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Long nighttime sleep duration and risk of renal tubular damage: evidence from rural China and a Mendelian randomization analysis

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ABSTRACT

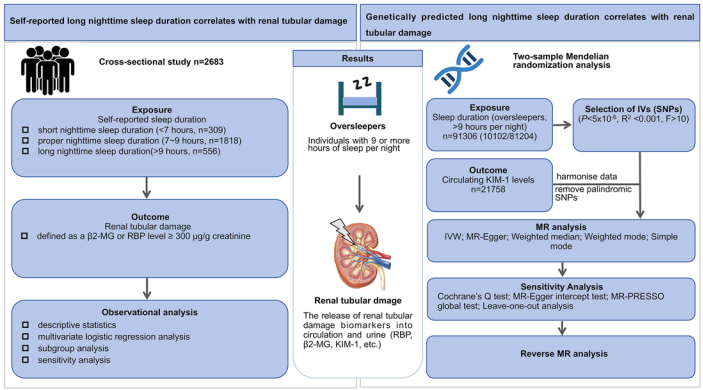
Objective: Renal tubular damage, a pivotal pathological feature of chronic kidney disease (CKD), predicts disease progression. While extreme nighttime sleep duration is linked to glomerular injury by prior studies, its impact on tubular damage remains unclear. Given that 7–9 h of sleep per night is widely recommended for maintaining overall health, this study aimed to assess whether long nighttime sleep duration is associated with renal tubular damage using both observational and genetic evidence.

Methods: We analyzed 2,683 adults in rural China to assess the link between nighttime sleep duration and renal tubular damage (measured by retinol-binding protein and β2-microglobulin). Mendelian randomization (MR) analysis was performed to assess the causal relationship between prolonged nighttime sleep duration and elevated kidney injury molecule-1 (KIM-1) levels.

Results: Multivariate logistic regression indicated that sleeping more than 9 h per night was associated with a 1.38-fold increased risk of renal tubular damage (95% CI: 1.11–1.71) compared to 7–9 h of sleep, with particularly pronounced effects observed in elderly individuals and women. MR analysis further supported a causal relationship between genetically predicted long nighttime sleep duration and elevated KIM-1 levels (β: 0.994, 95% CI: 0.282–1.707), suggesting a genetic predisposition linking prolonged sleep duration with renal tubular damage.

Conclusions: Our findings provide observational and genetic evidence linking prolonged nighttime sleep to increased renal tubular damage risk. Given that 7–9 h of sleep per night is the widely accepted recommendation for maintaining overall health, our results emphasize the potential risks of excessive sleep duration exceeding 9 h.

GRAPHICAL ABSTRACT



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1. Introduction

Chronic kidney disease (CKD) is a global public health issue, impacting over 10% of adults globally, with about 82 million cases reported in China [1]. It often goes undetected in its early stages, making timely intervention challenging. Renal tubular damage is not only an early pathological feature of CKD but also an independent predictor of its progression, underscoring its importance for routine early screening [2]. However, its causes are not fully understood. Identifying modifiable risk factors for renal tubular damage is crucial for preventing CKD [3].

To date, though the known classical factors for renal tubular damage, such as environmental poisons, drugs and chronic metabolic diseases (e.g., hyperlipidemia, diabetes, and hypertension) [4–8], have explained a considerable proportion of the clinical renal tubular damage events, they still cannot fully clarify all the events. Increasing observational studies have demonstrated the relationship between lifestyle (e.g., diet, exercise, and sleep) and kidney damage [9–11]. Sleep, which occupies one-third of our lives, is extensively reported to be associated with glomerular damage reflected by eGFR or proteinuria. For example, some studies have found a U-shaped association between sleep duration and higher proteinuria or reduced eGFR, suggesting that both short and long sleep durations are associated with the increasing risk of glomerular damage [12,13]. Meanwhile, other studies have only observed that either long sleep duration [14] or short sleep duration [15] is associated with glomerular damage. However, the effects of sleep duration on renal tubular damage have not yet been explored.

Previous observational studies have struggled to account for environmental or lifestyle confounders, leading to inconsistent results. Mendelian randomization (MR) addresses this by using genetic variants (SNPs) as instrumental variables to establish causal relationships between exposures and outcomes. This method effectively reduces biases from confounding and reverse causality, complementing real-world research to confirm causal links between risk factors and diseases [16,17]. Despite its usefulness, there is limited MR research on the relationship between sleep duration and kidney health [18–20].

Therefore, we investigated the association of nighttime sleep duration with the risk of renal tubular damage in a large-scale rural population, and further confirmed the causal effect by the MR analyses. Findings of current study may help to identify modifiable risk factors for renal tubular damage and raise public awareness of the primary prevention for CKD.

2. Methods

2.1. Study population and data sources

2.1.1. Study population of observational study

Our observational study involved participants from a cross-sectional survey conducted in rural Hunan province, China, during 2016–2017, with details of the study design previously reported [21,22]. After excluding those missing data on sleep times, β2-microglobulin (β2-MG), retinol-binding protein (RBP), urine creatinine, and covariates, we included 2,683 adults who had lived locally for at least 5 years. The study, detailed in Figure S1, was approved by the Ethical Committee of Xiangya Hospital, Central South University, and all participants provided written informed consent.

2.1.2. Data sources of MR study

We performed the two-sample MR analysis to examine the causal link between long nighttime sleep duration and renal tubular damage biomarkers. This analysis rests on three crucial assumptions: genetic variants must strongly correlate with the exposure, remain uncorrelated with confounding factors, and influence the outcome solely through the exposure. To ensure transparency and methodological rigor [23], the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization (STROBE-MR) checklist is presented in Table S12. These assumptions are fundamental to the validity of MR findings. The two samples MR data in our study were obtained from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk). Exposure SNPs for long nighttime sleep duration were derived from a GWAS dataset comprising 91,306 individuals of European ancestry (Gwas ID: ebi-a-GCST006685), defining oversleepers as those with 9 or more hours of sleep per night [24]. Kidney injury molecule-1 (KIM-1) is a type 1 transmembrane glycoprotein found in proximal renal tubular cells. Normally, KIM-1 levels in serum and urine are low, but they significantly increase when renal tubules are injured. Therefore, KIM-1 is widely used as a biomarker for renal tubular injury and repair [25]. KIM-1 levels were sourced from a GWAS dataset comprising 21,758 individuals of European ancestry (GWAS ID: ebi-a-GCST90012041) [26]. Details of the GWAS datasets are given in Table S2. Ethical approval and patient consent were obtained for the original GWAS studies, obviating the need for separate approval in our analysis.

2.2. Exposure and outcome assessment for observational analyses

2.2.1. Measurement of nighttime sleep duration

Self-reported sleep data were obtained from standardized questionnaires administered by trained interviewers. Participants provided their usual bedtime and wake-up time, from which nighttime sleep duration was calculated as the interval between sleep onset and waking up. According to the joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult, 7–9 h of sleep each night was appropriate to support adults' optimal health [27]. Therefore, we categorized self-reported nighttime sleep into three groups: <7 h (short nighttime sleep duration), 7–9 h (proper nighttime sleep duration, used as the reference), and >9 h (long nighttime sleep duration).

2.2.2. Definition of renal tubular damage

Generally, high-molecular-weight proteins are typically filtered poorly through the glomerular basement membrane, and therefore the urinary albumin is mainly considered to be a consequence of the increased filtration due to the damage of glomerular barriers, although it is also influenced by the tubular reabsorption dysfunction. Therefore, low-molecular-weight proteins, such as β2-MG and RBP, which filter freely and are fully reabsorbed by renal tubules, served as reliable biomarkers for renal tubular damage. In our observational study, first-morning urine samples were used to measure urinary creatinine, RBP, and β2-MG levels. Urinary creatinine was measured using the sarcosine oxidase method, while RBP and β2-MG were measured by immune transmission turbidimetry and immune latex turbidimetry, respectively. To correct for urinary dilution or concentration, we standardized tubular indicator levels by dividing them by the urinary creatinine concentration. Based on previous reports [28], subclinical renal tubular damage was defined as a β2-MG or RBP level ≥300 μg/g creatinine.

2.3. Assessment of covariates for observational analyses

Socio-demographic characteristics and lifestyle information including age, sex, educational level, marital status, household yearly income level, smoking status, drinking status, exercise status, and daytime napping duration were collected through the face-to-face questionnaires by trained interviewers. Anthropometric measurements (weight and height) were taken to calculate body mass index (BMI). Blood pressure for participants was measured by a digital sphygmomanometer after resting for at least 5 min in a sitting position. The hypertension in our study was defined as a mean blood pressure ≥140/90 mmHg or a history of hypertension diagnosed by the certificated physician and a treatment of anti-hypertensive medication currently. Blood samples were collected after an 8-h overnight fast and analyzed using biochemical auto-analyzers. We measured fasting blood glucose (FBG) and lipid profile, including total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Hyperlipidemia was diagnosed by elevated lipid levels: TG ≥2.26 mmol/L, TC ≥6.22 mmol/L, HDL-C <1.04 mmol/L, LDL-C ≥4.14 mmol/L, or a previous diagnosis by a physician. Diabetes was diagnosed with an FBG ≥7.0 mmol/L or a previous physician diagnosis along with current antidiabetic medication use.

2.4. Statistical analysis

2.4.1. Observational analysis

Descriptive statistics were performed to describe the demographic and clinical characteristics as well as lifestyle of the study subjects by different nighttime sleep duration. Categorical variables were presented as numbers (percentages) and compared by Chi-square analysis. Continuous variables were expressed as means (standard deviations) for normally distributed data and median (25th, 75th) for skewed data, compared by one-way ANOVA or Kruskal–Wallis *H* test, respectively. Post hoc tests were applied if significant. Additionally, associations between nighttime sleep duration and renal tubular damage risk in the overall population and subgroups were estimated by multivariate logistic regression analysis, with *post hoc* power calculations conducted using G*Power 3.1.9.7. Missing data were handled through imputation (mean for normally distributed continuous variables, median for skewed continuous variables, and a separate 'missing' category for categorical variables), and sensitivity analyses were performed to evaluate potential selection bias arising from exclusions. All statistical analyses were done by Stata version 16.0 (Stata Corp., College Station, TX) and $p < .05$ (two-tailed) was considered to be statistically significant. No adjustments were made for multiple comparisons, and findings of secondary analyses should be interpreted as exploratory [29].

2.4.2. The bidirectional two-sample Mendelian randomization analysis

To ensure sufficient instrumental variables for achieving the desired statistical power, we followed the approach adopted in previous studies and relaxed the SNPs selection threshold from $p < 5 \times 10^{-8}$ to $p < 5 \times 10^{-6}$ (the same in the inverse analysis) [17,30]. These were pruned for linkage disequilibrium ($r^2 < 0.001$, kb = 10,000) and weak instrument bias (*F* statistic >10) [31]. SNPs associated with confounding factors and outcome were excluded using the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/). Inverse-variance weighted (IVW) method, which was traditionally considered as the most accurate method for estimating causal effects in MR analysis, was implemented in our main analysis to evaluate the causal relationship between long nighttime sleep duration and KIM-1 levels. Additional methods, including MR-Egger, weighted mode, weighted median and simple mode were used as supplementary analysis approaches [30].

Besides, we used MR-Egger and MR-PRESSO for horizontal pleiotropy assessment, Cochran's *Q* test for heterogeneity evaluation, and a funnel plot was employed to ascertain whether the outcomes were biased. To determine the significant independent effect of single SNP on MR estimates, the leave-one-out analysis was conducted. Once any outlier SNP, heterogeneity or horizontal pleiotropy was noteworthy, the MR analysis will be repeated after removing the certain SNPs. Additionally, to avoid the potential effects of reverse causality, we also performed the reverse MR analysis by employing the same GWAS datasets described above.

The post hoc power calculations for IVW analyses were performed by an online MR power calculation tool (https://sb452.shinyapps.io/power/). All statistical analyses were performed using R 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and the 'TwoSample MR' package. A possible association is indicated at a level of $p < .05$ in the MR analysis, and a $p < .05$ in the analyses of heterogeneity and pleiotropy represented the existence of heterogeneity and pleiotropy.

3. Results

3.1. Descriptive analysis of the observational study

Table 1 summarizes the general characteristics of participants based on nighttime sleep duration categories. Among 2683 participants, approximately 67.8% reported proper (7–9 h) nighttime sleep duration, while 11.5% and 20.7% reported short (<7 h) and long (>9 h) nighttime sleep duration, respectively. Compared to those with proper nighttime sleep duration, participants sleeping over 9 h were older, mostly women, less educated, with lower incomes, less physically active, and less likely to be married, smokers, or drinkers. They also had shorter daytime naps and higher rates of renal tubular damage (34.2% vs. 26.6%), hypertension, and diabetes. Conversely, those sleeping less than 7 h were typically younger, male, married, well-educated, with higher income, and exhibited higher rates of smoking, drinking, exercising, and daytime napping.

Table 1. Baseline characteristics of study participants according to nighttime sleep duration (N = 2683).

	Nighttime sleep duration (hours/night)			
Variables	<7 (N = 309, 11.5%)	7–9 (N = 1818, 67.8%)	>9 (N = 556, 20.7%)	p Value
Age (years), mean ± SD	48.3 ± 9.7	50.4 ± 12.5	56.9 ± 15.6	<.001
Sex, N (%)				<.001
Men	220 (71.2)	1,069 (58.8)	239 (43.0)	
Women	89 (28.8)	749 (41.2)	317 (57.0)	
Education, N (%)				<.001
Primary or below	66 (21.4)	640 (35.2)	353 (63.5)	
Junior high school	90 (29.1)	504 (27.7)	114 (20.5)	
High school or above	153 (49.5)	674 (37.1)	89 (16.0)	
Marriage, N (%)				<.001
Married	284 (91.9)	1,590 (87.5)	426 (76.6)	
Other	25 (8.1)	228 (12.5)	130 (23.4)	
Income, RMB/year, N (%)				<.001
<10,000	55 (17.8)	542 (29.8)	268 (48.2)	
10,000–30,000	112 (36.2)	617 (33.9)	176 (31.7)	
30,000–50,000	91 (29.5)	411 (22.6)	78 (14.0)	
>50,000	51 (16.5)	248 (13.7)	34 (6.1)	
Smoking, N (%)				<.001
Never	146 (47.2)	1,110 (61.1)	385 (69.3)	
Current	127 (41.1)	533 (29.3)	123 (22.1)	
Former	36 (11.7)	175 (9.6)	48 (8.6)	
Drinking, N (%)				<.001
Never	223 (72.2)	1,427 (78.5)	448 (80.6)	
Current	69 (22.3)	303 (16.7)	69 (12.4)	
Former	17 (5.5)	88 (4.8)	39 (7.0)	
Exercise, N (%)				<.001
No	151 (48.9)	1,013 (55.7)	397 (71.4)	
Yes	158 (51.1)	805 (44.3)	159 (28.6)	
Hypertension, N (%)				<.001
No	193 (62.5)	1,002 (55.1)	243 (43.7)	
Yes	116 (37.5)	816 (44.9)	313 (56.3)	
Diabetes, N (%)				.003
No	289 (93.5)	1,723 (94.8)	505 (90.8)	
Yes	20 (6.5)	95 (5.2)	51 (9.2)	
Dyslipidemia, N (%)				.068
No	33 (10.7)	238 (13.1)	89 (16.0)	
Yes	276 (89.3)	1,580 (86.9)	467 (84.0)	
Renal tubular damage, N (%)				.002
No	223 (72.2)	1334 (73.4)	366 (65.8)	
Yes	86 (27.8)	484 (26.6)	190 (34.2)	
BMI (kg/m^2), mean ± SD	24.3 ± 3.4	23.9 ± 3.4	23.4 ± 3.4	.962
SBP (mmHg), mean ± SD	130.3 ± 19.1	133.1 ± 20.2	140.5 ± 24.1	<.001
DBP (mmHg), mean ± SD	83.0 ± 13.5	82.9 ± 13.2	83.5 ± 13.3	.819
TG (mmol/L), median (25th, 75th)	1.5 (1.0, 2.2)	1.4 (1.0, 2.1)	1.3 (0.9, 1.9)	.002
TC (mmol/L), mean ± SD	4.8 ± 0.9	5.0 ± 1.0	5.0 ± 0.9	<.001
HDLC (mmol/L), mean ± SD	1.4 ± 0.3	1.4 ± 0.4	1.4 ± 0.3	<.001
LDLC (mmol/L), mean ± SD	2.9 ± 0.9	2.8 ± 0.9	2.8 ± 0.8	.124
FBG (mmol/L), mean ± SD	4.7 ± 1.6	4.8 ± 1.5	5.1 ± 1.4	.005
Urinary β2-MG (μg/g creatinine), median (25th, 75th)	65.4 (27.5, 180.0)	72.3 (30.5, 190.8)	75.6 (24.3, 228.9)	.787
Urinary RBP (μg/g creatinine), median (25th, 75th)	37.3 (17.2, 136.9)	36.0 (17.5, 143.7)	53.9 (21.7, 263.1)	<.001
Daytime napping duration (hours), N (%)				<.001
0	133 (43.1)	875 (48.1)	340 (61.2)	
0–1	99 (32.0)	560 (30.8)	120 (21.6)	
>1	77 (24.9)	383 (21.1)	96 (17.2)	

SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; FBG: fasting blood-glucose; β2-MG: β2-microglobulin; RBP: retinol-binding protein.

p Values for the difference among the three groups.

3.2. Association was found in the observational study

To explore the association between nighttime sleep duration and renal tubular damage, logistic regression models calculated odds ratios and 95% confidence intervals (CIs). Table 2 shows these associations. Both crude and adjusted models found that long nighttime sleep duration was associated with higher odds of renal tubular damage compared to proper sleep duration. After adjusting for age, gender, marriage, education, income, smoking status, drinking status, exercise, BMI and daytime napping duration, participants sleeping more than 9 h per night had a 1.38-fold (95% CI: 1.11–1.71) increased risk of renal tubular damage compared to those sleeping 7–9 h per night (*p* value for linear trend across categories of nighttime sleep duration: 0.032). A *post hoc* power analysis was conducted to evaluate the statistical power of the logistic regression model. Assuming a two-tailed test, an alpha level of 0.05, a target power of 0.80, and an expected odds ratio of 1.39, the analysis indicated that the sample size and event rate (case/control = 556/1,818) were sufficient to detect significant associations. The achieved power was 0.85, indicating that the study was adequately powered for the primary analysis.

Table 2. Odds ratios (95% CI) for nighttime sleep duration associated with renal tubular damage (*N* = 2683).

Category of nighttime sleep duration (hours/night)	Model 1		Model 2	
	OR (95% CI)	*p* for trend	OR (95% CI)	*p* for trend
<7	1.06 (0.81, 1.39)	.009	1.05 (0.79, 1.38)	.032
7–9	Ref (1)		Ref (1)	
>9	1.43 (1.17, 1.75)		1.38 (1.11, 1.71)	

Model 1: crude model. Model 2: adjusted for age, gender, marriage, education, income, smoking status, drinking status, exercise, BMI, and daytime napping duration.

3.3. Subgroup analysis of the observational study

Subgroup analysis was performed to examine the association of nighttime sleep duration with renal tubular damage risk according to age, gender, smoking, drinking, exercise, BMI, hypertension, diabetes, and dyslipidemia (shown in Figure 1). We found that the associations between long nighttime sleep duration and the risk of renal tubular damage appeared to be stronger in elderly individuals, women, nonsmokers, nondrinkers, non-diabetics, those with BMI <24 kg/m^2, and those with hypertension and dyslipidemia. Nonetheless, significant interactions were found only for age and gender ($p_{interaction}$ = .008 and .015, respectively) (shown in Table S1). Elderly and female participants sleeping more than 9 h per night had a 70% and 44% increased risk of renal tubular damage, respectively, compared to those sleeping 7–9 h per night. However, this association was not significant in younger individuals and men.

3.4. Sensitivity analysis of the observational study

To address potential biases due to missing data, we conducted a sensitivity analysis using a simple imputation

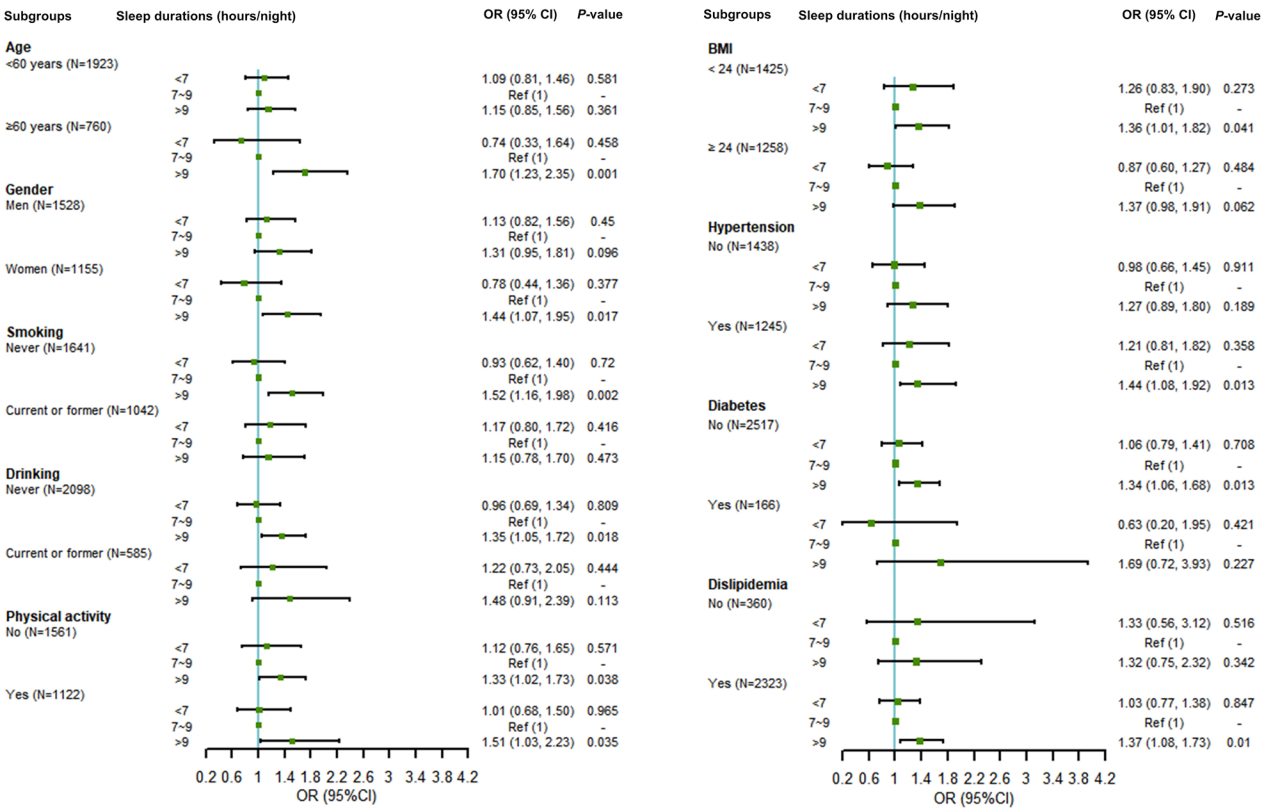

Figure 1. Forest plot of the effects of nighttime sleep duration on renal tubular damage in subgroups (*N* = 2,683).

method. We supplemented the baseline statistical descriptions (Table S9), regression analysis (Table S10), and subgroup analysis (Table S11) results for the imputed data set and compared them with those from the missing data set. The findings indicated that the analysis results from the imputed data set were largely consistent with those from the missing data set, despite minor variations in effect sizes. These results further substantiate the robustness of our study conclusions.

3.5. Causal relationship was identified by the MR analysis

The causal influence between long nighttime sleep duration and renal tubular damage (explained by KIM-1 levels) was evaluated using a two-sample MR analysis. No SNPs for long nighttime sleep duration were identified when the threshold of genome-wide significance was set at $p < 5 \times 10^{-8}$, so the threshold was relaxed to $p < 5 \times 10^{-6}$, yielding 24 long nighttime sleep duration-associated genetic variants. After pruning, 19 instrumental variables were finally included in the MR analysis (shown in Table S3 and Figure S2). The IVW model identified a significant causal relationship between long nighttime sleep duration and KIM-1 levels (β: 0.994, 95% CI: 0.282–1.707, p = .006) (shown in Figure 2(A)) with a statistical power of 100%. This relationship remained statistically significant in the weighted median analysis, and other methods showed consistent β values (shown in Table S4). Although not all the supplementary analyses were significant, there was no evidence of heterogeneity or horizontal pleiotropy (Cochran's Q: PQ = 0.623, MR-Egger: p = .425, MR-PRESSO: p = .669), confirming the reliability of the results (shown in Table S5) [32]. As shown in Figure 2(B), the forest plot visually displayed the associations between long nighttime sleep duration and KIM-1 levels. The funnel plot showed a symmetrical SNP distribution, and the leave-one-out analysis discovered that no single SNP drove the overall effect of long nighttime sleep duration on KIM-1 levels (shown in Figures S3 and S4).

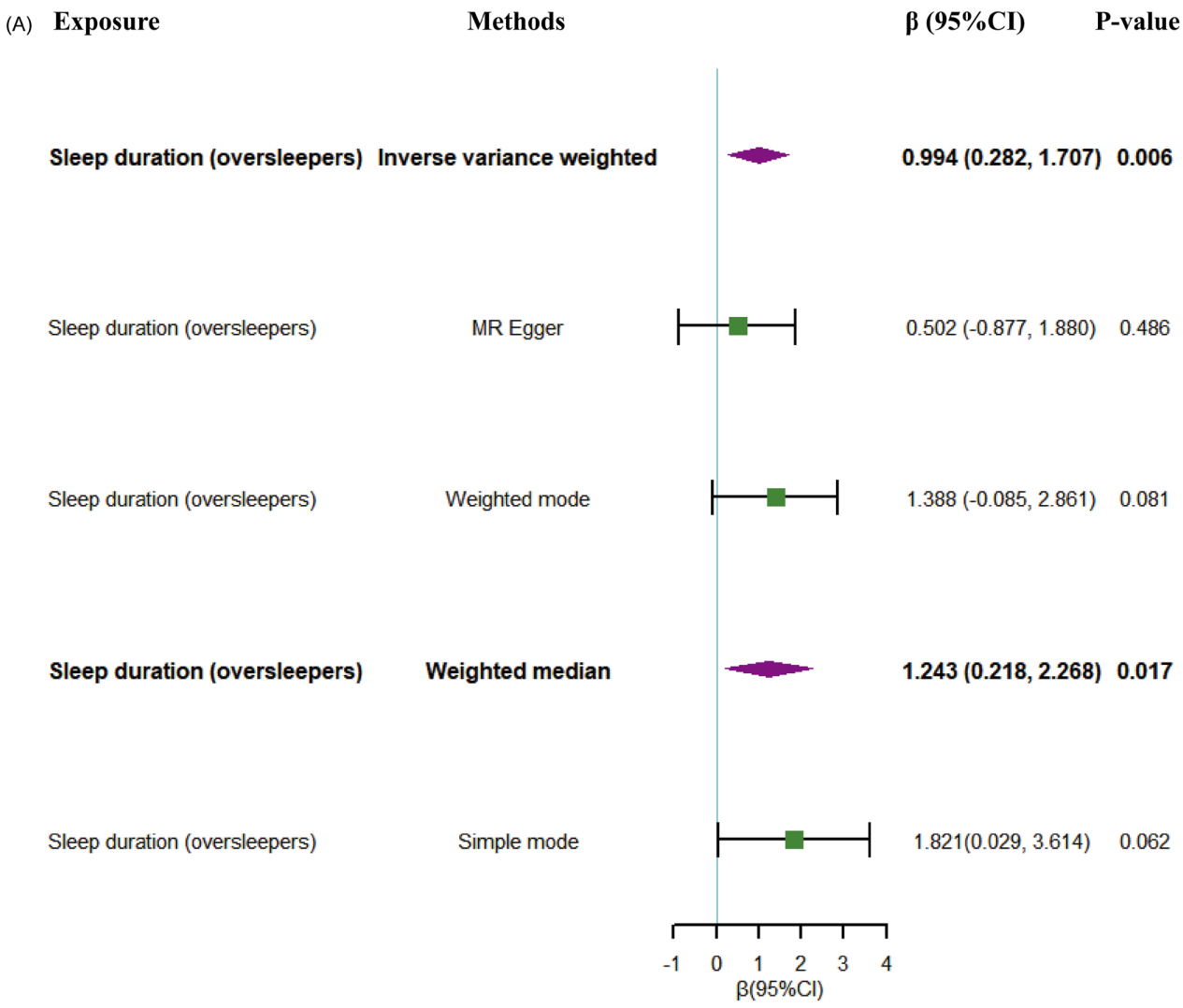

Figure 2. Causal relationships between long nighttime sleep duration and renal tubular damage in two-sample MR analyses. (A) Forest plot of the estimates from five methods to access the causality between long nighttime sleep duration and KIM-1 levels. (B) Forest plot displaying the causality between the single nucleotide polymorphisms associated with nighttime sleep duration and KIM-1 levels.

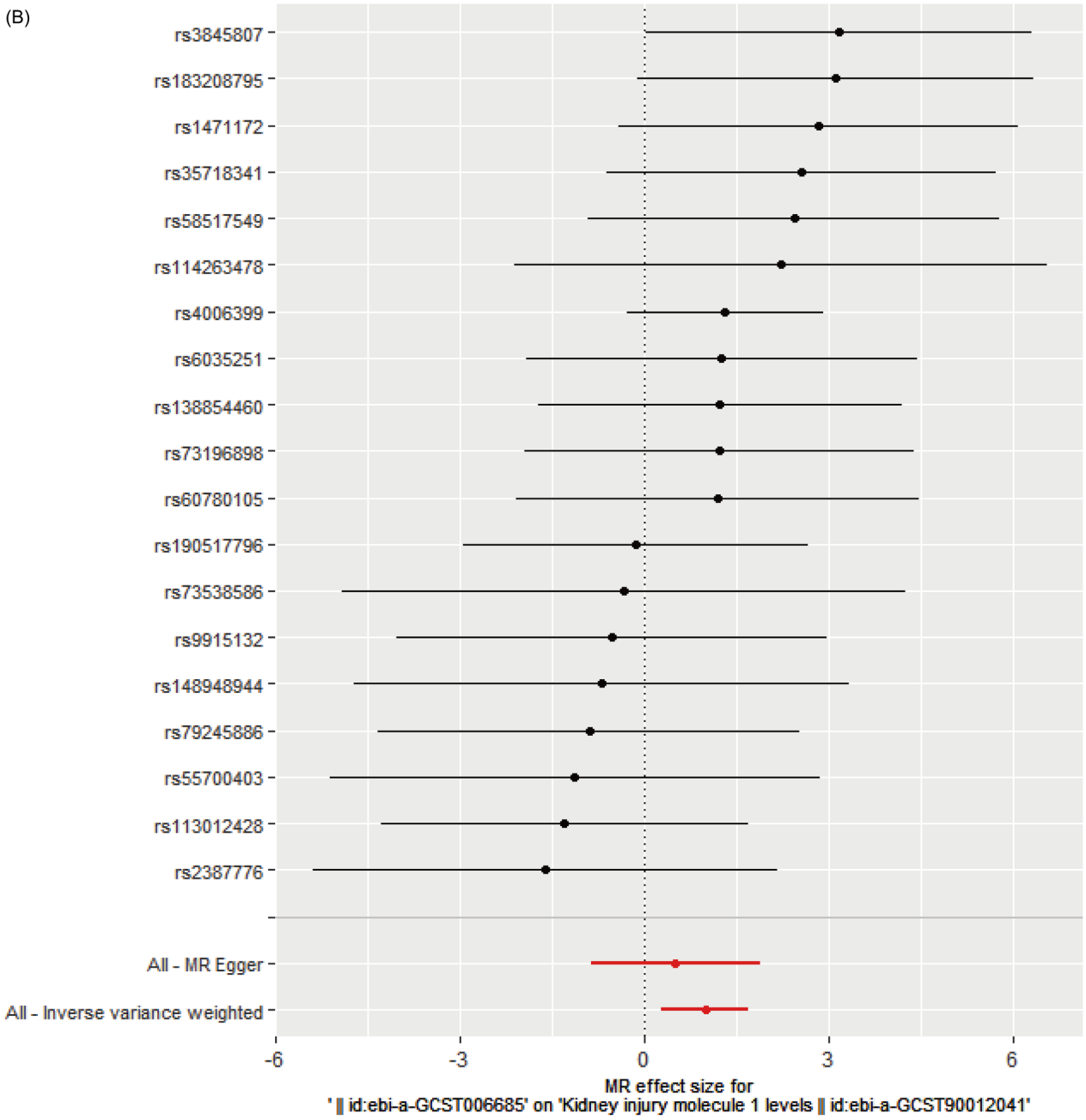

Figure 2. Continued.

Moreover, we extracted 26 KIM-1 levels-associated genetic variants ($p < 5 \times 10^{-6}$) and finally included 24 SNPs in the reverse MR analysis (shown in Table S6). The results showed no evidence that renal tubular damage influences long nighttime sleep duration (shown in Table S7) with a statistical power of 2.9%, and the forest plot visually displayed no significant genetic correlation between KIM-1 levels and long nighttime sleep duration (shown in Figure S5). Besides, no obvious horizontal pleiotropy was detected in MR-Egger intercept test and MR-PRESSO global test (shown in Table S8). Although a heterogeneity was observed in Cochran's *Q* test, it had less impact on the results of random-effects IVW model that performed in our main analysis [33], thus, the conclusions we reached remained robust. Leave-one-out analysis showed insignificant meta effects for remaining SNPs (shown in Figure S6), and the funnel plot indicated a symmetrical distribution (shown in Figure S7), supporting our conclusions.

4. Discussion

In this study, we combined a real-world study with two-sample MR analysis to explore the relationship between nighttime sleep duration and renal tubular damage. We conducted a cross-sectional study with 2,683 individuals from rural China, investigating this association for the first time

and confirming the causal effect through MR analysis. Our findings indicated that long nighttime sleep duration was a risk factor for renal tubular damage, especially in the elderly and female populations.

The relationship between nighttime sleep duration and renal tubular damage was not well-studied, though its connection to glomerular damage (eGFR and proteinuria) had been widely explored [12–15]. Research suggested extreme sleep durations may harm renal function, but findings were inconsistent. For example, a study of 82,001 Japanese participants found long sleep duration may decrease eGFR compared to optimal sleep [14], supported by other evidence [19,34]. However, Yamamoto et al. reported that short sleep increased proteinuria incidence by 28% in Japanese adults [35]. Other studies found short sleep associated with reduced eGFR, but not long sleep [15,36]. Besides, prior MR studies have established a causal association between sleep duration and renal damage. Evidence indicates that both short sleep and insomnia increase the risk of kidney injury [18,20,37], while excessively long sleep may also compromise renal function [19]. Our study found a link between long nighttime sleep and renal tubular damage but did not find a connection between insufficient sleep and renal tubular damage. Inconsistencies likely stem from different reference groups, definitions of extreme sleep, kidney injury detection indicators, ethnicity, sample sizes, and lack of very short sleep durations in our study. Overall, the relationship between nighttime sleep duration and renal tubular damage remains unclear. More research is needed to confirm our findings.

In the present study, we observed age and sex differences in renal tubular damage caused by long nighttime sleep duration. Previous reviews indicated that the elderly (≥60 years) and Asians [38] were more vulnerable to the adverse effects of long sleep duration, which was consistent with our results. Rural elderly tend to sleep longer due to less physical and social activity, and their higher prevalence of metabolic diseases may also contribute to this association. Additionally, our study confirmed a stronger link between long sleep and renal damage in women, consistent with global data showing a higher prevalence of CKD in women (11.8%) compared to men (10.4%) [39]. Studies by Hirano et al. and Choi et al. also found that long sleep was specifically associated with poor renal outcomes in women [14,34]. However, subgroups with small sample sizes in our study may have reduced precision, limited generalizability, and increased the risk of type II errors due to inadequate capture of population variability and potential effect misestimation. Therefore, these subgroup findings should be interpreted with caution, and future studies with larger sample sizes are needed to validate and strengthen our findings.

Currently, the relationship between long nighttime sleep duration and renal tubular damage can be explained through both direct and indirect pathways. Some of this association could be mediated by metabolic diseases like hyperlipidemia, diabetes, and hypertension, which are also linked to long nighttime sleep duration. These conditions cause chronic renal inflammation and oxidative stress, leading to epithelial cell apoptosis and interstitial fibrosis [7,40]. Additionally, renal physiological processes, such as sodium excretion, the renin–angiotensin system, renal blood flow, and genetic transcription, follow a circadian rhythm. Long nighttime sleep can disrupt these processes, causing systemic inflammation and kidney damage [13]. The heightened susceptibility of women to renal tubular damage associated with prolonged sleep duration may be partially attributed to the modulatory effect of sleep on sex hormone secretion, as estrogen exhibits antioxidant and anti-inflammatory properties in females [41,42]. Moreover, extended nighttime sleep can contribute to urine retention, thereby elevating the risk of retrograde urinary tract infections, particularly in women with anatomical features that predispose them to a higher incidence of urinary tract infections [43,44]. The potential mechanisms by which prolonged nighttime sleep leads to renal tubular damage in the elderly may be associated with the decline of the immune system [45], exacerbated blood pressure fluctuations [46], and impaired self-repair capacity of aging kidneys in response to the adverse effects of sleep disturbances [47]. Nonetheless, further investigations are warranted to elucidate the impact of long nighttime sleep on kidney health, particularly among women and older adults.

This was the first study of nighttime sleep duration and renal tubular damage in a rural Chinese population. By combining a real-world study with two-sample MR, we identified long nighttime sleep duration as a potential risk factor for renal tubular damage, which could inform public health strategies for CKD. However, several limitations should be noted. First, sleep data relied on retrospective self-reporting rather than polysomnography, possibly introducing recall bias. Nevertheless, given the widespread use of self-reported data in large-scale studies and the consistency between subjective and objective measurements demonstrated in previous research [48], the current data are relatively reliable. Second, data limitations prevented adjustment for all potential confounders. Residual factors, such as sleep quality, toxin/drug exposure, and comorbidities (e.g., cancer, primary glomerular disease, and obstructive sleep apnea), may also influence the relationship [49,50]. Future access to comprehensive data will enable more robust analyses. Third, a single spot urine sample may not accurately reflect 24-h renal excretion, and 24-h urine collection would provide a more reliable assessment. Fourth, the MR analysis was based on a European population, potentially biased by differences in ethnicity and lifestyle, underscoring the need for data from diverse populations to strengthen external validity. Nevertheless, GWAS data on these exposures and outcomes are currently unavailable for Asian populations. Fifth, the small sample size in our subgroups may impact the reliability of the results, and we failed to clarify the biological or environmental factors underlying age and sex differences, leaving gaps in understanding. Finally, the cross-sectional design of our observational study precluded causal inference, and the prospective cohort studies are needed for validation.

5. Conclusions

In summary, we were the first to combine the observational study with two-sample MR to explore the underlying associations between long nighttime sleep duration and renal tubular damage. We found that long nighttime sleep duration posed a risk for renal tubular damage, especially among older individuals and women. These findings offer important implications for early CKD prevention in public health. Nevertheless, further prospective and mechanistic studies are necessary to validate and expand these findings.

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Author contributions

JJQ: conceptualization, writing – original draft, visualization, methodology, data curation, writing – review and editing. LC and ZWG: methodology and data curation. WLC, SL, and HBC: writing – original draft. ZJH and BY: data curation, writing – review and editing, supervision, and funding acquisition. All authors read and approved the final manuscript.

Ethics statement

The observational study was approved by the Medical Ethics Committee of the Xiangya Hospital, Central South University and all participants have provided written informed consent (approval number 201612637). Ethical approval and consent were not required for the MR study as this study was based on publicly available data.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The research data used to support the finding of this study has been submitted to the National Population Health Data Center of China (https://www.ncmi.cn/phda/browse.html) and can be obtained from the corresponding authors.

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