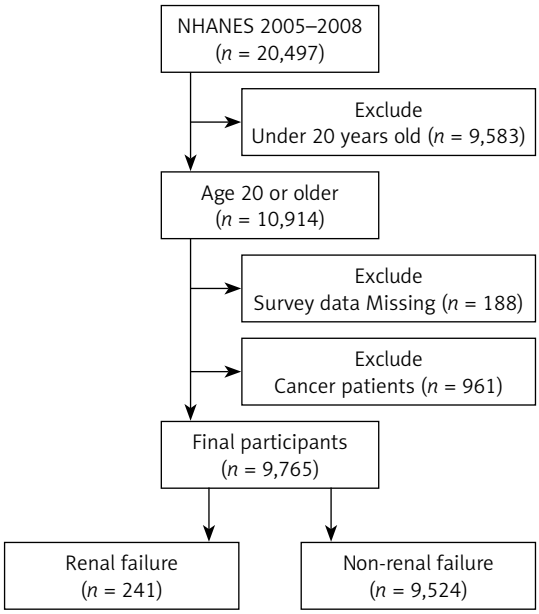

Figure 1. Flowchart of sample selection from NHANES (2005–2008)

Causal relationships between sleep disorder and kidney failure risk in MR

In a two-sample MR analysis, single nucleotide polymorphisms (SNPs) used as instrumental variables (IVs) must fulfill three key assumptions: (1) the IVs are strongly associated with the sleep disorder; (2) the IVs are independent of confounding factors that may affect both the exposure and the outcome; (3) the IVs affect the outcome only via the exposure and have no direct effect on the independent outcome.

Summary data for SD and kidney failure from GWAS

To ensure the reliability of our findings regarding the causal relationship, we conducted a comprehensive search for eligible summary-level data from the largest public genome-wide association studies (GWAS) for each trait. All the data used in our study were previously published and publicly available; no additional ethical approval was required. Specifically, we extracted summary statistics for kidney failure and different sleep disorders from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/datasets/). The diagnostic criteria and inclusion methods were consistent with the original literature.

Selection of genetic instrumental variables

In the GWAS data, we followed a specific process to identify suitable SNPs as instrumental variables (IVs). Firstly, we selected SNPs that were strongly associated with the exposure, controlling for a genome-wide significance level of $p < 1 \times 10^{-5}$. Additionally, to address potential biases, we performed clustering with a cutoff value of $R^2 = 0.001$ ($R^2 = 2 \times (1 - EAF) \times EAF \times \beta^2/(SE^2 \times N)$) [21]and a window size of 10,000 kb. We also utilized the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/) to screen for genetic variations associated with confounders. Finally, we aligned the exposure dataset with the outcome dataset to ensure the exclusion of allele-incongruent SNPs, thus ensuring the consistency of the effect alleles for both exposure and outcome.

Furthermore, to better satisfy key assumption one, we calculated the F ($F = R^2 \times (N - k - 1)/[k \times (1 - R^2)]$) [21] statistic for each SNP individually. The F-statistic, when greater than 10, suggests a slight possibility of encountering a weak instrumental variable (IV) deviation [22]. After applying

Table I. Drug names related to kidney function

Lisinopril	Propranolol
Atorvastatin	Hydrochlorothiazide; valsartan
Metoprolol	Benazepril
Simvastatin	Olmesartan
Hydrochlorothiazide	Isosorbide mononitrate
Atenolol	Felodipine
Furosemide	Gemfibrozil
Amlodipine	Irbesartan
Valsartan	Hydrochlorothiazide; losartan
Lovastatin	Triamterene
Hydrochlorothiazide; triamterene	Hydrochlorothiazide; irbesartan
Diltiazem	Hydrochlorothiazide; olmesartan
Ezetimibe; simvastatin	Captopril
Losartan	Amlodipine; atorvastatin
Enalapril	Fosinopril
Carvedilol	Telmisartan
Ezetimibe	Bisoprolol; hydrochlorothiazide
Amlodipine; benazepril	Candesartan
Nifedipine	Fluvastatin
Pravastatin	Labetalol
Rosuvastatin	Nisoldipine
Ramipril	Atenolol; chlorthalidone
Clonidine	Metolazone
Hydrochlorothiazide; lisinopril	Bumetanide
Quinapril	Indapamide
Terazosin	Torsemide
Doxazosin	Metformin; pioglitazone
Spironolactone	Sevelamer
Fenofibrate	Bisoprolol
Verapamil	Colesevelam

these screening steps, we collected the obtained SNPs as the final IVs for subsequent two-sample MR analyses.

Statistical analysis

Cross-sectional study

In the present investigation, the mobile examination center weight, as furnished by the National Health and Nutrition Examination Survey (NHANES), served as the weighting variable. Continuous variables were summarized using weighted means accompanied by their respective standard errors, while categorical variables were depicted through frequencies expressed as weighted percentages. To evaluate the correlations among the variables, we used either Pearson's or Spearman's correlation coefficients, based on the nature of the data. For the regression analysis, we adopted weighted multiple logistic regression models augmented with restricted cubic splines (RCS) to capture potential nonlinear relationships. Statistical significance was established at a two-sided *p*-value threshold of less than 0.05.

In our NHANES analysis, we employed a rigorous multivariable-adjusted logistic regression framework to explore the association between sleep disorders and renal failure. We evaluated three distinct covariate-adjusted models: Model 1 represented an unadjusted baseline; Model 2 incorporated adjustments for demographic factors including age, race, family poverty income ratio (PIR), education level, and marital status; and Model 3 further adjusted for an array of health-related variables, namely diabetes, smoking status, alcohol consumption, hypertension, body mass index (BMI), drug use, and physical activity. Given the intricate probability clustering design inherent in NHANES, we meticulously incorporated weights into our statistical analyses. All statistical proce-

dures were executed using R Studio version 4.3.2, an open-source software environment for statistical computing and graphics (available at http://www.R-project.org/).

Bidirectional MR analysis

In the context of two-sample Mendelian randomization studies, this study used SNPs as instrumental variables (IVs) for MR analysis and adhered to the three basic assumptions of MR analysis. A combination of several statistical methods was used, with inverse variance weighting (IVW) being the main method. In addition to IVW, we used MR-Egger regression, weighted median, simple mode, weighted mode, and MR multidirectional residuals and outliers (MR-PRESSO) as secondary methods for reference.

IVW, which includes fixed- and random-effects estimates, played a major role in analyzing the influence of exposure factors on outcomes [23]. MR-Egger regression, based on the assumption of instrumental strength independent of direct effects (InSIDE), involved weighted linear regression. The statistical significance threshold was set at $p < 0.05$. However, due to limitations in assessing the weighted median of the instrumental variable estimates, we used the weighted median method to evaluate the overall causal effect using a large number of genetic instruments.

To investigate heterogeneity identified by the IVW and MR-Egger regression methods, we calculated the Cochran statistic. If the *p*-value was less than 0.05, indicating the presence of heterogeneity, we employed a random-effects model for subsequent analyses. Otherwise, a fixed-effects model was used. To assess the potential bias of individual SNPs in the overall causal effect, we conducted "leave-one-out" sensitivity analyses. All two-sample MR analyses were conducted using the two-sample MR and MR-PRESSO packages. A similar analytical procedure was repeatedly applied, swapping exposure and outcome factors to achieve a bidirectional MR study to assess reverse causality. Cochran's Q test was used to identify heterogeneity. In the presence of heterogeneity ($p < 0.05$), a random-effects model was selected; otherwise, a fixed-effects model was applied. MR-PRESSO was conducted to assess pleiotropy, and in the case of a global *p*-value < 0.05, further investigation using MR-PRESSO to identify and remove potential outliers was undertaken.

Mediation analysis

A mediation analysis using a two-step Mendelian randomization (MR) design was performed to investigate the role of sleep disorders as a mediating factor for the effect of creatinine on renal failure. The overall effect can be divided into the direct effect of creatinine on renal failure and the mediating effect. The mediating effect is the influence of sleep on the effect of creatinine on renal failure, where the percentage mediated by the mediating effect is represented by the ratio of the mediating effect to the direct effect.

Results

Baseline characteristics of the study population in NHANES

Participant characteristics for the statistical analysis were derived from NHANES 2005-2008. Table II illustrates that 241 out of the 9,524 (1.9%) participants included in the study self-reported a diagnosis of renal failure. In comparison with the non-renal failure group (9,765 individuals), those with renal failure were characterized by older age, female gender, non-Hispanic White ethnicity, higher educational attainment, married status, absence of diabetes, and high blood pressure ($p < 0.05$). Significant differences were found between the renal failure group and the non-renal failure group in various subcategories of sleep disorders including anemia sleep apnea, insomnia, waking up during the night, feeling unrested during the day, and experiencing excessive daytime sleepiness ($p < 0.01$).

Logistic regression analysis of the relationship between sleep disorder and kidney failure

Three logistic regression models were used for kidney failure. Model 1 was unadjusted, and Model 2 was adjusted for age, gender, race, education level. In Model III, adjusted for all covariates, logistics regression analysis revealed a relationship between kidney failure and sleep disorder.

When sleep disorders are considered as exposure factors, it was found that sleep disorder (Model 1: OR = 1.03, 95% CI: 1.02–1.05, $p < 0.001$; Model 2: OR = 1.03, 95% CI: 1.02–1.05, $p < 0.001$; Model 3: OR = 1.02, 95% CI: 1.01–1.04, $p = 0.011$), insomnia (Model 1: OR = 0.98, 95% CI: 0.97–0.99, $p < 0.001$; Model 2: OR = 0.98, 95% CI: 0.97–0.99, $p = 0.004$; Model 3: OR = 0.99, 95% CI: 0.97–1.00, $p = 0.046$), time to fall asleep in minutes (Model 1: OR = 1.00, 95% CI: 1.00–1.00, $p < 0.001$; Model 2: OR = 1.00, 95% CI: 1.00–1.00, $p = 0.007$; Model 3: OR = 1.00, 95% CI: 1.00–1.00, $p = 0.026$), waking up during the night (Model 1: OR = 0.99, 95% CI: 0.99–1.00, $p < 0.001$; Model 2: OR = 0.99, 95% CI: 0.99–1.00, $p = 0.007$; Model 3: OR = 1.00, 95% CI: 0.99–1.00, $p = 0.006$), feeling unrested during the day (Model 1: OR = 1.00, 95% CI: 0.99–1.00, $p = 0.002$; Model 2: OR = 0.99, 95% CI: 0.99–1.00, $p = 0.001$; Model 3: OR = 1.00, 95% CI: 0.99–1.00,

Table II. Baseline characteristics of the study population

Characteristic	Overall, *N* = 9765 (100%)[2]	Renal failure, *N* = 241 (1.9%)[2]	Non-renal failure, *N* = 9524 (98%)[2]	*P*-value[3]
Age [years]	44 (32, 56)	52 (37, 67)	44 (32, 56)	< 0.001
Race				0.044
Non-Hispanic white	4480 (69%)	101 (64%)	4379 (69%)	
Non-Hispanic black	2164 (12%)	71 (19%)	2093 (12%)	
Mexican American	1922 (8.6%)	43 (8.0%)	1879 (8.7%)	
Other Hispanic	775 (4.4%)	19 (4.9%)	756 (4.3%)	
Other race – including multi-racial	424 (6.0%)	7 (4.2%)	417 (6.0%)	
Education level				0.014
9–11th grade (includes 12th grade with no diploma)	1637 (12%)	55 (17%)	1582 (12%)	
College graduate or above	1841 (26%)	27 (16%)	1814 (26%)	
High school graduate/GED or equivalent	2361 (25%)	57 (25%)	2304 (25%)	
Less than 9th grade	1274 (6.6%)	51 (13%)	1223 (6.4%)	
Some college or AA degree	2646 (30%)	51 (29%)	2595 (30%)	
Family PIR	3.07 (1.58, 5.00)	1.94 (1.15, 3.13)	3.11 (1.60, 5.00)	< 0.001
Marital status				< 0.001
Divorced	1007 (10%)	30 (13%)	977 (10.0%)	
Living with partner	773 (7.9%)	8 (3.2%)	765 (8.0%)	
Married	5162 (57%)	112 (47%)	5050 (57%)	
Never married	1701 (18%)	44 (21%)	1657 (18%)	
Separated	309 (2.3%)	5 (1.8%)	304 (2.3%)	
Widowed	813 (5.4%)	42 (14%)	771 (5.3%)	
Annual family income				0.05
$20,001–$55,000	1904 (41%)	47 (48%)	1857 (41%)	
$55,001–-$75,000	503 (14%)	8 (8.7%)	495 (14%)	
< $20,000	1049 (17%)	41 (28%)	1008 (16%)	
> $75,001	940 (29%)	9 (15%)	931 (29%)	
Diabetes				< 0.001
Yes	1058 (7.6%)	87 (29%)	971 (7.2%)	
No	8544 (92%)	147 (71%)	8397 (93%)	
Smoke				0.2
No	5244 (53%)	111 (48%)	5133 (53%)	
Yes	4515 (47%)	130 (52%)	4385 (47%)	
BMI	27 (24, 32)	28 (25, 33)	27 (24, 32)	0.13
Hypertension				< 0.001
Yes	3094 (28%)	162 (59%)	2932 (27%)	
No	6656 (72%)	79 (41%)	6577 (73%)	
Uric acid	315 (262, 375)	327 (274, 405)	315 (262, 375)	0.073
Total calcium	2.35 (2.30, 2.43)	2.35 (2.30, 2.43)	2.35 (2.30, 2.43)	0.5
Creatinine	80 (64, 88)	88 (70, 124)	79 (64, 88)	< 0.001
Anemia				< 0.001
No	9501 (98%)	220 (94%)	9281 (99%)	
Yes	264 (1.6%)	21 (6.3%)	243 (1.5%)	
Hyperlipidemia				0.4
No	4770 (48%)	115 (51%)	4655 (48%)	
Yes	4995 (52%)	126 (49%)	4869 (52%)	

Table II. Cont.

Characteristic	Overall, *N* = 9765 (100%)[2]	Renal failure, *N* = 241 (1.9%)[2]	Non-renal failure, *N* = 9524 (98%)[2]	*P*-value[3]
Sleep apnea	374 (4.0%)	24 (8.2%)	350 (3.9%)	0.005
Insomnia				0.031
No	9613 (99%)	232 (97%)	9381 (99%)	
Yes	152 (1.3%)	9 (2.8%)	143 (1.3%)	
Restless legs				0.3
No	9733 (100%)	239 (99%)	9494 (100%)	
Yes	32 (0.3%)	2 (0.7%)	30 (0.3%)	
Snore				0.033
Never	2691 (28%)	58 (23%)	2633 (28%)	
Rarely (1–2 nights/week)	1589 (18%)	28 (12%)	1561 (18%)	
Occasionally (3–4 nights/week)	1582 (16%)	39 (17%)	1543 (16%)	
Frequently (5 or more nights/week)	2861 (30%)	78 (33%)	2783 (30%)	
Fall asleep time [min]	15 (5, 30)	20 (10, 45)	15 (5, 30)	< 0.001
Wake up during night				< 0.001
Never	3804 (36%)	72 (29%)	3732 (36%)	
Rarely (once a month)	1804 (20%)	27 (11%)	1777 (20%)	
Sometimes (2–4 times a month)	2240 (24%)	65 (30%)	2175 (23%)	
Often (5–15 times a month)	1166 (13%)	44 (19%)	1122 (13%)	
Almost always (16–30 times a month)	744 (7.2%)	33 (11%)	711 (7.2%)	
Feel unrested during the day				0.032
Never	3317 (28%)	70 (26%)	3247 (28%)	
Rarely (1 time a month)	1482 (17%)	25 (11%)	1457 (17%)	
Sometimes (2–4 times a month)	2630 (29%)	60 (24%)	2570 (29%)	
Often (5–15 times a month)	1406 (17%)	43 (23%)	1363 (17%)	
Almost always (16–30 times a month)	914 (9.7%)	43 (16%)	871 (9.6%)	
Overly sleepy during day				< 0.001
Never	3601 (32%)	77 (30%)	3524 (32%)	
Rarely (1 time a month)	1979 (23%)	34 (15%)	1945 (23%)	
Sometimes (2–4 times a month)	2491 (27%)	61 (26%)	2430 (27%)	
Often (5–15 times a month)	1086 (12%)	32 (14%)	1054 (12%)	
Almost always (16–30 times a month)	601 (5.7%)	37 (16%)	564 (5.6%)	
Sleep hours	7.00 (6.00, 8.00)	7.00 (6.00, 8.00)	7.00 (6.00, 8.00)	> 0.9

[1]N not missing (unweighted), [2]median (IQR) for continuous; n (%) for categorical, [3]design-based Kruskal-Wallis test; Pearson's χ^2: Rao & Scott adjustment.

p = 0.019), and feeling overly sleepy during the day (Model 1: OR = 0.99, 95% CI: 0.99–1.00, p < 0.001; Model 2: OR = 0.99, 95% CI: 0.99–1.00, p = 0.002; Model 3: OR = 1.00, 95% CI: 0.99–1.00, p = 0.029) have a weak protective effect on the occurrence of renal failure. Sleep disorders can increase the risk of renal failure. Other relevant data can be found in Table III.

In patients with renal failure, the presence of sleep disorders as an outcome factor was associated with decreased likelihood of falling asleep quickly (Model 1: OR = 0.00, 95% CI: 0.00–0.04, p < 0.001; Model 2: OR = 0.01, 95% CI: 0.00–0.16, p = 0.005; Model 3: OR = 0.01, 95% CI: 0.00–0.40, p = 0.022). Sleep apnea (Model 1: OR = 0.94, 95% CI: 0.92–0.97, p < 0.001; Model 2: OR = 0.94, 95% CI: 0.91–0.97, p = 0.001; Model 3: OR = 0.97, 95% CI: 0.94–1.00, p = 0.003), waking up during the night (Model 1: OR = 0.61, 95% CI: 0.54–0.70, p < 0.001; Model 2: OR = 0.64, 95% CI: 0.56–0.74, p < 0.001; Model 3: OR = 0.73, 95% CI: 0.62–0.86, p = 0.003), feeling unrested during the day (Model 1: OR = 0.64, 95% CI: 0.50–0.83, p = 0.001; Model 2: OR = 0.58, 95% CI: 0.45–0.75, p < 0.001; Model 3: OR = 0.65, 95% CI: 0.48–0.89, p = 0.015), and experiencing excessive daytime sleepiness (Model 1: OR = 0.62, 95% CI: 0.49–0.78, p < 0.001; Model 2: OR = 0.60, 95% CI: 0.48–0.75,

Table III. Weighted multivariable adjusted logistic regression results for sleep disorders and renal failure in NHANES, 2005–2008

Exposure	Renal failure			Outcome	Renal failure		
	OR	95% CI	*P*-value		OR	95% CI	*P*-value
Sleep disorder				Sleep disorder			
Model 1	1.03	1.02, 1.05	< 0.001	Model 1	1.11	1.07, 1.16	< 0.001
Model 2	1.03	1.02, 1.05	< 0.001	Model 2	1.11	1.06, 1.16	< 0.001
Model 3	1.02	1.01, 1.04	0.011	Model 3	1.08	1.03, 1.13	0.009
Sleep apnea				Sleep apnea			
Model 1	0.97	0.95, 0.99	0.001	Model 1	0.94	0.92, 0.97	< 0.001
Model 2	0.97	0.95, 0.99	0.003	Model 2	0.94	0.91, 0.97	0.001
Model 3	0.98	0.96, 1.00	0.065	Model 3	0.97	0.94, 1.00	0.044
Insomnia				Insomnia			
Model 1	0.98	0.97, 0.99	< 0.001	Model 1	0.96	0.93, 0.98	0.003
Model 2	0.98	0.97, 0.99	0.004	Model 2	0.96	0.93, 0.99	0.008
Model 3	0.99	0.97, 1.00	0.046	Model 3	0.97	0.93, 1.00	0.055
Restless legs				Restless legs			
Model 1	0.99	0.96, 1.01	0.200	Model 1	0.98	0.94, 1.02	0.300
Model 2	0.99	0.96, 1.01	0.300	Model 2	0.98	0.94, 1.02	0.300
Model 3	0.99	0.96, 1.01	0.300	Model 3	0.98	0.94, 1.03	0.400
Snore				Snore			
Model 1	1.00	1.00, 1.00	0.001	Model 1	0.55	0.40, 0.77	< 0.001
Model 2	1.00	1.00, 1.00	0.078	Model 2	0.72	0.49, 1.04	0.076
Model 3	1.00	1.00, 1.00	0.090	Model 3	0.68	0.42, 1.08	0.091
Fall asleep minutes				Fall asleep minutes			
Model 1	1.00	1.00, 1.00	< 0.001	Model 1	0.00	0.00, 0.04	< 0.001
Model 2	1.00	1.00, 1.00	0.007	Model 2	0.01	0.00, 0.16	0.005
Model 3	1.00	1.00, 1.00	0.026	Model 3	0.01	0.00, 0.40	0.022
Wake up during night				Wake up during night			
Model 1	0.99	0.99, 1.00	< 0.001	Model 1	0.61	0.54, 0.70	< 0.001
Model 2	0.99	0.99, 1.00	< 0.001	Model 2	0.64	0.56, 0.74	< 0.001
Model 3	1.00	0.99, 1.00	0.006	Model 3	0.73	0.62, 0.86	0.003
Feel unrested during the day				Feel unrested during the day			
Model 1	1.00	0.99, 1.00	0.002	Model 1	0.64	0.50, 0.83	0.001
Model 2	0.99	0.99, 1.00	0.001	Model 2	0.58	0.45, 0.75	< 0.001
Model 3	1.00	0.99, 1.00	0.019	Model 3	0.65	0.48, 0.89	0.015
Overly sleepy during day				Overly sleepy during day			
Model 1	0.99	0.99, 1.00	< 0.001	Model 1	0.62	0.49, 0.78	< 0.001
Model 2	0.99	0.99, 1.00	< 0.001	Model 2	0.59	0.46, 0.75	< 0.001
Model 3	0.99	0.99, 1.00	0.015	Model 3	0.67	0.50, 0.89	0.014
Sleep hours				Sleep hours			
Model 1	1.00	1.00, 1.00	0.500	Model 1	1.11	0.83, 1.48	0.500
Model 2	1.00	1.00, 1.00	0.400	Model 2	1.12	0.85, 1.49	0.400
Model 3	1.00	1.00, 1.00	> 0.90	Model 3	1.00	0.72, 1.40	> 0.90

Model 1: crude model, Model 2: adjusted for age, race, family PIR, education level, marital status, Model 3: adjusted for age, race, education level, marital status, family PIR, diabetes, smoking, alcohol consumption, hypertension, BMI, drug taking, physical activity.

$p < 0.001$; Model 3: OR = 0.67, 95% CI: 0.50–0.89, $p = 0.014$). The occurrence of sleep disorders was found to be higher in renal failure patients compared to non-renal failure patients (Model 1: OR = 1.11, 95% CI: 1.07–1.16, $p < 0.001$; Model 2: OR = 1.11, 95% CI: 1.06–1.16, $p < 0.001$; Model 3: OR = 1.08, 95% CI: 1.03–1.13, $p = 0.009$). Additional relevant data can be found in Table III.

Nonlinear correlation between sleep disorders and creatinine levels

To investigate the relationship between creatinine levels and the risk of sleep disorders, we employed restricted cubic spline (RCS) analysis, setting the median creatinine level of 78 µmol/l as OR1. The analysis revealed significant nonlinear correlations between serum creatinine and sleep apnea ($p < 0.01$), snoring ($p < 0.01$), time to fall asleep in minutes ($p < 0.01$), waking up during the night ($p < 0.01$), feeling unrested during the day ($p < 0.01$), and experiencing daytime sleepiness ($p < 0.01$), as illustrated in Figure 2. Our findings indicate that as creatinine levels increase, the risk of experiencing sleep disorders gradually rises. Individuals with elevated creatinine levels typically exhibit reduced sleep duration, decreased nocturnal sleep disruption, and increased daytime sleep disorders.

After incorporating creatinine levels, which are closely associated with sleep quality and renal failure, into Model IV and adjusting for all covariates and creatinine, logistic regression analysis revealed a relationship between renal failure and sleep disorder.

In patients with renal failure, the presence of sleep disorders as an outcome factor was associated with poor sleep quality, including: time to fall asleep in minutes (Model 1: OR = 0.00, 95% CI: 0.00–0.04, $p < 0.001$; Model 2: OR = 0.01, 95% CI: 0.00–0.34, $p = 0.005$; Model 3: OR = 0.02, 95% CI: 0.00–0.70, $p = 0.022$; Model 4: OR = 0.01, 95% CI: 0.00–0.59, $p = 0.034$), waking up during the night (Model 1: OR = 0.61, 95% CI: 0.54–0.70, $p < 0.001$; Model 2: OR = 0.64, 95% CI: 0.56–0.74, $p < 0.001$; Model 3: OR = 0.73, 95% CI: 0.62–0.85,

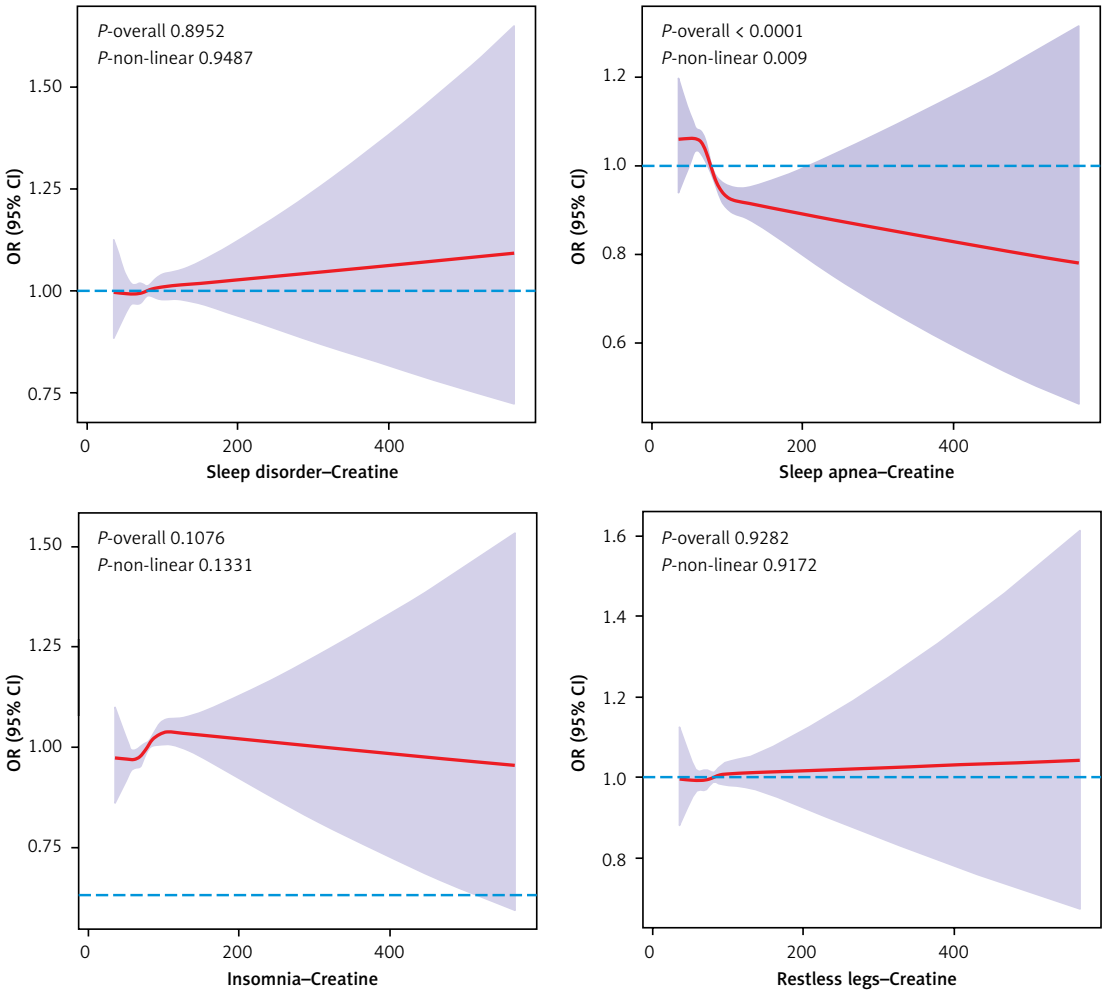

Figure 2. RCS modeling of sleep disorders and creatinine levels. The solid red line represents the combined restricted cubic spline curve model, and the shaded area represents the 95% confidence interval of the combined curve

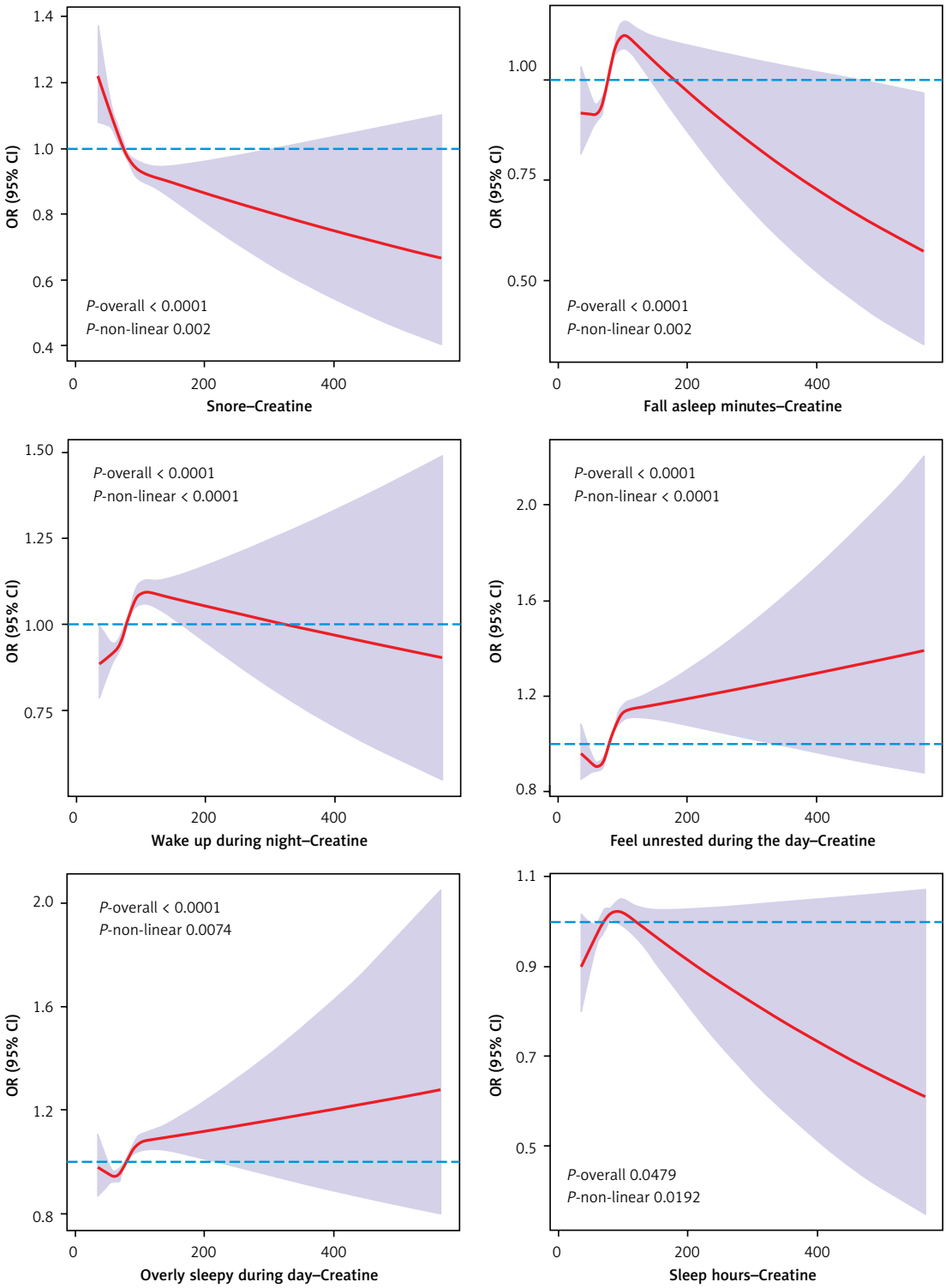

Figure 2. Cont.

p = 0.003; Model 4: OR = 0.73, 95% CI: 0.61–0.86, p = 0.018), feeling unrested during the day (Model 1: OR = 0.64, 95% CI: 0.50–0.83, p = 0.001; Model 2: OR = 0.58, 95% CI: 0.45–0.75, p < 0.001; Model 3: OR = 0.65, 95% CI: 0.48–0.89, p = 0.014; Model 4: OR = 0.64, 95% CI: 0.45–0.91, p = 0.038) and feeling overly sleepy during the day (Model 1: OR = 0.62, 95% CI: 0.49–0.78, p < 0.001; Model 2: OR = 0.59, 95% CI: 0.46–0.78, p < 0.001; Model 3: OR = 0.67, 95% CI: 0.50–0.89, p = 0.014; Model 4: OR = 0.65, 95% CI: 0.48–0.90, p = 0.030). When sleep disorders were considered as exposure factors, no significant association between sleep disorders and renal failure was found. Other relevant

data can be found in Supplementary Table SI.

Mendelian analysis of mediation

Results of MR analysis between creatinine and kidney failure

At the $p < 1.0 \times 10^{-5}$ level, we screened SNPs that could be used as instrumental variables by using creatinine and kidney failure, All SNPs had an F-statistic greater than 10, indicating that there were no weak IVs in the results and this analysis is reliable. The selected SNPS and F values are shown in Supplementary Table SII.

Elevated creatinine levels contribute to the progression of various types of renal failure. Increased risks are observed for acute renal failure (OR = 1.242, 95% CI: 1.117–1.380, $p < 0.001$), chronic renal failure (OR = 2.402, 95% CI: 2.170–2.660, $p < 0.001$), and renal failure (OR = 1.496, 95% CI: 1.307–1.713, $p < 0.001$), as shown in Figure 3 A. The rest can be viewed in Supplementary Table SIII. For chronic renal failure (Egger intercept = –0.011, pval = 0.121, MR-Egger Q = 227.147, MR-Egger Q *p*val = 0.00096, Ivw Q = 234.603, Ivw Q *p*val = 0.0938), renal failure (Egger intercept = –0.009, *p*val = 0.094, MR-Egger Q = 171.557, MR-Egger Q *p*val = 0.110, Ivw Q = 174.809, Ivw Q *p*val = 0.090) and for acute renal failure the specific details are presented in Table IV. All the MR-Egger intercept tests and MR-PRESSO (MR pleiotropy residual sum and outlier method) yielded non-significant results, indicating an absence of horizontal pleiotropy (Supplementary Table SIV). Additionally, evidence of directional heterogeneity was observed in the MR analysis (Supplementary Table SV). After conducting the outlier test, no abnormal values were found, indicating that the causal inference relationship remains unaffected. Additionally, a sensitivity analysis (leave-one-out analysis) demonstrated the stability of the results, showing consistent findings even when individual SNPs were excluded in Supplementary Figures S1 and S2.

Creatinine levels and sleep disorders were identified as having a causal relationship (exposure to mediator)

In the exploration of indicators related to renal failure, we found that serum creatinine levels are associated with a decreased likelihood of sleep-wake state transitions (OR = 0.491, 95% CI: 0.252–0.959, $p < 0.05$), an increased duration of sleep (OR = 1.018, 95% CI: 1.003–1.033, $p < 0.05$), and a higher risk of sleep apnea syndrome (OR = 1.143, 95% CI: 1.044–1.251, $p < 0.05$), as shown in Figure 3 A. The rest can be viewed in Supplementary Table SVI.

The selected SNPS and *F* values are shown in Supplementary Table SVII. For sleep apnea syndrome, Egger intercept = –0.0006, *p*val = 0.883,

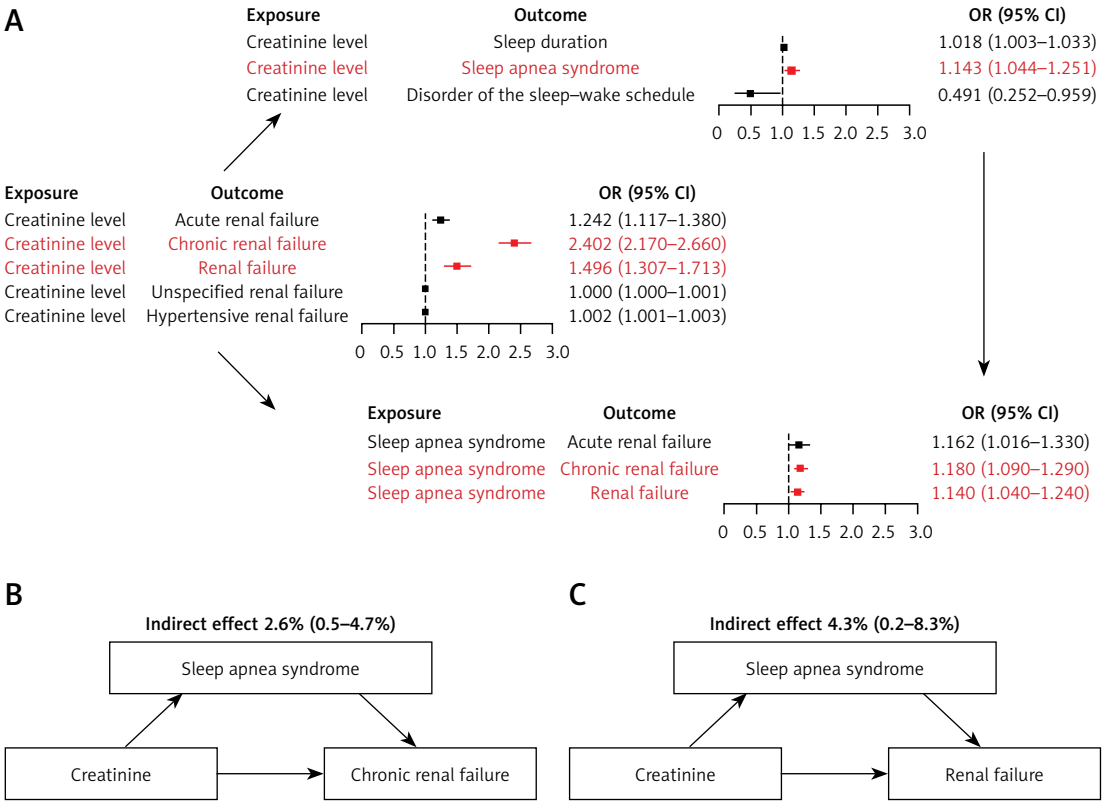

Figure 3. Sleep apnea syndrome may act as a mediator of creatinine-induced renal failure

Table IV. Detailed results of MR analysis

Exposure	Outcome	OR (95% CI)	Ivw *p*val	Egger intercept	Egger intercept *p*val	MR-Egger Q	MR-Egger Q *p*val	Ivw Q	Ivw Q *p*val
Creatinine levels	Chronic renal failure	2.402 (2.170–2.660)	6.31E–36	–0.0108	0.121167	227.147	0.00096	234.603	0.0937991
Creatinine levels	Renal failure	1.496 (1.307–1.713)	0.0000382	–0.00924	0.093799	171.5566	0.109807	174.8092	0.08981
Creatinine levels	Sleep apnea syndrome	1.143 (1.044–1.251)	0.0228956	–0.00057	0.882585	207.2359	0.014342	207.2634	0.016335
Sleep apnea syndrome	Chronic renal failure	1.180 (1.090–1.290)	0.0000697	–0.004802313	0.627649	81.21288	0.003446	81.59976	0.004169
Sleep apnea syndrome	Renal failure	1.140 (1.040–1.240)	0.0289972	–0.00307484	0.750052	55.87564	0.232347	55.99268	0.260124

MR-Egger Q = 207.236, MR-Egger Q *p*val = 0.014, Ivw Q = 207.263, Ivw Q *p*val = 0.016. The MR-Egger intercepts test yielded non-significant results, indicating an absence of horizontal pleiotropy. MR-PRESSO yielded significant results (MR pleiotropy residual sum) (Supplementary Table SVIII), but upon conducting the outlier test, no abnormal values were found, indicating that the causal inference relationship was unaffected (Supplementary Table SIX). Additionally, sensitivity analysis (leave-one-out analysis) demonstrated the stability of the results, showing consistent findings even when individual SNPs were excluded (Supplementary Figure S3).

Sleep disorders and renal failure were identified as having a causal relationship (mediator to outcome)

When considering sleep disorders as an exposure factor, sleep apnea syndrome was associated with an increased risk of renal failure. Our results indicated that sleep apnea syndrome increased the risk of chronic renal failure (OR = 1.180, 95% CI: 1.090–1.290, $p < 0.001$) and renal failure (OR = 1.140, 95% CI: 1.040–1.240, $p < 0.01$). Insomnia was associated with increased risk of acute renal failure (OR = 2.06, 95% CI: 1.52–2.78, $p < 0.001$) and chronic renal failure (OR = 1.52, 95% CI: 1.16–1.98, $p < 0.01$). Increased sleep duration was linked to a reduced risk of acute renal failure (OR = 0.63, 95%: 0.49–0.81, $p < 0.001$), while daytime dozing or sleeping (narcolepsy) was found to increase the risk of chronic renal failure (OR = 1.95, 95% CI: 1.25–2.65, $p < 0.01$). Conversely, trouble falling asleep was associated with a reduced risk of renal failure (OR = 0.00, 95% CI: 0.00–0.16, $p < 0.01$). Overall, sleep disorders were shown to elevate the risk of renal failure (OR = 1.11, 95% CI: 1.01–1.24, $p < 0.05$).

When sleep disorders were considered as an outcome, renal failure showed no significant causal effect on sleep apnea syndrome. Acute renal failure was associated with an increased likelihood of trouble falling or staying asleep, or sleeping too much (OR = 1.05, 95% CI: 1.01–1.09, $p < 0.05$), and a longer sleep duration (OR = 1.01, 95% CI: 1.00–1.02, $p < 0.05$). Chronic renal failure was linked to an increase in sleep duration (OR = 1.05, 95% CI: 1.01–1.09, p < 0.05), a reduced incidence of daytime dozing or sleeping (narcolepsy) (OR = 0.97, 95% CI: 0.95–1.00, $p < 0.05$), and a decrease in sleeping too much (OR = 0.99, 95% CI: 0.98–1.00, $p < 0.05$). Unspecified renal failure significantly decreased the risk of trouble falling or staying asleep (OR = 2.49E-12, 95% CI: 1.11E-20–0.0006, $p = 0.006$). The rest can be viewed in Supplementary Table SX.

For chronic renal failure (Egger intercept = –0.005, *p*val = 0.628, MR-Egger Q = 81.213, MR-Egger Q *p*val = 0.003, Ivw Q = 81.600, Ivw Q *p*val = 0.004) and renal failure (Egger intercept = –0.003, pval = 0.750, MR-Egger Q = 55.876, MR-Egger Q *p*val = 0.232, Ivw Q = 55.993, Ivw Q *p*val = 0.260), no evidence of horizontal pleiotropy was observed, as indicated by non-significant and MR-Egger intercept/MR-PRESSO values >0.05. Heterogeneity was indicated by significant Cochran's Q test < 0.05, but conducting the outlier test, no abnormal values were found, indicating that the causal inference relationship was unaffected.

Additionally, a sensitivity analysis (leave-one-out analysis) demonstrated the stability of the results, showing consistent findings even when individual SNPs were excluded. The rest can be viewed in Supplementary Tables SXI–SXIII and Supplementary Figures S4 and S5.

Mediated effect

Synthesizing the aforementioned results, our analysis concludes that sleep apnea syndrome can act as a mediating factor in renal damage caused by creatinine. Specifically, sleep apnea syndrome mediates 2.6% of the effect on chronic renal failure (proportion mediated: 2.6%; 95% CI = 0.5–4.7%) and 4.3% of the effect on renal failure (proportion mediated: 4.3%; 95% CI = 0.2–8.3%), as depicted in Figures 3 B and C.

Discussion

Sleep disorders in patients with renal failure pose a significant challenge, yet the underlying mechanisms remain unclear. In a cross-sectional study, a large-scale analysis of data related to sleep disorders and renal failure from the NHANES database for the years 2005–2008 was conducted. Adjusting with multiple models revealed an association between sleep disorders and the occurrence of renal failure. Creatinine, as a covariate, had a substantial impact on the fully adjusted results, suggesting a correlation between sleep disorders in renal failure populations and creatinine levels. Analysis of the relationship between creatinine levels and sleep disorders using restricted cubic spline (RCS) analysis demonstrated an increasing risk of sleep disorders with rising creatinine levels, characterized by daytime sleepiness and fatigue. Nocturnal sleep disorder tendencies initially increased with elevated creatinine levels, followed by a decline. Sleep duration showed an initial increase during the early stages of elevated creatinine levels, followed by a gradual decrease.

In Mendelian randomization analysis, we found that creatinine levels can promote various types of kidney failure (acute kidney failure, chronic kidney failure, generic kidney failure, non-specific kidney failure, and hypertension-induced secondary kidney failure). Simultaneously, creatinine levels can increase several sleep disorders, including sleep apnea syndrome, which in turn plays a facilitating role in kidney failure. Based on these findings, we conducted a mediation analysis of the relationship between these factors, demonstrating that sleep apnea syndrome may act as a mediating factor in promoting the occurrence of kidney failure through creatinine. Furthermore, sleep apnea syndrome participates in a positive feedback regulation among creatinine, sleep disorders, and kidney failure, accelerating creatinine-related damage to the kidneys.

The substantial medical burden of chronic kidney failure cannot be fully explained by conventional factors such as hypertension, diabetes, and metabolic syndrome, which often fail to account for the persistent damage to the kidneys. Progress in research has identified sleep disorders as a potential underlying factor in chronic kidney damage [24]. Sleep apnea syndrome, a common sleep disorder characterized by repeated episodes of upper airway obstruction during sleep leading to apnea or hypopnea [25], results in nocturnal hypoxemia and arousal. In-laboratory polysomnography continues to be recognized as the gold standard [26]; when the patient's apnea hypopnea index (AHI) exceeds 5, it is indicative of the presence of sleep apnea [27]. It also triggers activation of the sympathetic nervous system, causing damage to both the cardiovascular and renal systems [28]. Clinical manifestations typically include daytime sleepiness, snoring, apneic episodes, and diminished attention [29].

Studies indicate that sleep apnea is more prevalent among individuals with end-stage renal disease, increasing the mortality rate of those suffering from kidney failure [30]. The presence of sleep apnea syndrome in patients with chronic kidney failure is considered one of the indicators of progression of kidney disease. Sleep apnea syndrome is also associated with a higher incidence of cardiovascular events among patients with renal failure [31]. For patients with renal failure, the severity of sleep apnea is closely related to fluid load, and sleep apnea may be an important indicator to evaluate the effect of dialysis [32]. Early identification of patients with sleep apnea can significantly extend the survival of individuals with kidney failure [33]. Cross-sectional studies have found that sleep apnea syndrome can activate the renin-angiotensin-aldosterone system [34, 35], leading to hypoxemia and hyperfiltration in the glomeruli [36], which may result in renal damage [37]. This effect is more pronounced in severe cases of sleep apnea syndrome [38]. Screening for renal-related markers in populations with sleep apnea syndrome provides better survival benefits for patients with potential renal damage [39]. Home continuous positive airway pressure (CPAP) therapy is effective in treating sleep apnea syndrome [40], especially in patients with severe obstructive sleep apnea, worsened renal function, and a more recent diagnosis of diabetic kidney disease (DKD) [41].

Elevated creatinine levels in patients with chronic kidney disease have been identified as a contributing factor to the development of sleep apnea syndrome [42], while also leading to a reduction in sleep duration [43]. Effective dialysis can significantly lower creatinine levels in patients with kidney failure [44], and nocturnal dialysis has been shown to be more beneficial in improving the apnea-hypopnea index (AHI) and mean saturation of oxygen (SpO_2) associated with sleep apnea syndrome [45, 46]. Research on the relationship between creatinine levels and sleep disorders

is currently ongoing, and regular dialysis and the use of creatinine-lowering medications play a critical role in mitigating the progression of chronic kidney disease.

Continuous positive airway pressure therapy plays a pivotal role in the treatment of sleep apnea syndrome and its associated kidney injury [47]. Sleep apnea is characterized by repeated interruptions of breathing during sleep and has been linked to a number of adverse health effects including kidney injury. CPAP is effective in eliminating apnea episodes and associated hypoxemia, a key factor in the progression of kidney injury, by providing a steady flow of air to keep the upper airway open. Studies have shown that CPAP not only improves sleep apnea but also reduces kidney damage [48]. In patients with diabetic kidney disease who also suffer from obstructive sleep apnea, CPAP therapy has been shown to reduce the proteinuria level, which is a marker of deteriorating renal function [41]. CPAP therapy breaks the vicious cycle of hypoxemia, oxidative stress and inflammation, thereby reducing kidney injury. In short, CPAP therapy is the cornerstone of sleep apnea treatment, preventing kidney damage and promoting overall health.

The aim of this study was to investigate the potential influences on the development of sleep disorders in patients with renal failure, with a special focus on the role of creatinine levels and sleep apnea syndrome. The relationship between renal failure and sleep disorders was analyzed through a cross-sectional study, and the findings were validated using Mendelian randomization analysis. The study used a two-stage MR approach to quantify the specific contribution of creatinine to the development of renal failure through sleep apnea syndrome. The aim of this study was to reveal the characteristics of sleep disorders in patients with renal failure, to understand the role played by creatinine levels, and the possible mechanisms by which sleep apnea syndrome acts as a mediator. By integrating sleep, biochemical parameters and renal function data from the NHANES database, this study expects to provide new perspectives and strategies for the management and treatment of sleep disorders in patients with renal failure.

Our study has certain limitations. Firstly, as a cross-sectional study, it only includes data from a single time point, limiting the scope for long-term observation. Due to the limitations of the available years of sleep data within the NHANES database, the sample size obtained was relatively small. Consequently, there may be a risk of type II errors in the statistical analysis. In future studies, as the volume of research data increases, the occurrence of such errors may gradually decrease. Despite establishing multiple models to minimize confounding factors, the impact of potential variables cannot be entirely eliminated. Owing to the substantial professionalism required for the measurement and interpretation of polysomnography, it is impracticable to ascertain the presence of sleep apnea syndrome in survey participants solely through the questionnaires and pertinent examination items contained within the NHANES database. As a result, the evaluation of sleep apnea syndrome hinges upon clinical manifestations, which may potentially introduce a level of interference into the findings. A promising avenue for future research could entail the creation of a highly dependable scale, administered primarily via questionnaires, to enable a more streamlined assessment of sleep apnea syndrome.

Meanwhile, our study also has notable strengths. The cross-sectional approach captures characteristics of a large population, offering substantial generalizability and applicability. The use of Mendelian randomization compensates for the confounding inherent in cross-sectional studies by enabling causal inferences through a genetic lens. Additionally, intermediary research on sleep disorders provides new insights into the pathogenesis and progression of diseases. The exploration of therapeutic approaches targeting sleep disorder mediators has the potential to be demonstrated as an efficacious intervention for mitigating the progression of certain chronic illnesses. By exploring the intricate relationship between sleep disturbances and various health conditions, researchers aim to uncover novel strategies that can effectively modulate these mediators, thereby alleviating the symptoms and improving the overall prognosis of patients suffering from chronic diseases. This line of investigation not only broadens our understanding of the pathophysiological mechanisms underlying these conditions but also paves the way for the development of targeted therapies that address the root causes of disease progression.

In conclusion, our study demonstrates that patients with renal failure exhibit significant disruptions in sleep patterns compared to non-renal failure individuals. Creatinine, a marker of renal function, plays a crucial role in these sleep disturbances, particularly through its association with sleep apnea syndrome. Using Mendelian randomization analysis, we found that sleep apnea syndrome acts as a mediator, exacerbating creatinine-induced renal damage. This finding suggests a complex interplay between sleep disorders, creatinine levels, and the progression of renal failure. Regular dialysis and continuous positive airway pressure therapy may be essential in mitigating the progression of chronic kidney disease by addressing these interconnected factors. Further research is needed to validate these findings and explore potential therapeutic interventions targeting sleep disorders in renal failure patients.

Data availability statement

The original contributions presented in the study are included in the article and supplementary material. If there are any further inquiries or questions, they can be directed to the corresponding author, who will be pleased to provide additional information or clarification. The NHANES data content used in this paper and the methods used to collect it are publicly available on the NHANES website(https://www.cdc.gov/nchs/nhanes/). The Mendelian randomization data used in this paper can be obtained from GWAS database(https://gwas.mrcieu.ac.uk/).

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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