

Insomnia and Poor Sleep in CKD: A Systematic Review and Meta-analysis



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Rationale & Objective: Poor sleep quality and insomnia are pervasive among patients with advanced chronic kidney disease (CKD); however, these health issues have not been systematically evaluated.

Study Design: Systematic review and meta-analysis.

Setting & Study Populations: Adult patients with CKD not receiving kidney replacement therapy (KRT), as well as adults receiving KRT, including hemodialysis, peritoneal dialysis, and kidney transplantation.

Selection Criteria for Studies: A systematic literature search using PubMed, Embase, and PsycNET, was conducted for articles published between January 1, 1990, and September 28, 2018.

Data Extraction: Data on the prevalences of poor sleep quality and insomnia in patients with CKD, including those receiving and not receiving KRT, were extracted.

Analytical Approach: Pooled prevalences were estimated using a random-effects meta-analysis and were stratified according to age, CKD stage, World Health Organization region, risk of bias, Pittsburgh Sleep Quality Index score, and the

different criteria for insomnia that were used at diagnosis.

Results: Of 3,708 articles, 93 were selected, and significant methodological heterogeneity was present. The pooled prevalences of poor sleep quality for CKD without KRT, hemodialysis, peritoneal dialysis, and kidney transplantation were 59% (95% CI, 44%-73%), 68% (95% CI, 64%-73%), 67% (95% CI, 44%-86%), and 46% (95% CI, 34%-59%), respectively. The corresponding prevalences of insomnia were 48% (95% CI, 30%-67%), 46% (95% CI, 39%-54%), 61% (95% CI, 41%-79%), and 26% (95% CI, 9%-49%), respectively. Insomnia was significantly more prevalent among patients aged 51-60 years and those aged >60 years than among those aged <50 years. The prevalence of insomnia in the European region was the lowest of all World Health Organization regions.

Limitations: High interstudy heterogeneity.

Conclusions: Approximately half of the patients with advanced CKD had poor sleep quality or insomnia, and the prevalence was even higher among those who received KRT. Kidney transplantation may reduce the burden of poor sleep quality and insomnia.

Complete author and article information provided before references.

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Sleeplessness is an emerging global epidemic and has been closely associated with noncommunicable diseases such as type 2 diabetes, chronic kidney disease (CKD), cognitive dysfunction, and neuropsychiatric disorders.¹⁻³ When indirect costs such as reduced job productivity and increased use of health care services are accounted for, the annual costs related to sleeplessness and insomnia range from US\$30-\$107 billion.^{4,5}

Patients with CKD are vulnerable to sleeping disorders, particularly in the elderly, leading to chronic fatigue and reduced quality of life.⁶⁻⁸ An estimated 50%-75% of patients with kidney failure and approximately 8%-36% of patients with earlier stages of CKD have reported insomnia symptoms.⁹⁻¹¹ Poor sleep and insomnia may accelerate CKD progression and increase mortality in patients on maintenance dialysis.¹²⁻¹⁵ Additionally, patients with a more advanced stage of CKD, particularly kidney failure requiring kidney replacement therapy (KRT), encounter relatively more sleeping problems because of uremia-related metabolic abnormalities, such as refractory pruritus or restless leg syndrome.^{9,15-19} There have been several patient-centered studies emphasizing the need for approaches to address sleep

disorders in patients requiring KRT.²⁰⁻²² Medical therapies for sleep dysfunction, such as hypnotics or antipsychotics, may further magnify complications of CKD by increasing the risk of accidental events, particularly among older adults.^{23,24}

Although many studies have reported the prevalences of insomnia and poor sleep among patients with CKD, relatively less attention has been paid to quantitative syntheses related to studies on insomnia or poor sleep prevalences on a global scale.^{6,9} We hypothesized that the prevalences of poor sleep quality and insomnia would be higher in patients with CKD than in those without CKD. However, at the time of writing, to our knowledge, no systematic review in the literature had evaluated poor sleep quality and insomnia prevalences across all stages and severity levels of CKD, including early CKD, CKD not treated by KRT, hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation. To fill this knowledge gap, this systematic review and meta-analysis synthesized existing findings on the prevalence estimates for poor sleep quality and insomnia across the different CKD stages. We explored variations in prevalence estimates by investigating the effects that different CKD stages, diagnostic criteria,

PLAIN-LANGUAGE SUMMARY

Sleep disorders, such as insomnia and poor sleep quality, are common among patients with chronic kidney disease (CKD) and are often associated with health problems. By systematically reviewing the literature, the present study provides quantitative evidence showing that half of the patients with CKD have trouble falling asleep or staying asleep. Patients with CKD aged >50 years are particularly vulnerable to insomnia. The current study also found that patients with kidney failure who had undergone kidney transplantation were associated with better sleep than those with hemodialysis or peritoneal dialysis. These findings call for attention to sleep problems in patients with CKD and identify a critical, unmet need for designing effective interventions to improve sleep in this vulnerable population.

demographics, and methodological characteristics have on such estimates.

METHODS**Search Strategy and Selection Criteria**

The systematic search and review processes were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement and the Meta-Analysis of Observational Studies in Epidemiology criteria.^{25,26} We searched the PubMed or MEDLINE, Embase, and APA PsycNET databases for the period from January 1, 1990, to September 28, 2018, for epidemiologic studies that investigated the prevalences of sleep disorders in patients (1) with CKD, (2) on HD, (4) on PD, and (5) who received kidney transplantation, using Medical Subject Headings terms and other specific terms related to our key research concepts. [Table S1](#) details the search strategies.

Studies were included if they (1) were observational studies or randomized controlled trials; (2) investigated patients with CKD, with or without a comparison group; and (3) evaluated or provided relevant, quantitative data on the prevalence of poor sleep quality or insomnia. There was no language restriction for the included studies. Google Translate was used for translating studies using languages other than English.

After removing duplicates, we excluded studies that lacked original data, including reviews, editorials, letters, case reports, or commentaries. Studies involving study populations without CKD (except for the control group), those with fewer than 10 patients, and those without reported endpoints of interest were also excluded. Conference abstracts were also excluded. We assessed the remaining articles by reading the full text of each article and excluded studies without measured point prevalences and appropriate definitions of insomnia (see under

definitions). We identified the duplicate populations and excluded them. We excluded randomized controlled trials that did not show baseline sleep data on the selection of the participants because the data may have been altered after the intervention, which could, in turn, bias findings on the prevalences of poor sleep quality and insomnia. We also excluded studies in which insomnia was diagnosed before the patients had CKD. Studies that included children and used poor sleep assessments other than the Pittsburgh Sleep Quality Index (PSQI) were also excluded. The remaining studies were assessed for risk of bias. Studies with a total score > 8 were categorized as having a very high risk of bias and were excluded. We also excluded poor sleep-quality studies with population sizes < 100. This study followed the protocol registered in PROSPERO (www.crd.york.ac.uk/PROSPERO; protocol number, CRD42020133673).

Definition of Poor Sleep Quality and Insomnia

Poor sleep quality was defined by a PSQI score ≥ 5 .²⁷ Furthermore, owing to the significant variation in studies' insomnia definitions, studies were included only if the following conditions were met: (1) patients were determined to have insomnia by presenting at least 1 of 4 insomnia complaints listed in the primary criteria and at least 1 of 4 insomnia complaints listed in the secondary criteria in [Table S2](#) (modified from the insomnia inclusion criteria provided by the American Academy of Sleep Medicine Working Group Report from 2004, as shown in [Table S3](#)); (2) patients were diagnosed as having insomnia disorder according to the criteria of either the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, or the International Classification of Sleep Disorders, version 2; (3) patients were assessed according to the Athens Insomnia Scale and Insomnia Severity Index, with cutoff scores of ≥ 6 and >13 , respectively; and (4) patients had diagnoses of insomnia in their medical records.²⁸⁻³²

Data Abstraction

Two authors (L-HT and C-CK) independently evaluated all references by titles and abstracts and retrieved the full texts of any article that seemed relevant. We contacted the authors whose full-text articles were not accessible. Information such as study characteristics and prevalence estimates of poor sleep quality and insomnia were systematically extracted ([Tables S4](#) and [S5](#)). If >1 study reported the same population, the study with the largest sample size and most informative data was selected. Reviewers resolved disagreements on study inclusion through consensus. In studies that did not directly report the prevalence estimates, we calculated the prevalence estimates from the proportion of patients with poor sleep quality or insomnia. A study quality assessment form, which was modified on the basis of a published risk-of-bias tool for prevalence studies, was used to evaluate the quality of the included studies.³³ According to the specific justification of individual quality items, each of the 5

quality items had a range of scores between 0–2 (the smaller the better). All scores in each item were summated to calculate an overall score, categorized into low, moderate, and high risks of bias (Table S6; Fig S1). We excluded all studies with a very high risk of bias (total score > 8) from the analysis.

Data Analysis

All analyses were performed using the Metafor package for R (R Foundation for Statistical Computing). To manage the confidence intervals (CIs) outside the 0–1 range and to address variance instability, we applied the Freeman-Tukey (double arcsine) transformation (using the `escalc` function with the measure argument “PFT”) to calculate the pooled prevalence estimates from the raw data or the prevalence estimates provided in the indicated studies. The double arcsine-transformed prevalence is equal to $\frac{1}{2}\sin^{-1}\left(\sqrt{\frac{n}{N+1}}\right) + \sin^{-1}\left(\sqrt{\frac{n+1}{N+1}}\right)$, where N and n represent the population size and the number of people with the indicated condition (eg, insomnia), respectively; the prevalence estimates in the results have been back-transformed. The meta-analysis was conducted using a random-effects model (by using the “`rma`” function with the method argument “restricted maximum-likelihood estimator”) when the prevalence estimates and variances of poor sleep quality and insomnia (with 95% CIs) were pooled.³⁴ Results obtained using the fixed-effects models (using the “`rma`” function with the method argument “fixed-effects model”) have also been provided (Table S7).

Subgroup analyses were performed on the prevalence estimates of poor sleep quality and insomnia to explore potential sources of heterogeneity. We analyzed the following covariates: (1) mean age; (2) CKD stage; (3) World Health Organization (WHO) region; (4) risk of bias; and (5) PSQI cutoff score or the definition used to define insomnia. We further constructed univariate meta-regression plots to represent the correlations between pooled estimates and mean age, and we plotted each study with circles using inverse-variance weights to represent the sample size.

The heterogeneity of prevalence estimates was assessed using the I^2 statistic and the Cochran Q statistic:

$$I^2 = \left(\frac{Q-df}{Q}\right) \times 100\%$$

where df is the degree of freedom.

$$Q = \sum_{i=1}^k w_i (P_i - \bar{P})^2, \bar{P} = \frac{\sum_{i=1}^k w_i P_i}{\sum_{i=1}^k w_i}$$

where w_i and P_i are the weight and prevalence of each study, respectively.

The proportion of heterogeneity explained by a priori covariates was calculated as $[(\tau_0^2 - \tau^2)/\tau_0^2]$, where τ_0^2 represents the between-studies component of variance in the

null model and τ^2 represents the between-studies component of variance in the model, including covariates.³⁵ Publication bias was determined through a visual inspection of the funnel plot (using the “`funnel`” function) with a set of significance thresholds, including $P > 0.10$, $0.05 < P < 0.10$, $0.01 < P < 0.05$, and $P < 0.01$, for double arcsine-transformed prevalences and by testing for asymmetry using Egger’s tests (by applying the “`regtest`” function). All analyses were completed using R version 3.6.0 (R Foundation for Statistical Computing). The data collection form and analytic codes are available on request.

RESULTS

Overview of Enrolled Studies

We identified 3,708 studies in the secondary databases, and 411 studies were eligible for full-text screening (Fig 1). We identified 93 articles that met the inclusion criteria and provided prevalence data for either insomnia or poor sleep quality from the eligible articles. Of the 45,796 participants from the 93 included studies, 32,949 patients were diagnosed with CKD and the rest were controls who did not have CKD (Fig 1). Four studies included data on both poor sleep quality and insomnia.^{36–39}

Studies on Poor Sleep Quality

In 62 studies, the prevalence of poor sleep quality was estimated, and most of the studies focused primarily on patients on HD (41 studies; $n = 8,747$ patients) followed by patients with CKD without KRT (7 studies; $n = 2,038$), kidney transplantation (6 studies; $n = 1,756$), and PD (4 studies; $n = 8,638$; Table S4). The mean age of all enrolled patients with poor sleep quality was 55.6 years. Almost all studies in the group with poor sleep quality were cross-sectional and used the consecutive sampling method. In addition, all studies in the group with poor sleep quality collected data through a patient-administered questionnaire (Table S4). Fig 2A depicts the wide geographical distribution of study populations across the 5 continents, according to WHO regions. For instance, 15 studies were conducted in the eastern Mediterranean region, whereas no study was conducted in the African region (Fig 2A).

Studies on Insomnia

Thirty-five studies that evaluated the prevalence of insomnia were conducted, primarily with patients who required HD (25 studies; $n = 13,456$), followed by patients with CKD not receiving KRT (4 studies; $n = 2,006$), patients who required kidney transplantation (4 studies; $n = 1,178$), and patients who required PD (4 studies; $n = 372$). The mean age of all patients in the insomnia group was 56.7 years. Nearly all studies (94.3%) had a cross-sectional design. Twenty-seven (77.1%) studies used convenience sampling, and 8 (22.9%) studies used random sampling (Table S5). Most studies collected data through a patient-administered questionnaire (25 studies)

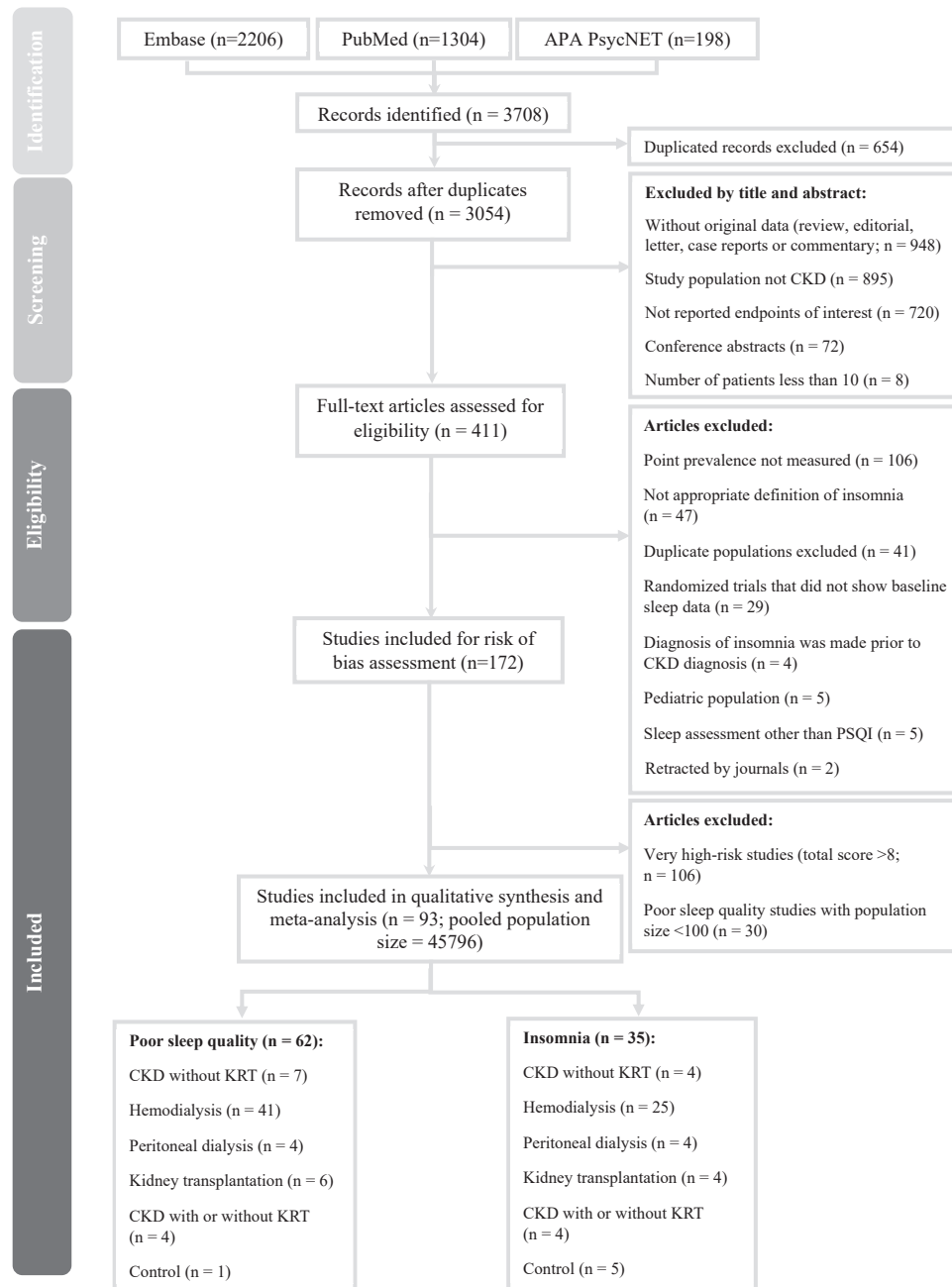


Figure 1. Flowchart of the selection process of the included studies. Abbreviations: APA, American Psychiatric Association; CKD, chronic kidney disease; KRT, kidney replacement therapy; PSQI, Pittsburgh Sleep Quality Index.

or interview-based assessment (9 studies; Table S5). A wide diversity in the study populations' geographical locations was observed, and 42.9% of studies were conducted in the European region (Fig 2B).

Risk Assessment of Bias

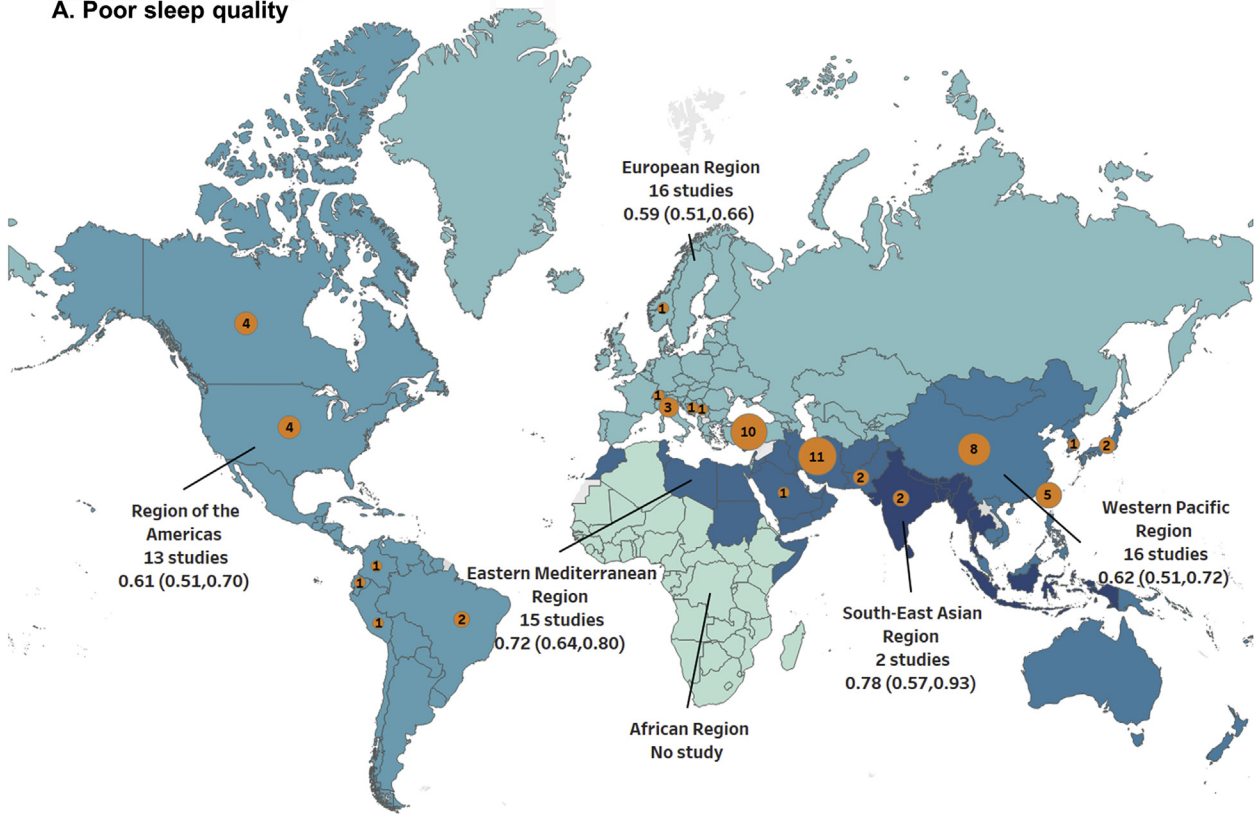
Summaries of the risks of bias of the selected studies for insomnia and poor sleep quality are presented in Fig S1. Of the 62 included studies on poor sleep quality, 49 (79.0%) studies were judged as having a moderate risk and 13 (20.1%) studies were deemed to have a high risk. Among the 35 included studies on insomnia, only 7 (20.0%)

studies were considered to have a low risk, whereas 14 (40.0%) studies had a moderate risk and 14 (40.0%) studies had a high risk (Fig S1).

Meta-analysis

The overall pooled prevalence of poor sleep quality among patients with CKD was 64% (95% CI, 59%-68%), with a high degree of heterogeneity ($I^2=97\%$). The overall pooled prevalence of insomnia was 45% (95% CI, 38%-51%), and the degree of heterogeneity was also high ($I^2=99\%$). Prevalence estimates of poor sleep quality ranged from 21%-

A. Poor sleep quality



B. Insomnia

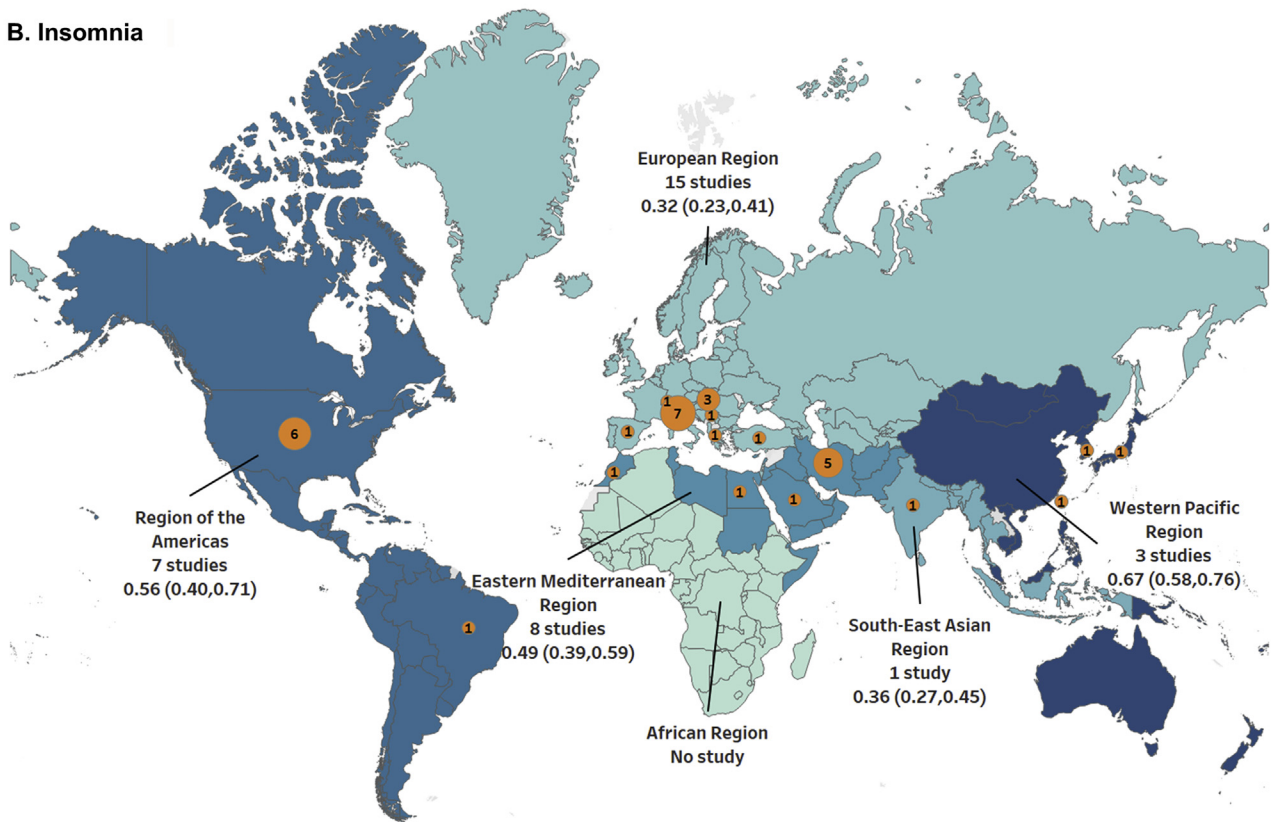


Figure 2. Geographic distribution showing the pooled prevalences of (A) poor sleep quality and (B) insomnia across WHO regions. The numbers in the orange circles indicate the number of studies from respective countries. The size of the orange circles is proportional to the number of studies. Abbreviation: WHO, World Health Organization.

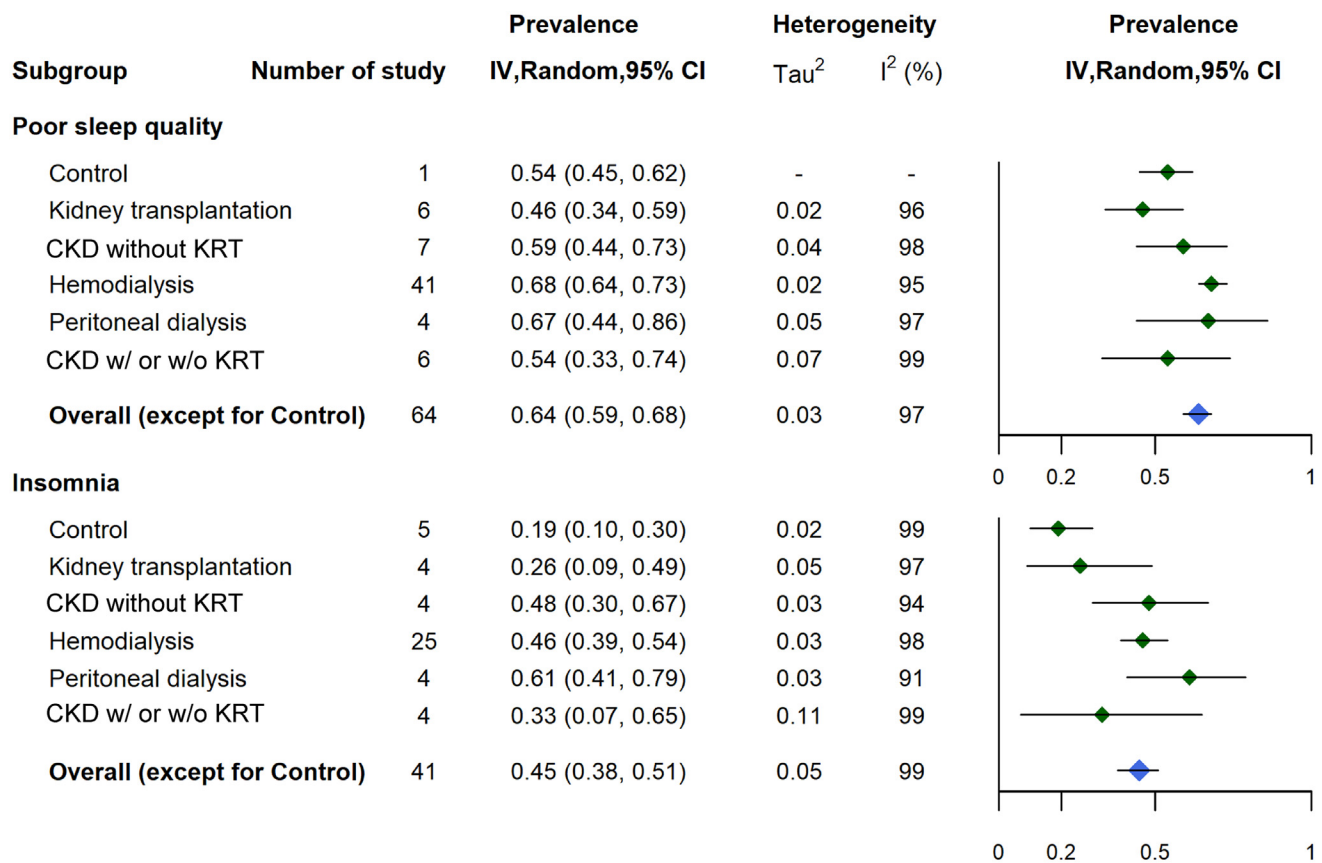


Figure 3. Summary pooled prevalence of poor sleep quality and insomnia according to the whole spectrum of CKD. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; IV, inverse variance; KRT, kidney replacement therapy.

98%, whereas those of insomnia ranged from 6%-85%. The pooled prevalences of poor sleep quality were 54% (95% CI, 45%-62%) in the control group, 46% (95% CI, 34%-59%) in the kidney transplantation–treated group, 59% (95% CI, 44%-73%) in the CKD without KRT group, 68% (95% CI, 64%-73%) in the HD group, and 67% (95% CI, 44%-86%) in the PD group (Fig 3; Fig S2). The corresponding pooled prevalences of insomnia were 19% (95% CI, 10%-30%), 26% (95% CI 9%-49%), 48% (95% CI, 30%-67%), 46% (95% CI 39%-54%), and 61% (95% CI 41%-79%) in the control, kidney transplantation, CKD without KRT, HD, and PD groups, respectively (Fig 3).

In the subgroup analysis and univariate random-effects meta-regression for poor sleep quality and insomnia, the control groups had the lowest prevalences than other groups. We also observed an increasing prevalence trend across the CKD stage spectrum (Tables 1 and 2; Fig 3). Furthermore, the group with kidney transplantation had a significantly lower prevalence of poor sleep quality than the group with PD ($P < 0.01$); for insomnia, a significantly lower prevalence was observed in the group with kidney transplantation than the group with HD ($P = 0.02$; Tables 1 and 2). The age category was not associated with

the prevalence of poor sleep quality; however, patients aged 51-60 years and those aged >60 years had significantly higher prevalences of insomnia than those belonging to other age groups (Tables 1 and 2; Fig 4). The prevalence of poor sleep quality declined with age among patients receiving HD; nevertheless, the trends of insomnia prevalence with age were similar in patients with CKD and HD (Fig S3). The prevalences of poor sleep quality in patients with automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD) were 62% and 67%, respectively (Fig S4). For insomnia, the prevalences were 83% and 81% for patients with APD and CAPD, respectively (Fig S4). There was no significant difference between these 2 subgroups. Risks of bias, definitions of insomnia, and PSQI cutoff scores did not alter the prevalence estimates of insomnia or poor sleep quality (Tables 1 and 2; Fig 4). In applying a univariate random-effects meta-regression for insomnia, we excluded the study by Elder et al¹⁵ from a WHO region analysis because it involved multiple WHO regions. The prevalence estimate of insomnia in the European region was significantly lower than that in other WHO regions, except in South-East Asia. The eastern Mediterranean region had a significantly higher pooled prevalence for poor sleep quality than the European region (Table 2). A visual inspection of the

Table 1. Univariate Random-effects Meta-regression for the Prevalence of Poor Sleep Quality According to Age Categories, CKD Stage, WHO Regions, Risk of Bias, and Diagnostic Criteria of Poor Sleep Quality

Variables	No. of Studies	Beta Estimates (95% CI)	Prevalence (95% CI)	P Value	I ² , %
Age, y					
Per 1-y increase	62	0.001 (−0.01 to 0.01)	0.63 (0.58 to 0.67)	0.72	96.99
<50	12	Ref	0.58 (0.48 to 0.68)	Ref	96.89
51-60	39	0.08 (−0.04 to 0.20)	0.66 (0.60 to 0.71)	0.20	
>60	11	−0.01 (−0.16 to 0.14)	0.57 (0.46 to 0.68)	0.92	
CKD stage					
Control	1	0.07 (−0.31 to 0.45)	0.54 (0.20 to 0.85)	0.71	96.48
Kidney transplantation	6	Ref	0.46 (0.32 to 0.61)	Ref	
CKD without KRT	7	0.12 (−0.07 to 0.32)	0.59 (0.45 to 0.71)	0.22	
Hemodialysis	41	0.22 (0.07 to 0.38)	0.68 (0.63 to 0.73)	0.005	
Peritoneal dialysis	4	0.21 (−0.02 to 0.43)	0.67 (0.49 to 0.82)	0.08	
CKD with or without KRT	6	0.07 (−0.13 to 0.28)	0.54 (0.40 to 0.68)	0.47	
WHO regions					
European	16	Ref	0.59 (0.50 to 0.68)	Ref	96.93
Americas	13	0.02 (−0.12 to 0.16)	0.61 (0.51 to 0.71)	0.77	
Western Pacific	16	0.03 (−0.10 to 0.16)	0.62 (0.53 to 0.70)	0.67	
Eastern Mediterranean	15	0.14 (0.01 to 0.27)	0.72 (0.63 to 0.80)	0.04	
South-East Asia Region	2	0.20 (−0.07 to 0.48)	0.78 (0.54 to 0.95)	0.14	
Risk of bias					
Low	-	-	-	-	96.97
Moderate	49	Ref	0.66 (0.61 to 0.71)	Ref	
High	13	−0.10 (−0.21 to 0.01)	0.56 (0.46 to 0.66)	0.09	
PSQI cutoff scores					
≥5	59	Ref	0.72 (0.55 to 0.87)	Ref	96.95
>6	6	−0.08 (−0.24 to 0.08)	0.64 (0.60 to 0.69)	0.31	

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy; PSQI, Pittsburgh Sleep Quality Index; Ref, reference; WHO, World Health Organization.

funnel plot showed potential publication bias in the group with insomnia but no evidence of publication bias in the group with poor sleep quality (Fig S5).

DISCUSSION

The results of this systematic review suggest that poor sleep quality and insomnia result in considerable health care burdens, with prevalences of 64% and 45%, respectively, in patients with CKD, which are much higher than the prevalences in the control populations without CKD in this systematic review (54% and 18%, respectively) or estimates derived from general adult populations in the literature (10%-48% for poor sleep quality and 10%-15% for insomnia).⁴⁰⁻⁴³ Kidney transplantation significantly reduced the prevalence of insomnia among patients receiving HD or PD. Non-European patients with CKD and patients aged >50 years tended to have higher prevalences of insomnia. Nonetheless, the meta-analysis findings must be carefully interpreted due to high heterogeneity, which reflected significant variation among the included studies in the definitions of outcomes, study designs, and study populations.

Insomnia and poor sleep quality often co-occur with cardiovascular disease, psychiatric illnesses, and impaired social and physical functioning, all of which frequently

complicate the course of CKD.⁴⁴⁻⁴⁷ Given the mutually dependent and reinforcing interactions of kidney-heart-brain crosstalk, the prevalences of insomnia and poor sleep quality have unsurprisingly increased substantially worldwide among patients with CKD.⁴⁸⁻⁵⁰ The gradient increase in the magnitude of prevalence of sleep disturbances across stages and severity levels of CKD and the ability to reduce the prevalence of these problems among patients with kidney failure treated with kidney transplantation further supports the hypothesis that CKD is an independent risk factor for insomnia and poor sleep quality.^{51,52} The progression of CKD likely creates a vicious cycle of sleep disorders, CKD, and CKD-related complications. However, due to insufficient robust evidence on the relationships between insomnia and poor sleep quality and CKD, the latest KDIGO guidelines for CKD care did not emphasize the problem or recommend specific treatments for insomnia and poor sleep quality.⁵³

Only a few clinical trials have evaluated the effects of cognitive behavioral therapy for insomnia on patients undergoing PD or HD.⁵⁴⁻⁵⁶ However, the sample sizes of these trials were small, and they did not evaluate health outcomes, such as mortality or cardiovascular events. Large, prospective studies are warranted to assess whether cognitive behavioral therapy for insomnia can modify the course of CKD and to further extend the breadth of

Table 2. Univariate Random-effects Meta-regression for the Prevalence of Insomnia According to Age Categories, CKD Stage, WHO Regions, Risk of Bias, and Diagnostic Criteria of Insomnia

Variables	No. of Studies	Beta Estimates (95% CI)	Prevalence (95% CI)	P Value	I ² , %
Age,Y					
Per 1-y increase	45	0.01 (0.00 to 0.02)	0.42 (0.36 to 0.49)	0.21	99.11
<50	8	Ref	0.24 (0.12 to 0.38)	Ref	98.64
51-60	24	0.26 (0.09 to 0.43)	0.49 (0.40 to 0.57)	0.003	
>60	13	0.19 (0.00 to 0.37)	0.41 (0.30 to 0.53)	0.05	
CKD stage					
Control	5	-0.10 (-0.36 to 0.17)	0.18 (0.07 to 0.34)	0.49	98.71
Kidney transplantation	4	Ref	0.26 (0.11 to 0.46)	Ref	
CKD without KRT	4	0.23 (-0.06 to 0.52)	0.49 (0.29 to 0.69)	0.12	
Hemodialysis	25	0.21 (-0.01 to 0.43)	0.46 (0.39 to 0.55)	0.06	
Peritoneal dialysis	4	0.35 (0.06 to 0.64)	0.61 (0.40 to 0.80)	0.02	
CKD with or without KRT	4	0.07 (-0.21 to 0.35)	0.33 (0.16 to 0.52)	0.63	
WHO regions^a					
European	15	Ref	0.32 (0.23 to 0.41)	Ref	97.67
Americas	7	0.24 (0.08 to 0.40)	0.56 (0.42 to 0.69)	0.003	
Western Pacific	3	0.36 (0.13 to 0.59)	0.67 (0.47 to 0.85)	0.002	
Eastern Mediterranean	8	0.17 (0.02 to 0.33)	0.49 (0.36 to 0.62)	0.03	
South-East Asia Region	1	0.04 (-0.33 to 0.41)	0.36 (0.07 to 0.71)	0.83	
Risk of bias					
Low	7	Ref	0.50 (0.35 to 0.65)	Ref	98.47
Moderate	13	-0.15 (-0.34 to 0.03)	0.35 (0.25 to 0.46)	0.10	
High	15	-0.01 (-0.19 to 0.17)	0.49 (0.39 to 0.59)	0.93	
Diagnostic criteria of insomnia					
Complaint-based ^b	16	Ref	0.49 (0.38 to 0.59)	Ref	98.66
Diagnostic tool-based ^c	19	-0.09 (-0.23 to 0.05)	0.40 (0.31 to 0.49)	0.21	

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy; Ref, reference; WHO, World Health Organization.

^aIn our analysis of WHO regions, we excluded the study by Elder et al,¹⁵ which comprised data from 3 WHO regions.

^bPrimary criteria (difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, and nonrestorative sleep), together with at least 1 of the secondary criteria listed in Table S2.

^cIncluded the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; International Classification of Sleep Disorders, version 2; Athens Insomnia Scale; and Insomnia Severity Index.

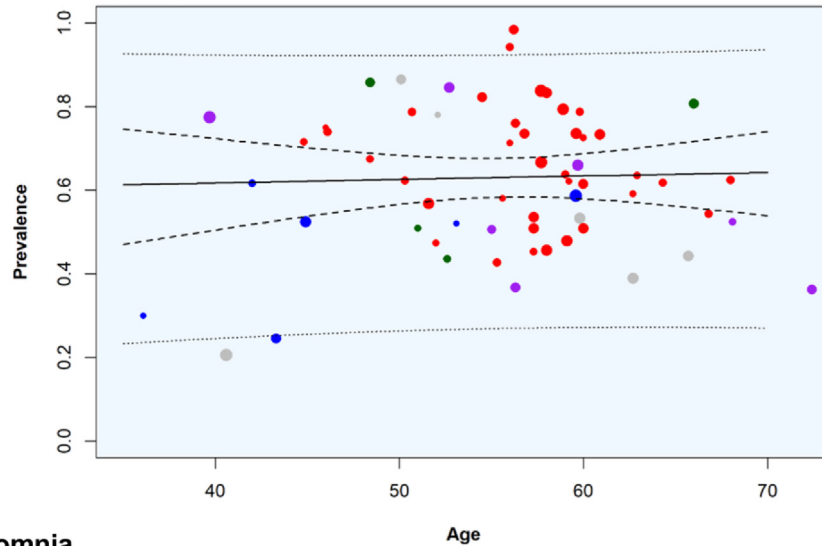
evidence to dialysis quality and improvement among patients with kidney failure. Similarly, insufficient evidence was found to support the effectiveness of pharmacological therapies for insomnia in patients with CKD in terms of drug selection, dosing, and duration.⁶ Some studies have reported that melatonin use at bedtime improved sleep problems in HD patients; however, the long-term efficacy of melatonin was not observed.⁵⁷⁻⁵⁹ It would be an urgent priority to pursue an effective, pragmatic intervention to alleviate the potential long-term, adverse impacts of insomnia on CKD, such as cardiovascular events and mortality, in this vulnerable population.⁶⁰

Insomnia and poor sleep quality have been linked to increased risks of mortality among patients with CKD, particularly when hypnotic therapy is used for a prolonged period.^{15,61-64} However, the causality remains debated, because sleep disturbances may only be a downstream marker of major underlying, confounding factors, such as chronic inflammation, a heavy burden of comorbid conditions, or inadequate dialysis.⁶⁵ For example, HD timing may affect sleep quality; several studies have reported that evening dialysis is associated with better sleep quality than is daytime dialysis.^{66,67}

The considerable heterogeneity in the present meta-analysis may be because of the poor methodological quality of most studies, which poses a serious threat to validity, especially when comparisons of the burden of sleep disturbances are being made with regard to dialysis modalities, geographical regions, and definitions of outcome diagnoses. For example, a high pooled prevalence of sleep disturbance was calculated among patients who received HD or PD; however, few studies have evaluated (with high interstudy heterogeneity) the prevalences and incidences of insomnia and poor sleep quality in patients who receive PD, which renders valid comparisons between HD and PD impossible.⁶⁸⁻⁷¹

The pathogenic mechanism underlying sleep disturbances in CKD remains unclear. Although chronic inflammation because of uremia has been implicated in the development of sleep disturbances, the associations between inflammatory markers, such as C-reactive protein, tumor necrosis factor α , interleukin 6, and interleukin 18, and insomnia and poor sleep quality are not universally present among patients with CKD who require dialysis.⁷²⁻⁷⁵ Other possible mechanisms, such as elevated blood orexin and the depletion of melatonin,

A. Poor sleep quality



B. Insomnia

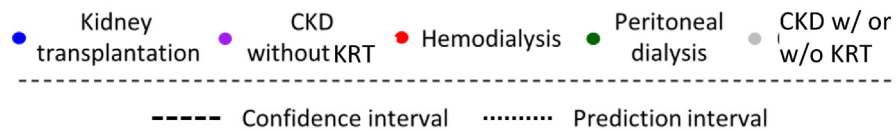
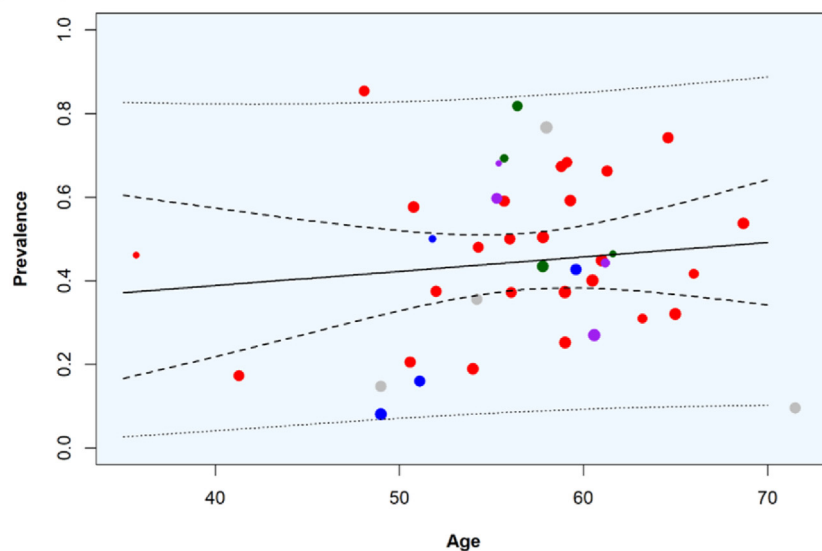


Figure 4. Random-effects meta-regression plots showing the relationships between age and the prevalences of (A) poor sleep quality and (B) insomnia, according to different CKD spectrums and types of kidney replacement therapy. Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy.

may induce sleep disturbances by altering patients' circadian rhythms.^{57,76} Common symptoms of CKD, and especially kidney failure treated by KRT, such as refractory pruritus, restless leg syndrome, depression, and anxiety, may also contribute to the development of insomnia and poor sleep quality.^{6,16-18,77}

This study has several limitations. First, the pooled prevalence estimates must be interpreted with caution because of high interstudy heterogeneity. Moreover, the observed publication bias regarding insomnia studies

compromised the validity of the prevalence estimates. Second, of the selected patients with kidney failure treated by dialysis, 21,422 (approximately 95.5%) received HD, whereas only 1,010 (approximately 4.5%) received PD. Such an imbalance prevented the comparison of the pooled prevalences between HD and PD. Third, only a few studies provided individual participant data, which rendered thorough investigations of the sources of heterogeneity and biases using aggregated data impossible. Fourth, this study may have missed

some relevant work because we did not include unpublished literature, such as conference abstracts or research theses, and we did not update the literature search to the present time. However, publication bias was not evident in our study. Fifth, we did not include studies measuring poor sleep quality using a tool other than the PSQI, such as the Kidney Disease and Quality of Life, Choices for Healthy Outcomes in Caring for ESRD Health Experience Questionnaire, or Medical Outcomes Study Instruments. Nonetheless, as we discovered in the initial phase of our study, regardless of the diagnostic criteria adopted, the pooled prevalences were 50%, 61%, 63%, and 48% for patients with CKD without KRT, HD, PD, and kidney transplantation.

In summary, insomnia and poor sleep quality are pervasive in patients with CKD, and kidney transplantation treatment may solve those problems. The actual prognostic benefits resulting from the improvement of sleep hygiene in patients with CKD warrant further investigation. More research, such as intervention trials, is also required to assess the effectiveness and potentially harmful consequences of the current treatments for sleep disturbances associated with CKD.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Risk assessment of bias for included studies.

Figure S2: Forest plots of the prevalence of insomnia and poor sleep, by chronic kidney disease (CKD) stage.

Figure S3: Random-effects meta-regression plots showing relationships between age and prevalences of (A) poor sleep quality and (B) insomnia in patients with hemodialysis.

Figure S4: Forest plots of the prevalences of insomnia and poor sleep by different peritoneal dialysis types.

Figure S5: Funnel plot of studies evaluating the prevalences of (A) poor sleep quality and (B) insomnia in patients with chronic kidney disease (CKD).

Table S1: Detailed search strategies for PubMed or MEDLINE, Embase, and APA PsycNET from January 1990 to September 2018.

Table S2: Inclusion criteria of insomnia disorders assimilated from the American Academy of Sleep Medicine (AASM) inclusion criteria.

Table S3: Fourteen American Academy of Sleep Medicine (AASM) inclusion criteria of insomnia before assimilation.

Table S4: Studies evaluating the prevalence of poor sleep among patients with chronic kidney disease (CKD).

Table S5: Studies evaluating the prevalence of insomnia among patients with chronic kidney disease (CKD).

Table S6: Risk assessment of bias for included studies.

Table S7: Pooled prevalence of poor sleep quality and insomnia calculated by random and fixed effects.

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