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Association of sleep duration with chronic kidney disease and proteinuria in adults: a systematic review and dose–response meta-analysis

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Abstract

Background and objectives Previous studies have found that sleep duration may be associated with chronic kidney disease (CKD) and proteinuria in adults. However, the correlation remains controversial. In this study, we aimed to assess the effects of sleep duration on CKD and proteinuria.

Methods PubMed, EMBASE, and Cochrane Library were searched from their inception up to April 5, 2019 for observational study. The outcomes were CKD and/or proteinuria and the exposure was sleep duration assessed by self-reported questionnaire or interview. Studies were included if they provided risk estimates of effects of sleep duration on patients with CKD or proteinuria. The overall effects were measured by odds ratios (OR) and 95% confidence intervals (CI). Heterogeneity was quantified using Q statistics and the I^2 statistics. The potential causes of heterogeneity were investigated using sensitivity analysis.

Results Eleven observational studies with 521,242 individuals were included. The adjusted ORs of CKD in individuals who slept ≤ 6 h/night and ≥ 8 h/night were 1.13 (95% CI, 1.02–1.25; $I^2 = 29\%$) and 1.14 (95% CI, 1.07–1.22; $I^2 = 0\%$), respectively. Meanwhile, the adjusted ORs of proteinuria in those who slept ≤ 6 h/night and ≥ 8 h/night were 1.24 (95% CI, 1.06–1.44; $I^2 = 61\%$) and 1.15 (95% CI, 1.04–1.29; $I^2 = 0\%$), respectively. Furthermore, a U-shaped relationship was observed between sleep duration and CKD or proteinuria, with the lowest risk at 7 h/night of sleep.

Conclusions Both short and long sleep durations are significantly associated with CKD and proteinuria. Our findings suggest curvilinear dose–response associations of sleep duration with CKD and proteinuria.

Keywords Chronic kidney disease · Proteinuria · Sleep duration · Systematic review · Dose–response meta-analysis

Introduction

Chronic kidney disease (CKD), an increasingly important worldwide health issue, is defined as a consistent progressive decline in kidney function, an increase in urinary albumin excretion, or both. It is one of the major causes of end-stage renal disease, cardiovascular events, and mortality [1], affecting more than 10% of the population [2]. Previous studies have confirmed that hypertension, insulin resistance, obesity, and metabolic abnormalities are all risk factors of CKD [3–5]. In addition, a review by Turek et al. reported that sleep disturbances may be a novel risk factor for the development and progression of CKD, and, therefore, optimizing sleep duration and quality and treating sleep disorders may relieve the severity and delay the progression of CKD [6].

Qinjian Hao and Min Xie are joint first authors and contributed equally to this work.

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Sleep, one of the most important conservative behaviors in humans, accounts for approximately one-third of a human lifespan. Insufficient or excessive sleep is detrimental to various physiological functions, such as the regulation of metabolism [6, 7]. An increasing number of studies have explored the association between sleep duration and physical diseases, and they have found that insufficient sleep is a crucial risk factor for hypertension (≤5 h vs 7 h, OR 1.61, 95% CI 1.28–2.02; 6 h vs 7 h, OR 1.24, 95% CI 1.20–1.28), Type 2 diabetes (≤5 h vs 7 h, OR 1.37, 95% CI 1.18–1.59; 6 h vs 7 h, OR 1.06, 95% CI 1.01–1.11), metabolic syndrome (<7 vs 7–8 h, OR 1.23, 95%CI 1.11–1.37), and obesity (short vs normal, OR 1.45, 95% CI 1.25–1.67) [8–11], while excessive sleep is a risk factor for hypertension (8 h vs 7 h, OR 1.12, 95% CI 1.10–1.14) and Type 2 diabetes (≥9 vs 7 h, OR 1.40 95%CI 1.08–1.80) [8, 9]. Furthermore, A previous meta-analysis revealed that there was a potential association between short sleep duration and proteinuria (RR 1.47, 95% CI 1.26–1.72), while a lack of significant association between short sleep duration and CKD (RR 1.51 95% CI, 0.99–2.55) [12]. Whether short or long sleep duration is a risk factor for CKD and whether long sleep duration is a risk factor for proteinuria are still uncertain. Thus, we carried out a systematic review and meta-analysis to evaluate the effects of sleep duration on CKD and proteinuria.

Materials and methods

Protocol

The protocol of our study was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42018105149). The performance of this work adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria [13, 14].

Data sources and search strategy

A comprehensive literature search was performed in all fields in the PubMed, EMBASE and Cochrane library databases up to April 5, 2019. The relevant key words and medical subject headings included "sleep," "sleep duration," "proteinuria," "proteinurias," "renal insufficiency, chronic," and other entry terms pertaining to CKD. The detailed search terms and strategies are available in supplementary materials Item S1. The manual search was performed by two investigators, and the references of the relevant articles were searched for additional relevant articles. We contacted authors for potential additional studies.

Study selection

Population-based or patient-based studies fulfilling the following criteria were included in the present analysis: (1) participants aged ≥ 18 years; (2) sleep duration classified as short sleep or long sleep at the baseline assessment, with the reference being approximately 7 h/night; (3) outcome measures of CKD and/or proteinuria; (4) cross-sectional or cohort study design published with original data; and (5) sufficient information to calculate the odds ratio (OR), risk ratio (RR), hazard ratio (HR) or standardized incidence ratio with 95% confidence intervals (CIs). No language restriction was applied.

Studies were excluded if they were nonhuman studies, clinical trials, reviews, commentaries, or letters. If a study sample was reported in more than one study, we only included the sample with the longest follow-up duration.

Data extraction and quality assessment

After completing the literature search, data extraction was carried out independently by two of the authors using standardized data extraction forms. From each study, we extracted the following information: general information, such as authors, year of publication, publication source, and country; study design (cohort or cross-sectional); study sample origin (population based or patient based); total sample size; sample sizes in the experimental and control groups; age and sex of the participants; and effect estimators (OR, RR, HR). To minimize the potential confounding factors, we extracted the effect estimator from the fully adjusted regression model; the definition, category, and assessment of sleep duration; and the definition and assessment of CKD and proteinuria. Any disagreements were resolved by discussion and consensus.

The quality assessment of the included studies was undertaken using the Newcastle–Ottawa Scale for observational studies [15]. This scale awards stars for three categories: selection, comparability, and exposure, and each of these three categories are further divided into subcategories. For each study, a maximum of one star can be awarded for each subcategory; however, for comparability, a maximum of two stars can be awarded. A maximum number of nine stars can be awarded to a single study, which indicates a complete absence of any bias.

Definition of exposure and outcomes

Sleep duration was mostly self-reported, either by questionnaire or interview. The short and long sleep duration categories differed among studies. Among the included studies, the reference category of sleep duration was defined as one

of the following: 7 h/night, 6–7 h/night, 6–8 h/night, 7–8 h/night, or 6.5–7.4 h/night (Table 1). The short sleep duration was defined as < 4 h, < 4.5 h, ≤ 5 h, or ≤ 6 h/night, and the long sleep duration was defined as ≥ 8 h, ≥ 8.5 h, or ≥ 9 h/night. In our study, short sleep was categorized as ≤ 5 h/night and/or ≤ 6 h/night, long sleep duration was set as ≥ 8 h/night and/or ≥ 9 h/night, and the reference group was set as 7 h/night.

CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 and/or a urinary albumin to creatinine ratio (UACR) ≥ 30 mg/mmol [16]. Proteinuria was defined as a urinary protein level ≥ 1 + by dipstick or a UACR ≥ 30 mg/g [17].

Data synthesis and analysis

The RRs and HRs were crudely regarded as ORs because the incidence rate of CKD was low [18]. In the present study, we used ORs (95% CI) to evaluate the effect sizes for studies that associated the outcomes of CKD or proteinuria with sleep duration. The adjusted and unadjusted ORs were calculated based on the probability of having CKD or proteinuria with a sleep duration of ≤ 5 h/night and/or ≤ 6 h/night and ≥ 8 h/night and/or ≥ 9 h/night, respectively, compared to the probability of having CKD or proteinuria with the sleep duration of the reference group. The results were displayed as a forest plot (Figs. 1, 2, 3, 4, 5). The heterogeneity among studies was quantified by the I^2 statistic and tested by the Q statistic. A P value > 0.10 in the Q statistic test indicated no heterogeneity. The I^2 values of 25%, 50%, and 75% corresponded to the cutoff points for low, moderate, and high degrees of heterogeneity, respectively. In consideration of the potential heterogeneity among the included studies, the random effects model was applied when the I^2 was > 50% and P was < 0.1. To explain the residual heterogeneity, we conducted sensitivity analyses via leave-one-out analyses to test the influence of each study.

We further conducted a one-stage random-effect dose–response meta-analysis based on the method of robust error meta-regression (REMR) to evaluate the potential dose–response relationships between sleep duration and CKD and proteinuria [19]. This method treated each study as a cluster within the whole population and used the sandwich variance estimator to account for the correlation of ORs within each study. We used restricted cubic spline with three automatically generated knots to fit the potential nonlinear curve between sleep duration and CKD or proteinuria. A Wald test was used to judge whether the nonlinearity by assuming the coefficient of the second spline to be zero. Detailed information about the dose–response analysis was reported in the supplementary material (Item S2).

We did not analyze the publication bias with formal statistical tests because we had fewer studies, limiting the power. A two-tailed P value < 0.05 was regarded as statistically significant. Stata version 15.0 and Review Manager version 5.3 were used to perform the statistical analyses.

Results

Search results and characteristics of included studies

As described in Fig. 1, the literature search yielded 5048 articles, the full texts of 37 of which were reviewed and used in the subsequent study. Twenty-six out of the 37 studies were excluded because of a lack of available data regarding sleep duration or outcomes or because the sleep duration categories did not fit our inclusion criteria. Finally, a total of 11 studies including 521,242 participants met the selection criteria and were eligible for further analysis [20–30].

The characteristics of the 11 included studies are shown in Table 1. Of the selected studies, four were from China, three were from South Korea, two were from Japan, and two were from the United States. All studies were observational studies (three cohort and eight cross-sectional studies). Among them, five studies evaluated the effects of sleep duration on CKD only, three assessed the association between sleep duration and proteinuria only, and three analyzed the associations between sleep duration and both CKD and proteinuria. Overall, the outcome of eight studies was CKD, and the effect size was not adjusted in one study [24], while another study only had adjusted results [22]; the outcome of six studies was proteinuria, and the effect size was not adjusted in two studies [20, 25]. Two studies were patient based, of which one study enrolled type 2 diabetic patients, and another study recruited hypertensive patients [20, 22]. The remaining nine studies were population based, two of which enrolled nurses and employees in particular company [21, 23]. The ascertainment of sleep duration was self-reported in eight of the studies, and others used interviews. All evaluators were blinded to whether the subjects had CKD or proteinuria. Seven studies used the sleep duration of 7–8 h/night or 7 h/night as a reference, two used 6–8 h/night as a reference, one used 6–7 h/night, and another used 6.5–7.4 h/night as a reference. In the present study, we evaluated the quality of the included studies using the Newcastle–Ottawa quality assessment criteria and found that six studies received 9 points, two studies received 8 points, two studies received 7 points, and one study received 6 points (scores for individual studies are presented in Table S1).

Association of sleep duration with CKD

The adjusted summary risks measured for each sleep duration group for CKD are shown in Fig. 2. We found

Table 1 Characteristics of studies included in the meta-analysis

Study	Country	Study design	Study population	Total number	Age (Y)	Male sex %	Exposure definition	Outcome definition	OR adjusted model and adjusted factors for OR
Bo et al. [29]	China	PCS	MJ Health management institution (Taipei, Taiwan) from 1996 to 2014	194,039	≥ 20	50.7	< 4 h, 4–6 h, 6–8 h, ≥ 8 h per night Reference: 6–8 h per night	CKD; Participants with eGFR < 60 ml/min per 1.73 m^2	LRM adjusted for age, sex, smoking status, alcohol consumption, physical activity, vegetable intake, fruit intake, BMI, fasting glucose, total cholesterol, systolic blood pressure, diastolic blood pressure, and baseline eGFR
Chang et al. [30]	China	PCS	MJ health screening center in Taiwan 1996–2004	26,249	≥ 20	54.3	< 4 h, 4–6 h, 6–8 h, ≥ 8 h per night Reference: 6–8 h per night	Proteinuria; urinary protein ≥ 1 +	LRM adjusted for age, sex, blood pressure, fasting glucose, body mass index, cholesterols, triglycerides, uric acids, physical activity, smoking, income/educational levels, alcohol consumption, and baseline eGFR
Yu et al. [28])	South Korea	CSS	Korea national health and nutrition examination survey (KNHANES) 2011–2014	19,994	≥ 19	51.5	< 5 h, 6 h, 7 h, 8 h, > 9 h per day Reference: 7 h per day	Albuminuria: UACR > 30 mg/g Macroalbuminuria: UACR > 300 mg/g	LRM adjusted for age, sex, BMI, smoking, alcohol, education, income, exercise, eGFR, diabetes mellitus, hypertension, and hypercholesterolemia
Li et al. [27]	China	CSS	The Kailuan cohort 2012	11,040	18–98	83.3	< 6 h, 6–7 h, 7–8 h, ≥ 8 h per night Reference: 7–8 h per night	CKD: Participants with eGFR < 60 ml/min/1.73 m^2 or proteinuria > 2 + or more (> 300 mg/dl)	LRM adjusted for age, sex, education level, income level, occupation, physical activity, smoking, alcohol consumption, and BMI, diabetes, hypertension, myocardial infarction, stroke, cancer, use of sleep medications, and plasma concentrations of TG, LDL, and HDL

Table 1 (continued)

Study	Country	Study design	Study population	Total number	Age (Y)	Male sex %	Exposure definition	Outcome definition	OR adjusted model and adjusted factors for OR
Kim et al. [26]	South Korea	CSS	The Kangbuk Samsung Health Study 2011–2014	241,607	40.6 ± 9.3	56.1	≤ 5 h, 6 h, 7 h, 8 h, ≥ 9 h per night Reference: 7 h per night	CKD: an eGFR < 60 ml/min/1.73 m2	LRM adjusted for age, center, year of screening exam, smoking status, alcohol intake, physical activity, marital status, education level, total caloric intake, depression, history of diabetes, hypertension, and CVD
Choi et al. [25]	South Korea	CSS	The Korean Genome and Epidemiology Study (KoGES)-Kangwha study 2010–2011	1360	36–88	40.0	< 6 h, 6 to < 7 h, 7 to < 8 h, 8 to < 9 h, ≥ 9 h per day Reference: 7 to < 8 h per day	CKD: either kidney damage or eGFR < 60 mL/min/1.73 m^2 Proteinuria: urinary protein ≥ 1 +	LRM adjusted for sex, age, BMI, SBP, smoking status, alcohol, consumption, physical activity, depression, diabetes mellitus, hypercholesterolemia, history of CVD, history of cancer, menopausal status, socioeconomic status, and sleep quality
Petrov et al. [24]	USA	CSS	National Health and Nutrition Examination Survey (NHANES) 2009–2012	8690	≥ 20	50.6	≤ 5 h, 6 h, 7 h, 8 h, ≥ 9 h per night Reference: 7 h per night	CKD: an eGFR < 60 mL/min/1.73 m^2 and/or ACR ≥ 30 mg/mmol Microalbuminuria: ACR ≥ 30 mg/mmol	LRM adjusted for age, sex, BMI, race/ethnicity, family income to poverty ratio, self-reported moderate physical activity, hypertension, CVD, stroke, diabetes, self-rated general health, and serum protein

Table 1 (continued)

Study	Country	Study design	Study population	Total number	Age (Y)	Male sex %	Exposure definition	Outcome definition	OR adjusted model and adjusted factors for OR
McMullan et al. [23]	USA	CCS	The Nurses' Health Study 1989–2000	4238	58.0 ± 6.6	0	≤ 5 h, 6 h, 7–8 h, ≥ 9 h per 24 h Reference: 7 -8 h per 24 h	CKD: an eGFR < 60 mL/min/1.73 m^2 Albuminuria: UACR ≥ 30 mg/g	LRM adjusted for age, SBP, BMI, baseline eGFR, history of diabetes, history of CVD, history of hypercholesterolemia, history of hypertension, incident hypertension during follow-up, acetaminophen use, ACE-I use (1988 and 2000), NSAID use (1990 and 2000), and smoking status
Guo et al. [22]	China	CSS	Hypertensive population in rural northeast China 2012–2013	5555	35–93	49.0	≤ 6 h, 6 to ≤ 7 h, 7 to ≤ 8 h, 8 to ≤ 9 h, > 9 h per night Reference: 7 to ≤ 8 h per night	CKD: an eGFR < 60 mL/min/1.73 m^2	LRM adjusted for age, gender and ethnicity, education level, family income, marital status, diet score, daytime somnolence, current smoking, drinking status and physical activity, BMI, WC, SBP, DBP, high TC, high TG, high LDL-C, low HDL-C, anemia, hyperuricemia, diabetes, use of ACE-I or angiotensin receptor blocker, history of heart disease and stroke, depressive symptoms, and quality of life

Table 1 (continued)

Study	Country	Study design	Study population	Total number	Age (Y)	Male sex %	Exposure definition	Outcome definition	OR adjusted model and adjusted factors for OR
Sasaki et al. [21]	Japan	PCS	Employees of various companies and local government who underwent annual health check-ups (2003–2004) follow-up (2004–2008)	3600	35–58	77.7	≤ 5 h, 6–7 h, ≥ 8 h per night Reference: 6–7 h per night	CKD: an eGFR < 60 mL/min/1.73 m^2	The Cox proportional hazards model adjusted for age, sex, eGFR, SBP, BMI, TC, TG, fasting glucose, uric acid, C-reactive protein, proteinuria ≥ 1 +, family history of renal disease, smoking, alcohol, exercise, education, work hours, and job strain
Ohkuma et al. [20]	Japan	CSS	Type 2 diabetic patients enrolled in the Fukuoka Diabetes Registry 2008–2010	4870	≥ 20	57.0	< 4.5 h, 4.5–5.4 h, 5.5–6.4 h, 6.5–7.4 h, 7.5–8.4 h, ≥ 8.5 h per night Reference: 6.5–7.4 h per night	Albuminuria: UACR ≥ 30 mg/g Macroalbuminuria: UACR ≥ 300 mg/g	None

ACE-I angiotensin-converting enzyme inhibitor, *BMI* body mass index, *CSS* cross-sectional study, *CVD* cardiovascular diseases, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate (in mL/min/1.73 m^2), *HDL* high-density lipoprotein, *HDL-C* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein, *LDL-C* low-density lipoprotein cholesterol, *LRM* logistic regression model, *NSAID* nonsteroidal anti-inflammatory drug, *PCS* prospective cohort study, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *UACR* urinary albumin to creatinine ratio, *WC* waist circumference

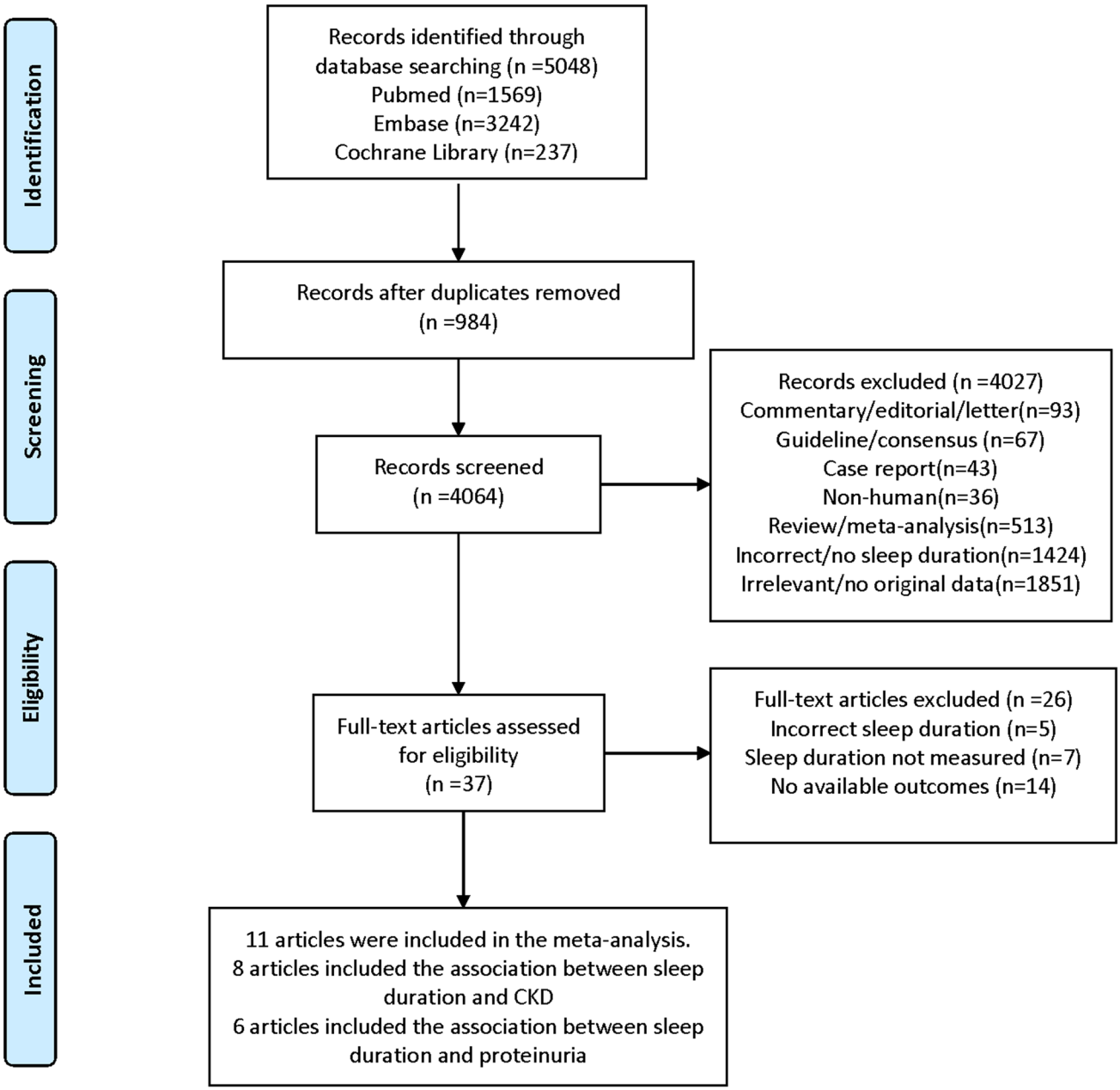

Fig. 1 Flowchart for the selection of the studies for the review. *CKD* chronic kidney disease

statistically significant associations between sleep duration and CKD. In the group of participants who slept ≤ 5 h/night vs. those who slept 7 h/night, the overall OR was 1.19 [95% CI, 1.00–1.41; $I^2 = 49\%$]. In the group of those who slept ≤ 6 h/night vs. those who slept 7 h/night, the overall OR was 1.13 (95% CI, 1.02–1.25; $I^2 = 29\%$). In the group of those who slept ≥ 8 h/night vs. those who slept 7 h/night, the overall OR was 1.14 (95% CI, 1.07–1.22; $I^2 = 0\%$). In the group of those who slept ≥ 9 h/night vs. those who slept 7 h/night, the overall OR was 1.32 (95% CI, 1.03–1.70; $I^2 = 10\%$). We applied a random effects model because of heterogeneity ($P < 0.10$, $I^2 > 50\%$).

The unadjusted summary risks measured for each sleep duration group for CKD are shown in Fig. 3. Overall, a statistically significant association was found between sleep duration and CKD. In the four groups (i.e., sleep duration: ≤ 5 h/ night, ≤ 6 h/ night, ≥ 8 h/ night and ≥ 9 h/ night) as described above, the overall ORs were 1.36 (95% CI, 1.20–1.54; $I^2 = 0\%$), 1.17 (95% CI, 1.04–1.32; $I^2 = 63\%$), 1.37 (95% CI, 1.29–1.46; $I^2 = 40\%$) and 2.19 (95% CI,

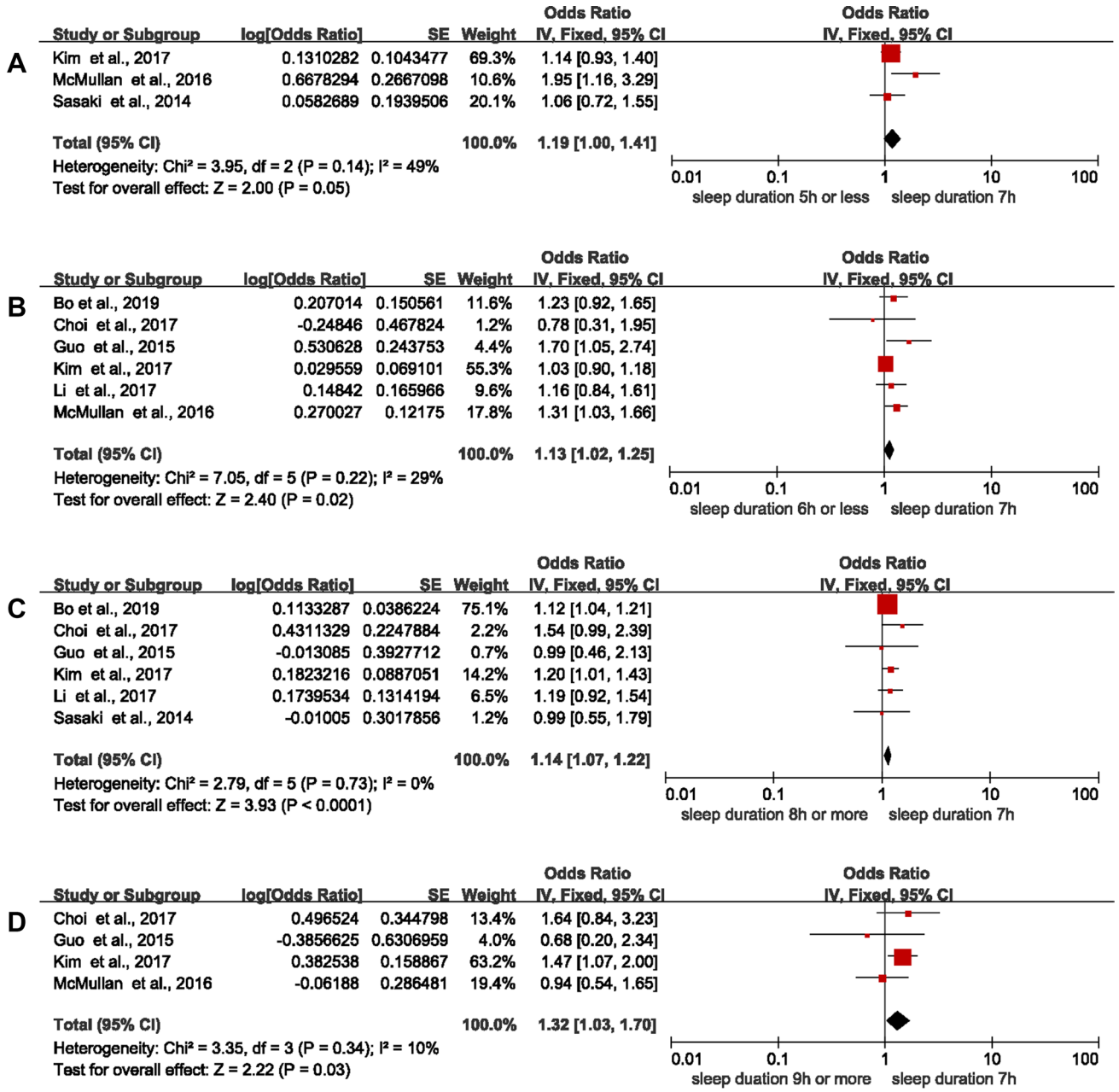

Fig. 2 Forest plot of the association between sleep duration and CKD with adjusted summary risks. Adjusted odds ratios (ORs) in the individual study are presented as squares with 95% confidence intervals (CIs) represented as extended lines. The ORs with their 95% CI are shown as diamonds. **a** Those who slept ≤ 5 h/night versus those who slept 7 h/night. **b** Those who slept ≤ 6 h/night versus those who slept 7 h/night. **c** Those who slept ≥ 8 h/night versus those who slept 7 h/night. **d** Those who slept ≥ 9 h/night versus those who slept 7 h/night

1.67–2.88; $I^2 = 62\%$), respectively. We applied a random effects model because of heterogeneity ($P < 0.10$, $I^2 > 50\%$).

Relationship of sleep duration with proteinuria

The adjusted summary risks measured for each sleep duration group for proteinuria are shown in Fig. 4. We found statistically significant relationships between sleep duration and proteinuria. In the group of participants who slept ≤ 5 h/night vs. those who slept 7 h/night, the combined OR was 1.43 (95% CI, 1.03–1.99; $I^2 = 66\%$). In the group of those who slept ≤ 6 h/night vs. those who slept 7 h/night, the combined OR was 1.24 (95% CI, 1.06–1.44; $I^2 = 61\%$). In the group of those who slept ≥ 8 h/night vs. those who slept 7 h/night, the combined OR was 1.15 (95% CI, 1.04–1.29; $I^2 = 0\%$). In the group of those who slept ≥ 9 h/night vs. those who slept 7 h/night, the combined OR was 1.32 (95% CI, 1.04–1.29; $I^2 = 0\%$). We

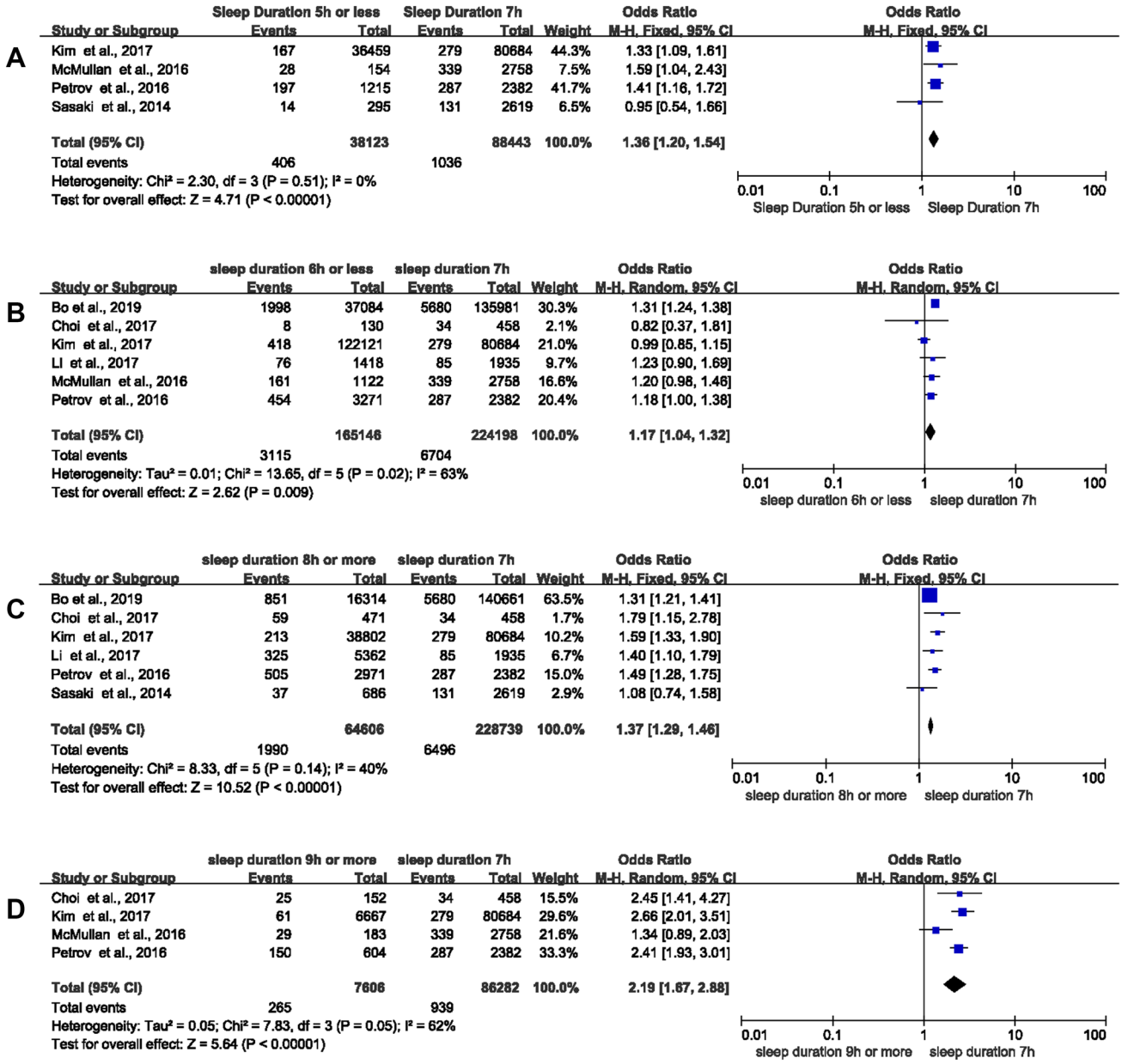

Fig. 3 Forest plot of the association between sleep duration and CKD with unadjusted summary risks. The unadjusted odds ratios (ORs) in the individual study are presented as squares with 95% confidence intervals (CIs) represented as extended lines. The pooled OR with its 95% CI is shown as a diamond. **a** Those who slept ≤ 5 h/night versus those who slept 7 h/night. **b** Those who slept ≤ 6 h/night versus those who slept 7 h/night. **c** Those who slept ≥ 8 h/night versus those who slept 7 h/night. **d** Those who slept ≥ 9 h/night versus those who slept 7 h/night

applied a random effects model because of heterogeneity ($P < 0.10$, $I^2 > 50\%$).

The unadjusted summary risks measured for each sleep duration group for proteinuria are shown in Fig. 5. Overall, we found statistically significant relationships between sleep duration and proteinuria. In all groups (i.e., sleep duration: ≤ 5 h/ night, ≤ 6 h/ night, ≥ 8 h/ night and ≥ 9 h/ night) as described above, the combined ORs were 1.63 (95% CI, 1.45–1.84; $I^2 = 0\%$), 1.23 (95% CI, 1.14–1.32; $I^2 = 0\%$), 1.41 (95% CI, 1.19–1.68; $I^2 = 69\%$) and 1.61 (95% CI, 1.37–1.89; $I^2 = 12\%$), respectively. We applied a random effects model to the groups because of heterogeneity ($P < 0.10$, $I^2 > 50\%$).

Dose–response analyses

Figure 6 shows the dose–response analysis of the associations between categories of sleep duration and CKD or proteinuria. It revealed U-shape associations between sleep

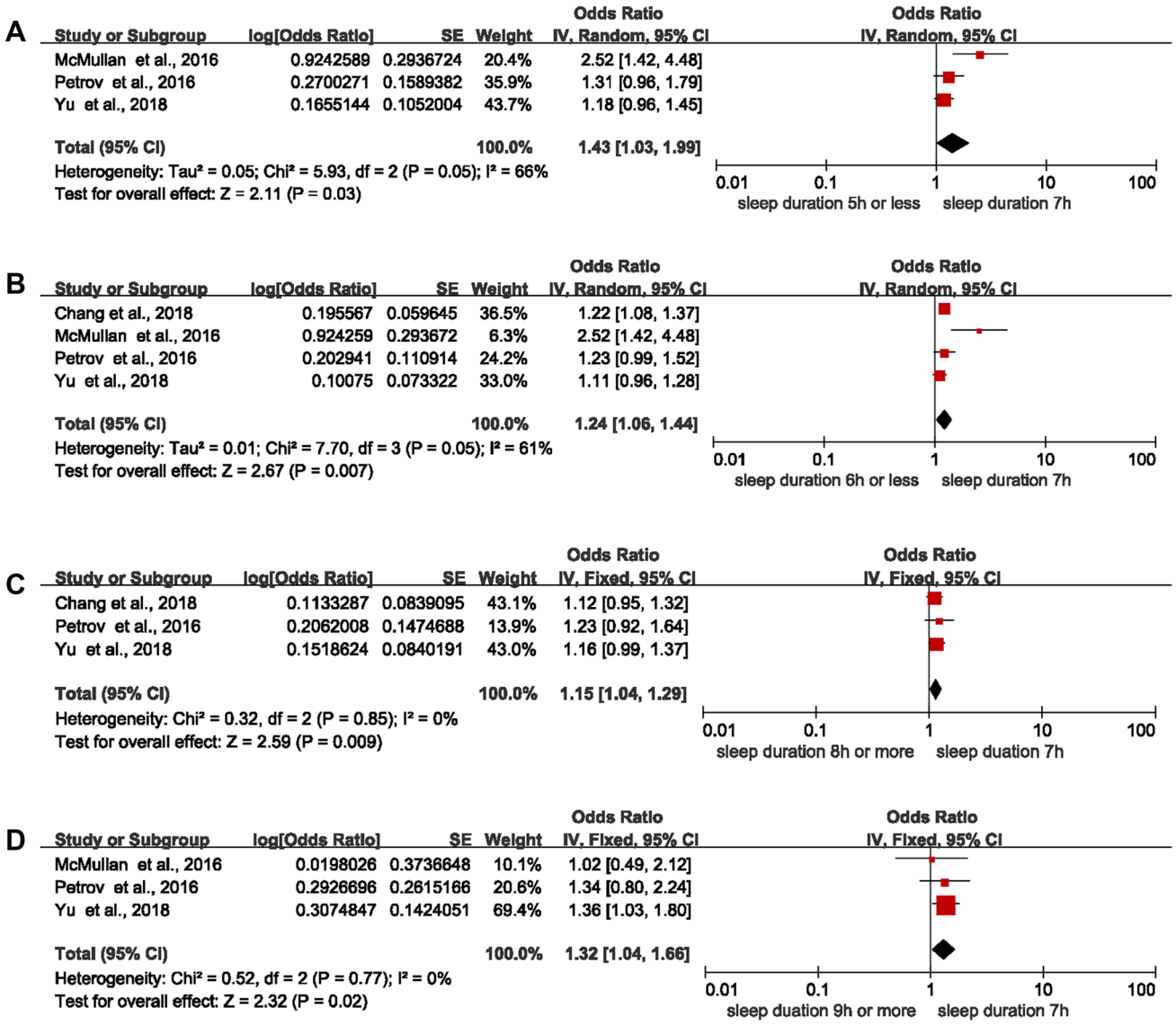

Fig. 4 Forest plot of the association between sleep duration and proteinuria with adjusted summary risks. Adjusted odds ratios (ORs) in the individual study are presented as squares with 95% confidence intervals (CIs) represented as extended lines. The pooled OR with its 95% CI is shown as a diamond. **a** Those who slept ≤ 5 h/night versus those who slept 7 h/night. **b** Those who slept ≤ 6 h/night versus those who slept 7 h/night. **c** Those who slept ≥ 8 h/night versus those who slept 7 h/night. **d** Those who slept ≥ 9 h/night versus those who slept 7 h/night

duration and CKD and proteinuria, and both had the lowest risk at 7 h/night of sleep. In Fig. 6, we used the adjusted results of the ORs with the reference category (i.e., 6–7 h/night, 6–8 h/night, 6.5–7.4 h/night, 7 h/night, 7–8 h/night) in each study as in the dose–response meta-analyses. In Fig. S1 and S2 (provided as online supplementary material), we used the unadjusted ORs with the reference of each study (i.e., 6–7 h/night, 6–8 h/night, 6.5–7.4 h/night, 7 h/night, 7–8 h/night) and the lowest category (i.e., < 4 h/night, < 4.5 h/night, ≤ 5 h/night or ≤ 6 h/night) of sleep and as the reference category, respectively, in the dose–response meta-analyses.

Sensitivity analysis

We carried out a sensitivity analysis to evaluate whether the removal of a study from this analysis would significantly affect the results and heterogeneity. In the adjusted summary risks analysis of the association of sleep duration and proteinuria, one study [23] carried out in individuals who slept ≤ 5 h/night vs 7 h/night and slept ≤ 6 h/night vs 7 h/night was left out, and the remaining effects were still statistically significant. In the pooled analysis of the association between sleep duration and CKD, two studies [26, 29] carried out in those individuals who slept ≤ 6 h/night

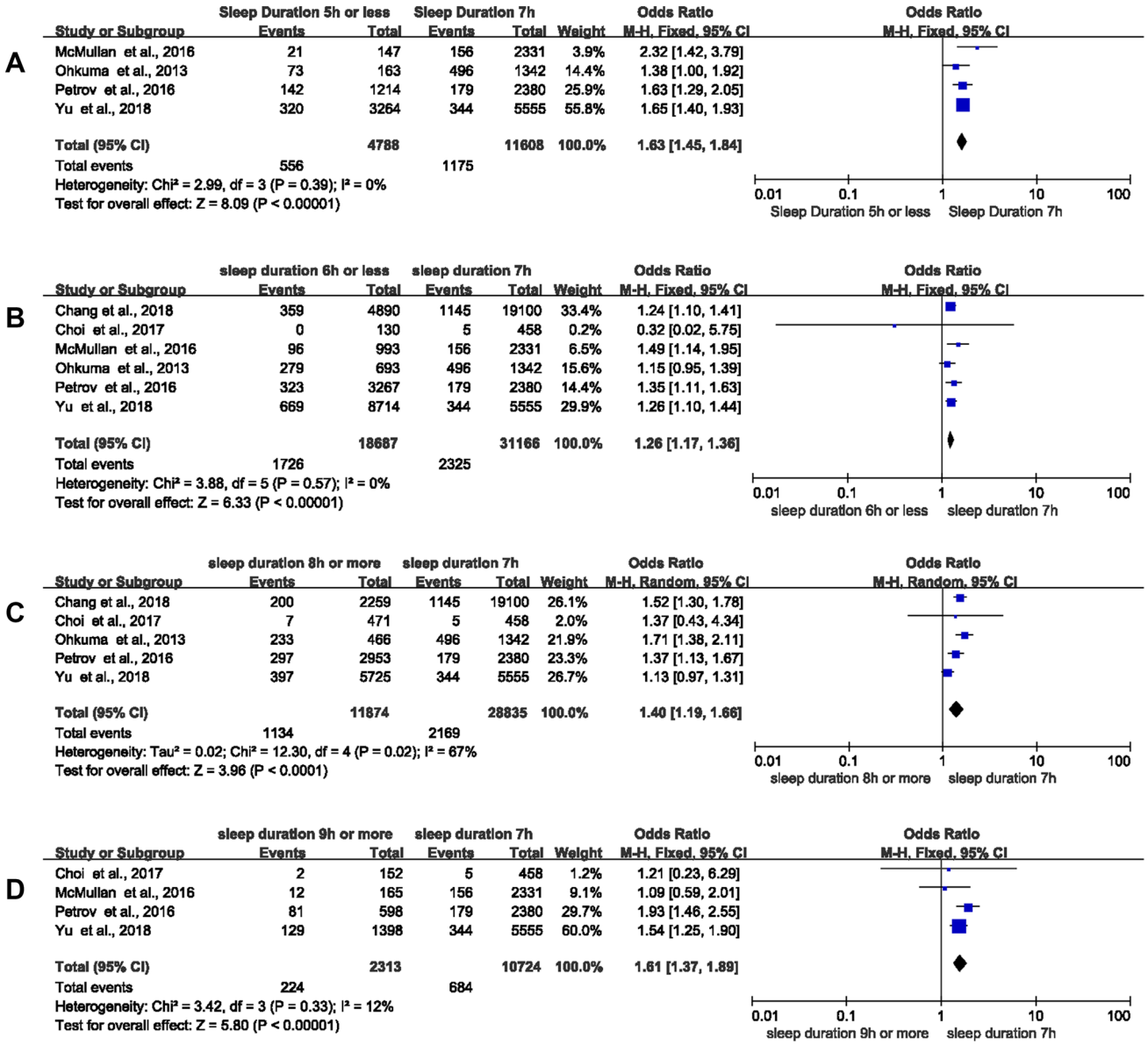

Fig. 5 Forest plot of the association between sleep duration and proteinuria with unadjusted summary risks. The unadjusted odds ratios (ORs) in the individual study are presented as squares with 95% confidence intervals (CIs) represented as extended lines. The pooled OR with its 95% CI is shown as a diamond. **a** Those who slept ≤ 5 h/night versus those who slept 7 h/night. **b** Those who slept ≤ 6 h/night versus those who slept 7 h/night. **c** Those who slept ≥ 8 h/night versus those who slept 7 h/night. **d** Those who slept ≥ 9 h/night versus those who slept 7 h/night

vs 7 h/night were left out, and the remaining effects were still statistically significant. One study [23] performed with individuals who slept ≥ 9 h/night vs 7 h/night was left out, and the remaining pooled effects were still statistically significant. In the association analysis of sleep duration and proteinuria, one study [28] performed in individuals who slept ≥ 8 h/night vs 7 h/night was left out, and the remaining pooled effects were still statistically significant (Table S2).

Discussion

In the present study, a comprehensive assessment of the literature and a quantitative estimation of the associations between sleep duration and the risk of CKD and proteinuria in adults showed that, compared to the reference category of sleep duration, durations of sleep that were both too short and long were associated with CKD and

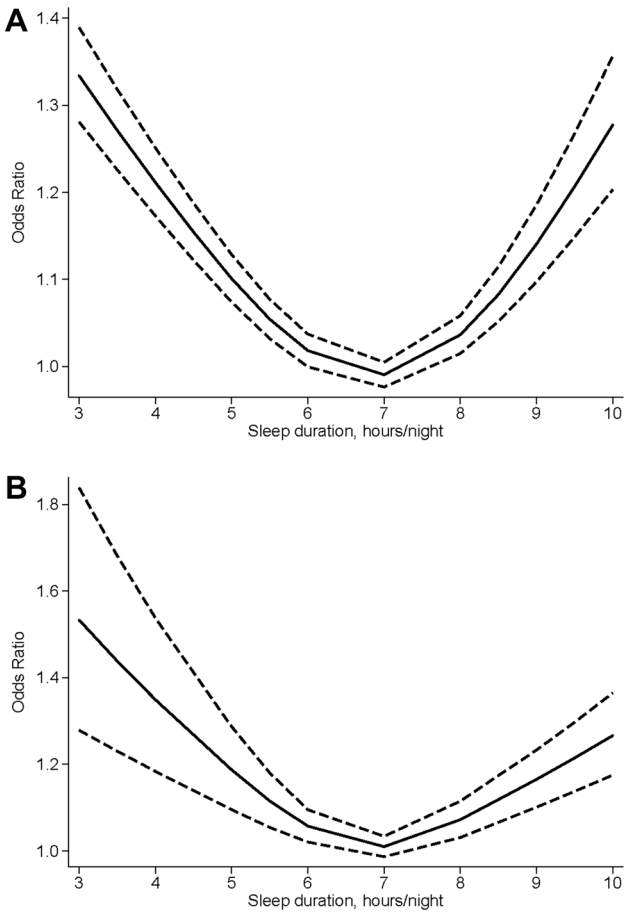

Fig. 6 Dose–response analyses of sleep duration (hour) and the risk of CKD (**a**), and sleep duration (hour) and the risk of proteinuria (**b**)

proteinuria. Furthermore, U-shaped associations were detected between sleep duration and CKD and proteinuria, both with the lowest risk at 7 h/night of sleep duration. Overall, our study indicated that durations of sleep that were both too short and too long may be risk factors for CKD and proteinuria.

Our study provides robust evidence that inadequate sleep and excessive sleep may increase the risk of CKD in adults. In a previous meta-analysis [12], there was a potential relationship between a short sleep duration and proteinuria but not CKD. The eight observational studies included in that meta-analysis used one of the following definitions of short sleep duration: ≤ 4 h/night, ≤ 5 h/night, ≤ 6 h/night or < 7.5 h/night. The reference groups of those with sleep durations that were not short included individuals with long sleep durations (> 4 h/night, > 5 h/night, > 6 h/night or > 7 h/night). It is possible that the effect of long sleep duration on CKD counteracted that of short sleep on CKD. Our analysis excluded five of the studies [31–35] that were included in the previous meta-analysis because their sleep duration categories did not meet our criteria. Meanwhile, our study further analyzed the associations between long sleep duration and CKD and proteinuria.

In the present study, we found that short sleep duration (≤ 5 h/night or ≤ 6 h/night) was significantly associated with CKD and proteinuria. Several studies found that a short sleep duration had adverse impacts on CKD and proteinuria [20, 22, 23, 29, 30], but a few studies indicated that there are no association between a short sleep duration and CKD and proteinuria [24, 27, 28, 30]. Sasaki et al. found that a short sleep duration was associated with CKD only in shift workers [21]. A population-based study in rural northeast China found that self-reported short sleep duration was significantly related to an increased risk of reduced GFR in a hypertensive population [22]. However, the underlying mechanisms of these associations have not been fully elucidated. There have been several hypotheses about the influence of sleep deprivation on renal physiology. First, the overactivation of the sympathetic nervous system is one of the possible biological mechanisms to explain the association between short sleep duration and an increased risk of CKD. Reduced sleep duration may lead to sympathetic hyperactivity [36], which has been confirmed as an important feature of CKD [37]. Second, another potential contributing mechanism is the overactivity of the renin–angiotensin–aldosterone system. Sleep deprivation may have adverse impacts on the renin–angiotensin–aldosterone system during both wakefulness and sleep [6]. The chronobiological alteration in renin–angiotensin–aldosterone system activity has been reported to play a critical role in CKD progression [38]. Third, systemic inflammation may participate in the pathogenesis of renal dysfunction. One study showed that acute total or partial sleep deprivation resulted in elevated high-sensitivity C-reactive protein (CRP) concentrations, which may promote low-level systemic inflammation and increase the risk of cardiovascular illness [39]. People with a large accumulated sleep deficit are more likely to suffer from CKD.

Meanwhile, we found that long sleep duration (≥ 8 h/night or ≥ 9 h/night) was an important risk factor for CKD and proteinuria. A few studies found that a long sleep duration had detrimental effects on CKD and proteinuria [20, 28, 29]; however, several studies showed that long sleep duration was not significantly related to CKD or proteinuria [22–24, 27]. Choi et al. found that long sleep duration (> 9 h/night) was associated with CKD only in females [25]. However, a large study of young and middle-aged adults found that long sleep duration was associated with CKD only in males [26]. Furthermore, the biological mechanisms underlying the relationship between long sleep duration and CKD are also unclear. Previous studies have suggested that the association between a long sleep duration and CKD could be explained by physical inactivity, systemic inflammation, immune system dysfunction, disease status or confounding

effects of unmeasured factors that lead to a prolonged sleep duration. In general, those who sleep for long periods often experience sleep fragmentation, excessive daytime sleepiness, poor sleep quality, and low levels of physical activity [28, 40, 41]. A meta-analysis found that a long sleep duration (> 8 h/night) was related to higher CRP and IL-6 levels, which are sensitive biomarkers of systemic inflammation [42]. Sleep fragmentation and alterations of the immune system may contribute to poor health outcomes in those who sleep for long durations. As is well known, patients with restless leg syndrome or sleep apnea often complain of excessive daytime sleepiness [43, 44]. Both above diseases are related to sleep fragmentation, poor sleep quality, and poor sleep quantity, which may cause chronic activation of the sympathetic nervous system, endothelial dysfunction and systemic inflammation.

In our sensitivity analysis of the summary results, the remaining studies of Bo et al. [29], Kim et al. [26], McMullan et al. [23] or Yu et al. [28] could explain the high heterogeneity. Of the six studies that evaluated the association between sleep duration and CKD (≤ 6 h/night vs 7 h/night), two studies (by Bo et al. [29] and Kim et al. [26]) were based on the general population and had the largest sample sizes. Additionally, out of the four studies that evaluated the association between a long sleep duration and CKD (≥ 9 h/night vs. 7 h/night), a prospective cohort study among the Nurses' Healthy Study showed that compared to the reference sleep duration (7–8 h/night), a short sleep duration (< 5 h/night or = 6 h/night) was associated with a more rapid decline in renal function. This study only enrolled female participants, and the number of those who slept for long durations (≥ 9 h/night, $n = 183$) was significantly smaller than the number of those who slept for the reference duration (7–8 h/night, $n = 2758$). In addition, the cross-sectional study conducted by Yu et al. reported that sleep duration has a U-shaped association with the UACR level. In the assessment of the association of sleep duration and proteinuria (≥ 9 h/night vs 7 h/night), Yu's study was based on a large sample ($n = 1398$) of the South Korean general population, and the number of participants in that study accounted for more than half of the total sample size of the four included studies.

The major strength of our study is that the included studies have a mean score (Newcastle–Ottawa Scale score) of approximately 8.2, which ensures the high quality of our study. In addition, this is the first review to explore a dose–response effect of sleep duration on CKD and proteinuria using a robust error meta-regression method. Furthermore, our study was based on a large number of participants in adults from the general population, which provides a much greater possibility of reasonable conclusions. The larger the sample, the smaller the standard error and the more accurate the estimate of the result. Except for Choi et al. [25] have a wide 95% confidence interval of OR due to small sample size, Other studies with larger sample sizes have produced more accurate estimates.

However, our study has several limitations. First, this study is a secondary analysis of the observational study. It may be not possible to avoid the influence of confounding factors on outcomes. Second, several studies included in our meta-analysis estimated sleep duration using self-reported questionnaires that may contain inaccurate information. Thus, the reliability of the results in our study may be compromised. Third, the criterion for CKD in a few included studies was based on a single eGFR assessment. Therefore, patients who have mild kidney damage without a decrease in the eGFR may have been excluded. Fourth, findings related to the secondary outcome of proteinuria were based on a much smaller number of participants ($n = 63{,}436$). Last, we only included published studies, and reporting bias cannot be excluded because the outcomes were not reported in all studies. In particular, kidney outcomes were not the primary outcomes in some of the included studies; thus, it is quite possible that some kidney outcomes were not reported because they were not statistically significant.

In conclusion, our systematic review and meta-analysis revealed that short and long sleep durations may both be risk factors for CKD and proteinuria in the adult population. Furthermore, a *U*-shaped relationship was observed between sleep duration and CKD or proteinuria, with the lowest risk at 7 h/night of sleep. It is an important finding for the clinical management of CKD. In the future, more cohort studies, longer follow-up periods and a unified assessment of exposure and outcomes are needed to confirm these results.

Author contributions Research idea and study design: Dr. Xie, Dr. Hao, Dr. Wang and Dr. Tang; search and data acquisition: Dr. Hao, Dr. Xie, Dr. Dou, Dr. Dai and Dr. Wang; data analysis/interpretation: Dr. Hao, Dr. Xie, Dr. Zhu and Dr. Wu; statistical analysis: Dr. Xie, Dr. Hao and Dr. Wang; supervision or mentorship: Dr. Wang. Each author contributed very important intellectual content during manuscript drafting or revision and accepts accountability for the work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. Dr. Wang take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Compliance with ethical standards

Conflict of interest The authors declare that they have no relevant financial interests.

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