Sleep Quality and Sleep Duration with CKD are Associated with Progression to ESKD

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Abstract

Background and objectives Shorter or longer sleep duration and poor sleep quality are risk factors for numerous cardio-metabolic diseases, cardiovascular disease, and mortality in subjects with normal kidney function. The association of sleep duration and sleep quality with health outcomes in patients with CKD remains uncertain.

Design, setting, participants, & measurements A 4-year prospective cohort study in 17 nephrology centers in Japan, the CKD Japan Cohort (CKD-JAC) Study, assessed an association of self-reported sleep duration and sleep quality, on the basis of the Pittsburgh Sleep Quality Index (PSQI) questionnaire, with incidence of ESKD in 1601 patients with eGFR 10–59 ml/min per 1.73 m^2 using multivariable-adjusted Cox proportional hazards models.

Results Baseline sleep duration and PSQI global score for the 1601 patients were mean±SD 7.0±1.3 hours and median 4 (interquartile range, 3–7), respectively. Poor sleep quality (PSQI global score ≥6) was common (*n*=588 [37%]). During a median of 4.0 (2.6–4.3) years of the follow-up period, 282 (18%) patients progressed to ESKD. After adjusting for age, sex, eGFR, urinary albumin excretion, smoking status, body mass index, history of diabetes and cardiovascular disease, systolic BP, blockade of the renin-angiotensin system, use of hypnotics, and Beck depression inventory score, both shorter (≤5 hour) and longer (>8 hour) sleep duration were associated with ESKD (adjusted hazard ratios [95% confidence intervals] for ≤5.0, 5.1–6.0, 6.1–7.0, 7.1–8.0, and ≥8.0 hours were 2.05 [1.31 to3.21], 0.98 [0.67 to 1.44], 1.00 [reference], 1.22 [0.89 to 1.66], and 1.48 [1.01 to 2.16]), suggesting a U-shaped relationship between sleep duration and ESKD. PSQI global score ≥6 was also associated with incidence of ESKD (adjusted hazard ratios [95% confidence intervals] for PSQI global score ≤5 and ≥6 were 1.00 [reference] and 1.33 [1.03 to 1.71]).

Conclusions Shorter (≤5 hour) and longer (>8 hour) sleep duration and poor sleep quality (PSQI global score ≥6) were associated with ESKD in patients with CKD.

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Introduction

Epidemiologic evidence demonstrates that patients with CKD, characterized by low GFR and/or proteinuria (1), are at high risk of ESKD (2), cardiovascular disease (3), and even mortality (3). The growing number of patients with CKD is a worldwide public health problem presenting an enormous economic burden (4). In Japan, the prevalence of CKD and ESKD was estimated to be approximately 13% (5) and 0.3% (6) of the adult population, respectively. The ESKD rate in Japan is one of the highest among industrialized nations (7). One potential approach to developing an effective CKD prevention program is to identify the lifestyle risk factors for incidence and progression of CKD.

One of the potential lifestyle factors for CKD is sleep. The most extensively studied sleep component is sleep duration (8). Systematic reviews identified shorter and/or longer sleep duration as associated with a wide variety of clinical outcomes, including obesity (9), metabolic syndrome (10), diabetes (11), hypertension (12), cardiovascular disease (13), stroke (14), and mortality (15). Regarding CKD, a few cohort studies identified shorter sleep duration to be associated with proteinuria (16) and GFR decline (17,18) in the general population. However, data regarding the clinical effect of sleep duration in patients with CKD are very limited (19).

Besides sleep duration, sleep quality may play a role in CKD progression. Several cohort studies suggested that self-reported sleep quality was associated with obesity (20), diabetes (21,22), cardiovascular disease (22), and mortality (23). Interventional trials to suppress deep nonrapid eye movement sleep, also known as slow-wave sleep, demonstrated adverse metabolic effects on glucose metabolism (24,25), the sympathetic nervous system (25), and adrenocortical activity (25). Although poor sleep quality is common in patients with CKD (26–28), the clinical effect of sleep quality on ESKD incidence remains to be elucidated (19).

The aims of this 4-year prospective cohort study, the CKD Japan Cohort (CKD-JAC) study, were to assess

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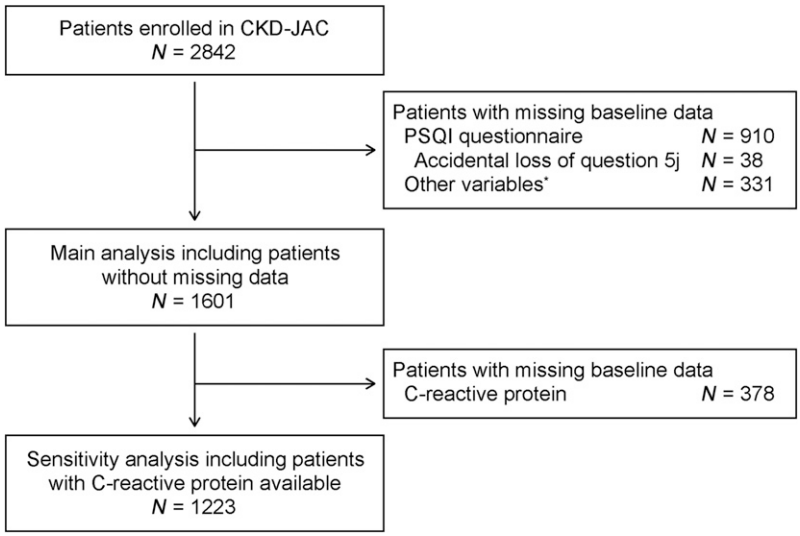

Figure 1. | **Inclusion and exclusion process of this study.** *Age, sex, smoking status, history of diabetes and cardiovascular disease, body mass index, systolic and diastolic BP, serum creatinine, eGFR, urinary albumin excretion, blockade of renin-angiotensin system, and Beck depression inventory score. CKD-JAC, CKD Japan Cohort study; PSQI, Pittsburgh Sleep Quality Index.

the association between self-reported sleep duration and quality and ESKD in patients with eGFR 10–59 ml/min per 1.73 m^2 using the Pittsburgh Sleep Quality Index (PSQI) (29), the most widely used sleep quality questionnaire (8,30,31). The results of this study shed light on sleep as one of the key lifestyle risk factors for progression of CKD.

Materials and Methods

Participants

The CKD-JAC study (University Hospital Medical Information Network (UMIN) clinical trial number: UMIN000020038) was a prospective cohort study to determine the incidence rates of ESKD (32) and cardiovascular disease (33) and to identify their risk factors (34,35) during the 4-year follow-up period in Japanese patients with CKD. The study protocol has been described in detail elsewhere (36). Briefly, the CKD-JAC study enrolled patients aged 20–75 years with eGFR 10–59 ml/min per 1.73 m^2. To calculate eGFR, a three-variable equation modified for Japanese patients was used: eGFR (ml/min per 1.73 m^2) $=194\times\text{age (year)}^{-0.287}\times\text{serum creatinine (mg/dl)}^{-1.094}\times 0.739$ (if female) (37). Patients with a history of transplants or kidney replacement therapy (KRT) were not eligible for the study. All patients provided written informed consent before enrollment in this study. The study protocol was approved by the institutional review board of each participating hospital.

Between April of 2007 and December of 2008, 2966 patients with CKD were registered in the CKD-JAC study at 17 hospitals in Japan. After excluding patients ≥76 years of age (n=40), with eGFR≥60 or <10 ml/min per 1.73 m^2 (N=13 and 69, respectively), or with a history of KRT (N=2) at their baseline visit, 2842 patients were enrolled in the CKD-JAC study. Baseline sleep duration and quality were measured using the PSQI questionnaire, comprising 18 questions (Supplemental Appendix) (29). Because completing the PSQI questionnaire was not mandatory in the CKD-JAC study, this was done primarily on a voluntary basis. Accidentally, a question pertaining to frequency of sleep disturbance (PSQI question 5j) was not included in the PSQI questionnaire in the CKD-JAC study. Depending on their answers to the missing question 5j, 38 (1%) patients had two possible PSQI global scores, whereas the rest had a single global score regardless of their answer to question 5j. After excluding the 38 (1%) patients with two possible PSQI global scores, 872 (31%) patients with missing answers to other PSQI questions, and 331 (12%) patients with missing data for other variables, this study finally included 1601 (56%) patients with CKD (Figure 1).

Measurements

The main exposures of this study were baseline sleep duration (PSQI component 3) and sleep quality (PSQI global score) during the month before the baseline visit. Poor sleep quality was defined as PSQI global score ≥6, a common cutoff value for poor sleep quality (29,30). Other baseline variables included age, sex, smoking status (non-, past, or current smoker), history of diabetes and cardiovascular disease, body mass index (body weight [kg]/height^2 [m^2]), systolic and diastolic BP, serum creatinine, eGFR, urinary albumin excretion, serum C-reactive protein (if available) and renin-angiotensin system (RAS) blockade, use of hypnotics (PSQI component 6), and Beck depression inventory score (38) at their baseline visit. Patients with any history of angina, myocardial infarction, congestive heart failure, stroke, and/or arteriosclerosis obliterans were regarded as those with history of cardiovascular disease. RAS blockade included use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists. Because the numbers of patients with hypnotic use <1 and 1–2 times/wk were small (n=41 [3%] and 34 [2%], respectively), they were classified into a single category. The Beck depression inventory is a 21-item self-administered questionnaire for depression screening (38). A score of 11 or

higher is the originally defined cutoff value for depression in the general population and it is validated for use in patients with CKD (39). To assess changes in sleep duration and PSQI global score during the follow-up period, answers to the PSQI questionnaire were remeasured 2 years and 3.5 years after entry into the study.

The outcome measure of interest in this study was time to incidence of ESKD requiring KRT. Incidence of ESKD was ascertained from patient medical records by clinical research assistants and physicians in each facility. The follow-up period was defined as time from the baseline visit to (*1*) incidence of ESKD or (*2*) the last visit before March of 2013, whichever came first. Death before ESKD incidence was regarded as censored.

Statistical Analyses

Differences in baseline characteristics between the patients included in and those excluded from this study were assessed using unpaired *t* test, Wilcoxon rank sum test, or chi-squared test, as appropriate. The incidence rates of ESKD were compared using a Poisson regression model. After classifying baseline sleep duration into five categories (≤5.0, 5.1–6.0, 6.1–7.0, 7.1–8.0, and >8.0 hours), dose-dependent associations between baseline sleep duration and other baseline characteristics were assessed using the Cochran–Armitage trend test or the Jonckheere–Terpstera trend test, as appropriate. Baseline characteristics between patients with PSQI≤5 and ≥6 were compared using unpaired *t* test, Wilcoxon rank sum test, or chi-squared test, as appropriate. Correlations of sleep duration between the baseline visit and 2 and 3.5 years after study entry were assessed using Pearson's *r* and those of PSQI global score were assessed using Kendall's τ because of its tied values.

Associations of sleep duration and PSQI global score with incidence of ESKD were assessed using nested Cox proportional hazards models, whereby covariates from each prior model were retained as follows. Model 1 included age and sex. Model 2 added eGFR (ml/min per 1.73 m^2) and urinary albumin excretion. Because of its skewed distribution, urinary albumin excretion was included in model 2 after logarithmic transformation (log g/g creatinine (gCr)). Model 3 added smoking status (non-, past, or current smoker), body mass index (kg/m^2), history of diabetes and cardiovascular disease, systolic BP (mm Hg), and RAS blockade. Model 4 added Beck depression inventory score (≤10 versus ≥11) and use of hypnotics (none, 1–2 times per week, or ≥3 times per week). PSQI global score was not adjusted for use of hypnotics, which was included as component 6 of the PSQI global score. The proportional hazards assumption for covariates was checked using Schoenfeld residuals. Effect modifications between the baseline variables were assessed, including their interaction terms, in a fully adjusted model (model 4).

The incremental contribution of sleep duration and PSQI global score in each model were evaluated using the net reclassification improvement (NRI) approach. Continuous (category-less) NRI at a set time of 4 years comparable to the median follow-up time was estimated using the bootstrapping method (40).

As a sensitivity analysis, we assessed a potential confounding effect of serum C-reactive protein level as an inflammation marker on association of sleep duration and PSQI global score with incidence of ESKD in 1223 (76%) patients with a baseline measurement available. We made a nested Cox proportional hazards model, additionally adjusting for C-reactive protein. Because C-reactive protein serum level was 0 mg/dl (under the detection limit) in 207 (17%) patients, and its distribution was right-skewed, its serum concentration was transformed to log (C-reactive protein [mg/dl]+0.01) before inclusion in multivariable-adjusted models.

Continuous variables were expressed as mean±SD or median (interquartile range), and categorical variables were expressed as number and proportion, as appropriate. The statistical significance level was set at $P<0.05$. All statistical analyses were conducted using SAS Release 9.4 (SAS Institute, Cary, NC), R version 3.5.0 (www.r-project.org/; The R Foundation for Statistical Computing), and Stata, version 15 (www.stata.com; Stata Corp).

Results

Among 2842 eligible patients aged 20–75 years with eGFR 10–59 ml/min per 1.73 m^2, 1601 (56%) patients with median (IQR) age 61 (54–69) years and mean±SD body mass index 23.5±3.8 kg/m^2 were included in this study (Figure 1, Supplemental Table 1). Compared with the excluded patients, the included patients were significantly younger and had higher prevalence of male sex, higher diastolic BP and serum levels of C-reactive protein, and lower prevalence of nonsmokers, diabetes, cardiovascular disease, and users of hypnotics (Supplemental Table 1). Baseline sleep duration and PSQI global score were comparable between the two groups (mean±SD sleep duration, 7.0±1.3 versus 6.9±1.3 hours; PSQI global median [IQR] score, 4 [3–7] and 5 [3–7]). During a median 4.0 years of follow-up, 523 (18%) of 2842 patients developed ESKD requiring KRT. Incidence rates of ESKD in patients included in and excluded from this analysis were comparable (0.051 versus 0.059 per person-year, P=0.11).

The baseline characteristics of the 1601 patients stratified by five categories of sleep duration are listed in Table 1. Mean±SD sleep duration for 152 (9%), 300 (19%), 541 (34%), 420 (26%), and 188 (12%) patients with ≤5.0, 5.1–6.0, 6.1–7.0, 7.1–8.0, and >8.0 hours of sleep duration was 4.7±0.7, 5.9±0.2, 6.9±0.2, 7.8±0.2, and 9.2±0.7 hours, respectively. Compared with patients with longer sleep duration, those with shorter sleep duration were younger; had lower prevalence of male sex and history of cardiovascular disease, and lower levels of serum creatinine; and had higher levels of body mass index, diastolic BP, eGFR, Beck depression inventory score, and PSQI global score ($P_{trend}<0.05$) (Table 1). Baseline median (IQR) PSQI global score in 1601 patients with CKD was 4 (3–7). More than one-third of patients with CKD (N=588 [37%]) had poor sleep quality defined as PSQI global score ≥6. Compared with patients with PSQI global score ≤5, those with PSQI global score ≥6 had significantly lower prevalence of male sex, lower levels of urinary albumin excretion, higher Beck depression inventory scores, higher prevalence of use of hypnotics, and shorter sleep duration ($P<0.05$) (Table 2). Baseline sleep duration and PSQI global score were moderately correlated with those at 2 and 3.5 years after the study entry (sleep duration [hour], Pearson's *r* 0.65 and

Table 1. Baseline sleep duration and clinical characteristics of 1601 patients

Characteristic	Sleep Duration (h)				
	≤5.0	5.1–6.0	6.1–7.0	7.1–8.0	>8.0
Number	152	300	541	420	188
Sleep duration, h	4.7±0.7	5.9±0.2	6.9±0.2	7.8±0.2	9.2±0.7
Age, yr	60 (52–66)	57 (47–66)	60 (51–68)	63 (57–70)	68 (61–72)
Men, *N* (%)	96 (63)	179 (60)	341 (63)	291 (69)	124 (66)
Smoking status, *N* (%)					
Nonsmokers	79 (52)	174 (58)	301 (56)	197 (47)	102 (54)
Past smokers	39 (26)	72 (24)	158 (29)	158 (38)	54 (29)
Current smokers	34 (22)	54 (18)	82 (15)	65 (15)	32 (17)
Diabetes, *N* (%)	55 (36)	114 (38)	164 (30)	150 (36)	75 (40)
Cardiovascular disease, *N* (%)	27 (18)	55 (18)	100 (18)	99 (24)	49 (26)
Body mass index, kg/m^2	24.4±4.2	23.5±4.2	23.4±3.7	23.5±3.4	23.0±3.7
Systolic BP, mm Hg	131±20	131±18	132±19	131±17	132±17
Diastolic BP, mm Hg	77±12	77±11	78±12	77±11	75±11
Serum creatinine, mg/dl	1.7 (1.3–2.4)	1.7 (1.3–2.4)	1.8 (1.4–2.5)	1.9 (1.5–2.6)	2.0 (1.5–2.7)
eGFR, ml/min per 1.73 m^2	33 (21–40)	32 (21–40)	29 (20–37)	28 (19–37)	25 (17–34)
45–59, *N* (%)	18 (12)	40 (13)	56 (10)	28 (7)	12 (6)
30–44, *N* (%)	64 (42)	127 (42)	206 (38)	168 (40)	55 (29)
15–29, *N* (%)	49 (32)	107 (36)	224 (41)	166 (40)	89 (47)
10–14, *N* (%)	21 (14)	26 (9)	55 (10)	58 (14)	32 (17)
Urinary albumin excretion, g/gCr	0.46 (0.12–1.10)	0.44 (0.11–1.33)	0.54 (0.15–1.24)	0.47 (0.13–1.29)	0.39 (0.08–1.18)
C-reactive protein, mg/dl[a]	0.10 (0.04–0.21)	0.06 (0.04–0.19)	0.07 (0.04–0.20)	0.08 (0.04–0.18)	0.10 (0.04–0.21)
Medications, *N* (%)					
RAS blockade	128 (84)	243 (81)	449 (83)	351 (84)	153 (81)
Hypnotics					
None	116 (76)	251 (84)	480 (89)	357 (85)	158 (84)
≤2 times/wk	13 (9)	18 (6)	23 (4)	15 (4)	6 (3)
≥3 times/wk	23 (15)	31 (10)	38 (7)	48 (11)	24 (13)
Beck depression inventory score	11 (6–18)	8 (5–13)	6 (3–11)	6 (3–11)	7 (4–12)
≥11, *N* (%)	82 (54)	112 (37)	155 (29)	114 (27)	61 (32)
PSQI global score	10 (8–13)	6 (5–9)	4 (3–6)	3 (2–5)	3 (2–4)
≥6, *N* (%)	140 (92)	185 (62)	164 (30)	70 (17)	29 (15)
Sleep duration					
At 2 yr[b], h	5.4±1.3	6.3±0.8	6.8±0.9	7.6±1.0	8.4±1.3
At 3.5 yr[c]	5.4±1.2	6.2±0.9	6.9±0.9	7.6±1.3	8.4±1.3

Data presented as mean±SD or median (interquartile range), unless otherwise specified. Cr, creatinine; RAS, renin angiotensin system; PSQI, Pittsburgh Sleep Quality Index.
[a]*n*=113, 232, 415, 314, and 149 for patients with ≤5.0, 5.1–6.0, 6.1–7.0, 7.1–8.0, and >8.0 h baseline sleep duration, respectively.
[b]*n*=101, 201, 387, 307, and 126 for patients with ≤5.0, 5.1–6.0, 6.1–7.0, 7.1–8.0, and >8.0 h baseline sleep duration, respectively.
[c]*n*=64, 153, 275, 188, and 82 for patients with ≤5.0, 5.1–6.0, 6.1–7.0, 7.1–8.0, and >8.0 h baseline sleep duration, respectively.

0.62, respectively; PSQI global score, Kendall's τ 0.53 and 0.52, respectively), suggesting that their baseline values reflected their values during the follow-up period.

During a median of 4.0 (interquartile range, 2.6–4.3) years of the observational period, 282 (18%) of 1601 patients progressed to ESKD. Incidence rates of ESKD for patients with ≤5.0, 5.1–6.0, 6.1–7.0, 7.1–8.0, and ≥8.0 hours of sleep duration were 0.057, 0.041, 0.043, 0.058, and 0.073 per person-year, respectively (Table 3). In model 1, which was adjusted for age and sex, sleep duration ≥8.0 hours was significantly associated with ESKD. Its significant association was still persistent even after multivariable adjustments (models 2–4). In contrast, ≤5.0 hours of sleep duration was associated with ESKD only after adjusting for eGFR and urinary albumin excretion. NRI analyses showed that the addition of sleep duration significantly improved prediction for all models. For sleep disorders, 239 (15%) patients received hypnotics during 1 month before the baseline visit. Use of hypnotics did not affect the association between sleep duration and incidence of ESKD, or was their use associated with incidence of ESKD (adjusted hazard ratio [95% confidence interval] for use of hypnotics in model 4: none, 1.00 [reference]; 1–2 times per week, 0.72 [0.29 to 1.78]; ≥3 times per week, 1.05 [0.71 to 1.56]).

Regarding PSQI global score, incidence of ESKD was 0.049 and 0.055 per person-year in patients with PSQI≤5 and ≥6, respectively (Table 4). Incidence of ESKD was comparable between patients with PSQI global score ≤5 and ≥6 after adjusting for age and sex. As with sleep duration, PSQI global score was significantly associated with incidence of ESKD after additionally adjusting for eGFR and urinary albumin excretion. Even in a fully adjusted model (model 4), PSQI global score was

Table 2. Baseline PSQI global score and clinical characteristics of 1601 patients

Characteristic	PSQI Global Score	
	0–5	6–19
Number	1013	588
PSQI global score	3 (2–4)	8 (7–10)
Age, yr	61 (54–68)	62 (53–69)
Men, *N* (%)	681 (67)	350 (60)
Smoking status, *N* (%)		
Nonsmokers	553 (55)	300 (51)
Past smokers	308 (30)	173 (29)
Current smokers	152 (15)	115 (20)
Diabetes, *N* (%)	342 (34)	216 (37)
Cardiovascular disease, *N* (%)	206 (20)	124 (21)
Body mass index, kg/m^2	23.5±3.6	23.5±4.1
Systolic BP, mm Hg	132±18	132±18
Diastolic BP, mm Hg	77±12	76±11
Serum creatinine, mg/dl	1.8 (1.4–2.5)	1.8 (1.4–2.5)
eGFR, ml/min per 1.73 m^2	29 (20–38)	29 (20–39)
45–59, *N* (%)	101 (10)	53 (9)
30–44, *N* (%)	389 (38)	231 (39)
15–29, *N* (%)	403 (40)	232 (39)
10–14, *N* (%)	120 (12)	72 (12)
Urinary albumin excretion, g/gCr	0.53 (0.15–1.30)	0.41 (0.09–1.18)
C-reactive protein, mg/dl[a]	0.08 (0.04–0.19)	0.09 (0.04–0.20)
Medications, *N* (%)		
RAS blockade	832 (82)	492 (84)
Hypnotics		
None	975 (96)	387 (66)
≤2 times/wk	17 (2)	58 (10)
≥3 times/wk	21 (2)	143 (24)
Beck depression inventory score	5 (3–10)	10 (6–17)
≥11, *N* (%)	236 (23)	288 (49)
Sleep duration, h	7.4±1.0	6.0±1.3
PSQI global score at 2 yr[b]	3 (2–5)	7 (5–10)
≥6, *N* (%)	114 (17)	242 (73)
PSQI global score at 3.5 yr[c]	4 (2–5)	8 (5–10)
≥6, *N* (%)	91 (21)	157 (70)

Data presented as mean±SD or median (interquartile range), unless otherwise specified. PSQI, Pittsburgh Sleep Quality Index; Cr, creatinine; RAS, renin angiotensin system.
[a]*n*=762 and 461 for patients with 0–5 and ≥6 baseline PSQI global score, respectively.
[b]*n*=654 and 233 for patients with 0–5 and ≥6 baseline PSQI global score, respectively.
[c]*n*=440 and 225 for patients with 0–5 and ≥6 baseline PSQI global score, respectively.

significantly associated with incidence of ESKD. Although PSQI global score was identified as a significant predictor of incidence of ESKD, NRI analyses revealed no significant improvement of prediction by adding PSQI global score.

Effect modifications between the main exposures and the baseline variables with a significant difference between included and excluded patients, including age, sex, history of diabetes and cardiovascular disease, and use of hypnotics, were assessed in fully adjusted models, but no obvious effect modification was observed (footnotes of Tables 3 and 4).

A potential confounding effect due to inflammation was assessed by including the baseline serum level of C-reactive protein in multivariable-adjusted models in 1223 (76%) patients (Supplemental Tables 2 and 3). Even after adjusting for C-reactive protein, similar associations were observed in sleep duration and PSQI global score, although sleep duration ≥8.0 hours was not significantly associated.

Discussion

This cohort study, including 1601 patients with CKD, revealed that short and long sleep duration (≤5.0 and >8.0 hours) and poor sleep quality (PSQI global score ≥6) were significantly associated with higher incidence of ESKD. These results suggest that a quick assessment of self-reported sleep duration and sleep quality might be an easy and effective way to identify patients with CKD at high risk of ESKD. Advantages of this study included its prospective cohort design, the clinically relevant hard outcome of ESKD, and its large sample size (*n*=1601), which enabled us to perform statistically meaningful analyses to identify predictors of ESKD.

Although several cohort studies have reported that shorter sleep duration was associated with incidence of proteinuria (16) and GFR decline (17,18), mainly in subjects with normal kidney function, few studies have reported an association between sleep duration and incidence of ESKD. The Chronic Renal Insufficiency Cohort (CRIC) study, a cohort study of patients with CKD in the United States, measured objective sleep duration using wrist actigraphy in 431 patients and identified sleep fragmentation, an index of sleep quality, as associated with the incidence of ESKD during a median 5.2 years of follow-up (19). The CRIC study reported conflicting results of an association between short sleep duration and kidney function; shorter sleep duration was associated with eGFR decline, but not with incidence of ESKD. This study clarified that shorter sleep duration predicted incidence of ESKD in a much larger cohort (*n*=1601), confirming the association of shorter sleep duration with kidney survival. The findings of this and previous studies suggest that modification of sleep duration may lead to a better prognosis of kidney function. One potential method for modifying sleep duration may be the use of hypnotics. However, this study showed no significant association between use of hypnotics and incidence of ESKD (Table 3). A large number of cohort studies have reported users of hypnotics to be at risk of early death (41,42), suggesting that hypnotics should be prescribed with great caution in patients with CKD with short sleep duration. The clinical effects of modification of sleep duration on kidney function need to be examined in future studies.

In addition to shorter sleep duration (≤5 hours), this study identified longer sleep duration (>8.0 hours) as a significant predictor of ESKD, indicating a U-shaped association between sleep duration and incidence of ESKD (Table 3). A similar U-shaped association between sleep duration and cardiovascular and all-cause mortality was observed in many large cohort studies, identifying short (<6- or 7-hour) and long (>8- or 9-hour) sleep

Table 3. Sleep duration and incidence of ESKD in 1601 patients with CKD

	Sleep Duration (h)					NRI (95% CI) of Sleep Duration
	≤5.0	5.1–6.0	6.1–7.0	7.1–8.0	≥8.0	
Number	152	300	541	420	188	
Incidence of ESKD, *N* (%)	29 (19)	43 (14)	82 (15)	83 (20)	45 (24)	
Incidence rate (per person-year)	0.057	0.041	0.043	0.058	0.073	
Adjusted hazard ratio (95% CI)						
Model 1	1.29 (0.85 to 1.97)	0.98 (0.68 to 1.42)	1.00 (reference)	1.31 (0.96 to 1.78)	1.70 (1.17 to 2.47)[a]	0.10 (0.02 to 0.18)[a]
Model 2	2.21 (1.44 to 3.39)[a]	0.98 (0.67 to 1.43)	1.00 (reference)	1.20 (0.88 to 1.63)	1.54 (1.06 to 2.24)[a]	0.15 (0.02 to 0.28)[a]
Model 3	2.27 (1.48 to 3.50)[a]	1.01 (0.70 to 1.48)	1.00 (reference)	1.24 (0.91 to 1.69)	1.56 (1.07 to 2.27)[a]	0.15 (0.05 to 0.26)[a]
Model 4[b,c]	2.05 (1.31 to 3.21)[a]	0.98 (0.67 to 1.44)	1.00 (reference)	1.22 (0.89 to 1.66)	1.48 (1.01 to 2.16)[a]	0.12 (0.02 to 0.26)[a]

Model 1 adjusted for age (yr) and sex. Model 2 adjusted for the covariates in model 1, eGFR (ml/min per 1.73 m^2), and urinary albumin excretion (log g/gCr). Model 3 adjusted for the covariates in model 2, smoking status (non-, past, or current smoker), body mass index (kg/m^2), history of diabetes mellitus and cardiovascular disease, systolic BP (mm Hg), and blockade of renin-angiotensin system. Model 4 adjusted for the covariates in model 3 and Beck depression inventory score (≤10 and >10) and use of hypnotics (none, 1–2 times, or ≥3 times per wk). NRI, net reclassification index; 95% CI, 95% confidence interval; Cr, creatinine.

[a]$P<0.05$.

[b]P for interaction of sleep duration with age, sex, history of diabetes and cardiovascular disease, and use of hypnotics=0.79, 0.47, 0.67, 0.49, and 0.78, respectively.

[c]Multivariable-adjusted hazard ratio (95% CI) for none, 1–2 times, and ≥3 times per week use of hypnotics: 1.00 (reference), 0.72 (0.29 to 1.78), and 1.05 (0.71 to 1.56), respectively.

durations as risk factors of cardiovascular (13) and all-cause mortality (15,43,44). Interestingly, some systematic reviews have suggested that the elderly population (≥60 years) (15,43) and the Asian population (15,43,44) are vulnerable to the detrimental effects of long sleep duration. The reasons that the previous studies (17,18) did not identify longer sleep duration to be associated with GFR decline might be due to the different baseline characteristics of the participants. Further studies are essential to assess the clinical effect of long sleep duration on kidney function in patients with CKD.

Poor sleep quality, a potential predictor of mortality in patients with ESKD (45), is common in patients with CKD (26,27); however, its clinical effect has not been elucidated. This study measured sleep quality using PSQI, the most widely used screening tool for poor sleep quality (30), with advantages including sound reliability, validity, responsiveness, and interpretability (31). Several cross-sectional studies of patients with CKD have suggested that poor sleep quality (PSQI global index ≥6) might have some cardiovascular effects, such as a "nondipper" pattern of ambulatory BP monitoring (46) and left ventricular hypertrophy (47). However, few cohort studies have assessed the prognostic power of the PSQI. This study identified poor sleep quality, defined as PSQI global score ≥6, as a significant predictor of ESKD, a hard outcome for patients

Table 4. PSQI global score and incidence of ESKD in 1601 patients with CKD

	PSQI Global Score		NRI (95% CI) of PSQI (≤5 versus ≥6)
	≤5	≥6	
Number	1013	588	
Incidence of ESKD, *N* (%)	172 (17)	110 (19)	
Incidence rate (per person-year)	0.049	0.055	
Adjusted hazard ratio (95% CI)			
Model 1	1.00 (reference)	1.19 (0.93 to 1.51)	0.02 (−0.04 to 0.09)
Model 2	1.00 (reference)	1.39 (1.09 to 1.77)[a]	0.02 (−0.34 to 0.09)
Model 3	1.00 (reference)	1.40 (1.09 to 1.79)[a]	0.03 (−0.12 to 0.11)
Model 4[b]	1.00 (reference)	1.33 (1.03 to 1.71)[a]	0.03 (−0.21 to 0.10)

Model 1 adjusted for age (yr) and sex. Model 2 adjusted for the covariates in model 1, eGFR (ml/min per 1.73 m^2), and urinary albumin excretion (log g/gCr). Model 3 adjusted for the covariates in model 2, smoking status (non-, past, or current smoker), body mass index (kg/m^2), history of diabetes mellitus and cardiovascular disease, systolic BP (mm Hg), and blockade of renin angiotensin system. Model 4 adjusted for the covariates in model 3 and Beck depression inventory (≤10 versus >10). PSQI, Pittsburgh Sleep Quality Index; NRI, net reclassification index; 95% CI, 95% confidence interval; Cr, creatinine.

[a]$P<0.05$.

[b]P for interaction of PSQI global score with age, sex, history of diabetes, and cardiovascular disease=0.20, 0.14, 0.71, and 0.52, respectively.

with CKD (Table 4). However, their causal relationship remains unknown. Because the PSQI questionnaire covers a broad range of indicators relevant to sleep quality (Supplemental Appendix) (29), associations might depend on the underlying diseases, including obstructive sleep apnea, restless leg syndrome, insomnia, and others. To evaluate the clinical effect of sleep quality on kidney survival, associations should be assessed in subgroups of the underlying diseases in greater detail.

This study had several limitations. First, the frequency of occurrence for "other" sleep disturbance (PSQI question 5j) was not included in the CKD-JAC study, accidentally. Thus, 38 patients whose PSQI global scores could not be calculated were excluded from this study. The exclusion of this very small number of patients was unlikely to have led to biased results. Second, many patients were excluded due to missing data (n=1241 [44%]), which might have led to biased results. Because the baseline variables with significant differences between the included and excluded patients had no obvious effect modifications with sleep duration and PSQI global score, exclusion of these patients with missing data probably had little effect on associations of sleep duration and PSQI global score with incidence of ESKD. Third, self-reported sleep duration might be biased, despite confirmation by previous studies that self-reported sleep duration was correlated moderately with the results of polysomnography (48,49) and actigraphy (50), suggesting that self-reported sleep duration was a clinical surrogate of sleep duration.

In conclusion, this cohort study, including 1601 patients with CKD, identified poor sleep quality (defined as PSQI global index ≥6) as a predictor of ESKD and revealed that both short (<5 hours) and long (≥8 hours) sleep duration were associated with ESKD incidence. Sleep duration and sleep quality may be easily measured and useful tools for identifying patients at high risk of ESKD.

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Disclosures

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Supplementary Appendix. Pittsburgh sleep quality index (PSQI)

From Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193-213.

Instructions:

The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?
   USUAL BED TIME (_____)
2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?
   NUMBER OF MINUTES (_____)
3. During the past month, when have you usually gotten up in the morning?
   USUAL GETTING UP TIME (_____)
4. During the past month, how many hours of *actual sleep* did you get at night? (This may be different than the number of hours you spend in bed.)
   HOURS OF SLEEP PER NIGHT (_____)

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you...
   (a) Cannot get to sleep within 30 minutes

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

   (b) Wake up in the middle of the night or early morning

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

   (c) Have to get up to use the bathroom

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

   (d) Cannot breathe comfortably

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

(e) Cough or snore loudly

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

(f) Feel too cold

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

(g) Feel too hot

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

(h) Had bad dreams

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

(i) Have pain

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

(j) Other reason(s), please describe (_____)

Not during the past month (__)*	Less than once a week (__)*	Once or twice a week (__)*	Three or more times a week (__)*

6. During the past month, how would you rate your sleep quality overall?

(__) Very good

(__) Fairly good

(__) Fairly bad

(__) Very bad

7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month (__)	Less than once a week (__)	Once or twice a week (__)	Three or more times a week (__)

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

(__) No problem at all

(__) Only a very slight problem

(__) Somewhat of a problem

(__) A very big problem

*Not available in CKD-JAC study

Scoring instructions for PSQI

The Pittsburgh Sleep Quality Index (PSQI) contains 19 self-rated questions and 5 questions rated by the bed partner or roommate (if one is available). Only self-rated questions are included in the scoring. The 19 self-rated items are combined to form seven "component" scores, each of which has a range of 0–3 points. In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty. The seven component scores are then added to yield one "global" score, with a range of 0–21 points,

"0" indicating no difficulty and "21" indicating severe difficulties in all areas. Scoring proceeds as follows:

Component 1: subjective sleep quality

Examine question #6, and assign scores as follows:

Response	Component 1 sore
"Very good"	0
"Fairly good"	1
"Fairly bad"	2
"Very bad"	3

Component 2: Sleep latency

1. Examine question #2, and assign scores as follows:

Response	Score
≤15 minutes	0
16–30 minutes	1
31–60 minutes	2
>60 minutes	3

2. Examine question #5a, and assign scores as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

3. Add #2 score and #5a score as follows:

Sum of #2 and #5a	Component 2 score
0	0
1–2	1
3–4	2
5–6	3

Component 3: sleep duration

Examine question #4, and assign scores as follows:

Response	Component 3 score
>7 hours	0
6–7 hours	1
5–6 hours	2
<5 hours	3

Component 4: Habitual sleep efficiency

1. Calculate the number of hours spent in bed:
   Getting up time (question #3) - Bedtime (question #1)
2. Calculate habitual sleep efficiency (%) as follows:
   Number of hours slept (question #4) / Number of hours in bed X 100
3. Assign component 4 scores as follows:

Habitual sleep efficiency (%)	Component 4 score
>85%	0
75–84%	1
65–74%	2
<65%	3

Component 5: Sleep disturbance[†]

1. Examine questions #5b–5j, and assign scores for *each* question as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

2. Add the scores of questions #5b–5j
3. Assign component 5 score as follows:

Sum of #5b–5j	Component 5 score
0	0

1–9	1
10–18	2
19–27	3

Component 6: Use of sleeping medication

Examine question #7 and assign scores as follows:

Response	Component 6 score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Component 7: Day time dysfunction

1. Examine question #8, and assign scores as follows:

Response	Score
Never	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

2. Examine question #9, and assign scores as follows:

Response	Score
No problem as all	0
Only a very slight problem	1
Somewhat of a problem	2
A very big problem	3

3. Add the scores for questions #8 and #9
4. Assign component 7 score as follows:

Sum of #8 and #9	Component 7 score
0	0
1–2	1
3–4	2
5–6	3

Global PSQI score: sum of component 1–7

Supplementary Table 1. Baseline clinical characteristics of included and excluded patients with missing data.

	Included patients	Excluded patients	Missing (N [%])
Number	1601	1241	
Baseline characteristics			
Age (year)*	61 (54–69)	64 (55–70)	0 (0)
Male (N [%])*	1031 (64)	734 (59)	0 (0)
Smoking status (N [%])*			421 (15)
Non-smokers	853 (53)	488 (60)	
Past smokers	481 (30)	193 (24)	
Current smokers	267 (17)	139 (17)	
Diabetes (N [%])*	558 (35)	507 (41)	0 (0)
Cardiovascular disease (N [%])*	333 (21)	313 (25)	0 (0)
Body mass index (kg/m^2)	23.5±3.8	23.6±3.9	279 (10)
Systolic blood pressure (mmHg)	132±18	132±19	37 (1)
Diastolic blood pressure (mmHg)*	77±11	76±12	40 (1)
Serum creatinine (mg/dL)	1.8 (1.4–2.5)	1.8 (1.4–2.5)	0 (0)
eGFR (mL/min/1.73m^2)	29 (20–38)	29 (20–38)	0 (0)
45–59 (N [%])	154 (10)	125 (10)	
30–44	620 (39)	455 (37)	
15–29	635 (40)	509 (41)	
10–14	192 (12)	152 (12)	
Urinary albumin excretion (g/gCr)	0.48 (0.12–1.26)	0.48 (0.01–1.32)	273 (10)
C-reactive protein (mg/dL)*	0.1 (0.0–0.2)	0.1 (0.0–0.2)	659 (23)
Medications (N [%])			
RAS blockade	1324 (83)	1010 (81)	0 (0)
Hypnotics*, none	1362 (85)	666 (81.1)	413 (15)
≤2 times/week	75 (2)	44 (2)	
≥3 times/week	164 (10)	118 (14)	
Beck depression inventory score	7 (4–12)	7 (3–13)	383 (13)
≥11 (N [%])	524 (33)	299 (35)	
Sleep duration (hour)	7.0±1.3	6.9±1.3	424 (15)
PSQI global score	4 (3–7)	5 (3–7)	875 (31)

≥ 6 (N [%])	588 (37)	148 (40)	
Follow-up period and ESKD			
Follow-up period (year)	4.0 (2.6–4.3)	3.9 (2.3–4.3)	0 (0)
ESKD (N [%])	282 (18)	241 (19)	0 (0)
Incidence rate (per person-year)	0.051	0.059	0 (0)

Mean±standard deviation; Median (interquartile range)

Cr, creatinine; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PSQI, Pittsburgh sleep quality index; RAS, renin-angiotensin system

*P < 0.05

Supplementary Table 2. Sleep duration and incidence of ESKD in 1223 patients with baseline C-reactive protein available.

	Sleep duration (hour)				
	≤5.0	5.1–6.0	6.1–7.0	7.1–8.0	≥8.0
Number	113	232	415	314	149
Incidence of ESKD (N [%])	23 (20)	36 (16)	62 (15)	58 (18)	35 (23)
Incidence rate (per person-year)	0.061	0.044	0.043	0.054	0.072
Adjusted hazard ratio (95% CI)					
Model 1	1.39 (0.86, 2.24)	1.07 (0.71, 1.61)	1.00 (reference)	1.23 (0.85, 1.76)	1.71 (1.12, 2.60)
Model 2	2.04 (1.26, 3.31)*	1.18 (0.77, 1.80)	1.00 (reference)	1.06 (0.74, 1.52)	1.49 (0.97, 2.27)
Model 3	2.00 (1.23, 3.36)*	1.19 (0.78, 1.82)	1.00 (reference)	1.07 (0.75, 1.55)	1.46 (0.95, 2.24)
Model 4	1.84 (1.11, 3.07)*	1.15 (0.75, 1.76)	1.00 (reference)	1.07 (0.74, 1.54)	1.37 (0.88, 2.12)
Model 5	1.82 (1.09, 3.04)*	1.15 (0.75, 1.77)	1.00 (reference)	1.08 (0.75, 1.55)	1.37 (0.88, 2.12)

CI, confidence interval; ESKD, end-stage kidney disease

*P<0.05

Model 1, Adjusted for age (year) and gender.

Model 2, Adjusted for the covariates in model 1, eGFR (ml/min/1.73 m^2) and urinary albumin excretion (Log g/gCr).

Model 3, Adjusted for the covariates in model 2, smoking status (non-, past, and current smokers), body mass index (kg/m^2), history of diabetes mellitus and cardiovascular disease, systolic blood pressure (mmHg), and blockade of renin-angiotensin system

Model 4, Adjusted for the covariates in model 3 and Beck depression inventory score (≤10 and >10) and use of hypnotics (none, 1–2 times, or ≥3 times per week).

Model 5, Adjusted for the covariates in model 4 and C-reactive protein (Log [mg/dl + 0.01])

Supplementary Table 3. Sleep duration and incidence of ESKD in 1223 patients with baseline C-reactive protein available.

	PSQI global score	
	≤5	≥6
Number	762	461
Incidence of ESKD (N [%])	126 (17)	88 (19)
Incidence rate (per person-year)	0.047	0.057
Adjusted hazard ratio (95% CI)		
Model 1	1.00 (reference)	1.24 (0.95, 1.63)
Model 2	1.00 (reference)	1.56 (1.18, 2.06)*
Model 3	1.00 (reference)	1.56 (1.17, 2.08)*
Model 4	1.00 (reference)	1.47 (1.10, 1.97)*
Model 5	1.00 (reference)	1.47 (1.09, 1.97)*

CI, confidence interval; ESKD, end-stage kidney disease; PSQI, Pittsburgh sleep quality index

*P < 0.05

Model 1, Adjusted for age (year) and gender.

Model 2, Adjusted for the covariates in model 1, eGFR (ml/min/1.73 m^2) and urinary albumin excretion (Log g/gCr).

Model 3, Adjusted for the covariates in model 2, smoking status (non-, past, and current smokers), body mass index (kg/m^2), history of diabetes mellitus and cardiovascular disease, systolic blood pressure (mmHg), and blockade of renin-angiotensin system

Model 4, Adjusted for the covariates in model 3 and Beck depression inventory score (≤10 and >10).

Model 5, Adjusted for the covariates in model 4 and C-reactive protein (Log [mg/dl + 0.01])