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Association of Sleep-Related Problems With CKD in the United States, 2005-2008

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Background: Sleep-related problems, which have been associated with poor health outcomes, have not been investigated thoroughly in people with chronic kidney disease (CKD). We examined the prevalence of a variety of sleep-related problems in persons with and without CKD.

Study Design: National cross-sectional survey (National Health and Nutrition Examination Survey 2005-2008).

Setting & Participants: Community-based survey of 9,110 noninstitutionalized US civilian residents 20 years or older.

Predictor: CKD, defined as estimated glomerular filtration rate (eGFR) of 15-59 mL/min/1.73 m² (stages 3 and 4) or eGFR \geq 60 mL/min/1.73 m² and albumin-creatinine ratio \geq 30 mg/g (stages 1 and 2).

Outcome: Sleep quality, defined using self-report in a multi-item sleep questionnaire including items from previously validated instruments.

Measurements: Albuminuria and eGFR assessed from urine and blood samples; sleep, demographics, and comorbid conditions assessed using a standardized questionnaire.

Results: Inadequate sleep (\leq 6 hours per night) differed by CKD severity (37.4%, 43.0%, and 30.9% for no CKD, CKD stages 1 and 2, and CKD stages 3 and 4, respectively; $P = 0.003$). Frequent sleeping pill use (8.4%, 9.9%, and 16.6%), leg symptoms (39.2%, 48.0%, and 50.9%), and nocturia (20.9%, 35.2%, and 43.6%; $P < 0.001$ for all) also differed by CKD severity. After adjustment for age, sex, race/ethnicity, obesity, diabetes, and cardiovascular disease, the prevalence of these sleep-related problems remained higher in people with CKD stages 1 and 2 relative to no CKD. Most other measures of sleep quality, disorder, and functional outcomes did not differ by CKD.

Limitations: Inability to establish causality and possible unmeasured confounding.

Conclusion: Providers should be aware of early sleep-related CKD manifestations, including inadequate sleep, leg symptoms, and nocturia, and of the high rate of reported sleep medication use in this population.

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INDEX WORDS: Chronic kidney disease; renal function; sleep duration; leg symptoms; sleep aids.

The prevalence of sleep-related problems and disorders is high in patients with end-stage renal disease (ESRD),^{1,2} particularly sleep apnea,³⁻⁸ restless legs syndrome,^{9,10} and overall poor sleep quality.^{11,12} However, relatively few studies have examined sleep problems in the considerably larger group of patients with pre-ESRD chronic kidney disease (CKD). A high prevalence of self-reported and measured sleep disorder has

been reported in patients with moderate to severe¹³⁻¹⁵ or recently diagnosed¹⁶ CKD; similar results have been reported in pediatric patients with CKD.¹⁷⁻¹⁹ Sleep-related problems have been associated with increased risk of mortality in the general population²⁰ and specifically in patients with CKD and ESRD.^{13,21}

CKD is a common disease, with a prevalence in US adults of up to 13%.²² However, <10% of

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selves from consideration of this manuscript, the peer-review and decision-making processes were handled entirely by a Co-Editor (James S. Kaufman, MD, Boston University) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Editorial Policies section of the AJKD website.

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patients with early CKD are aware of their disease.²³ CKD is fairly silent in its early stages and in many cases is treated only when symptoms manifest. Previous studies included persons with diagnosed and/or treated CKD who may have had more severe symptoms leading to diagnosis and treatment. Whether sleep problems in patients with CKD are related at least in part to these symptoms cannot be excluded in such studies. Additionally, most previous studies do not provide direct comparison groups for the assessment of an independent effect of CKD on sleep. Such comparisons are especially important given that sleep-related problems are common in the general US population²⁴ and many sleep problems increase with age,²⁵ as does the risk of developing CKD.

Our study describes and compares the prevalence of a comprehensive set of self-reported sleep-related problems in noninstitutionalized US adults 20 years or older across the spectrum of pre-ESRD CKD (no, mild, and moderate to severe CKD) using data from the National Health and Nutrition Examination Survey (NHANES). We also examined whether differences in symptom prevalence persisted after adjustment for likely confounders.

METHODS

Study Design

The NHANES is conducted by the National Center for Health Statistics of the US Centers for Disease Control and Prevention and consists of a standardized in-home interview followed by physical examination and blood and urine collection at a mobile examination center. NHANES is a representative sample of noninstitutionalized US civilian residents.²⁶ This analysis was limited to 9,110 NHANES 2005-2008 participants who met the inclusion criteria: 20 years or older, respondent to the sleep questionnaire, and with available serum creatinine and urine albumin and creatinine measurements. Those who were pregnant or had an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m² (n = 1,370) were excluded. All participants gave written informed consent. The protocol was approved by the National Center for Health Statistics Research Ethics Review Board.

Measurements

As part of the home interview portion of NHANES 2005-2008, interviewers administered a questionnaire²⁷ pertaining to sleep habits and sleep-related problems (Table 1), including items from 2 previously validated instruments: the Sleep Heart Health Study Sleep Habits Questionnaire²⁸ and the Functional Outcomes of Sleep Questionnaire,^{29,30} through a computer-assisted personal interviewing system. Nocturia was assessed during the same home interview session using a separate questionnaire. During the interviews, data were collected regarding self-reported demographics (age, sex, and race/ethnicity), socioeconomic status and health care access (education, insurance, and income), and health status and conditions (self-reported diagnosis of diabetes, hypertension, and cardiovascular disease [CVD]; self-reported smoking; self-rating of current

health [health status]; and depressive symptoms from the Patient Health Questionnaire 9,³¹ a validated clinical depression screening tool). Prescription medications were recorded by the interviewer from the bottles provided by the participant, and sleep aids, diuretics, and psychotropic medications were extracted from these data.

Serum creatinine was measured using the modified kinetic method of Jaffé. Urine albumin and creatinine were measured using frozen spot urine specimens with a solid-phase fluorescence immunoassay and modified Jaffé kinetic method in the same laboratory, respectively. Height, weight, and blood pressure (at least 3 auscultatory measurements) were measured during the examination.²⁶

Definitions

Sleep

Total hours of sleep were dichotomized by 6 or fewer or 7 or more hours per night according to National Sleep Foundation guidelines for adult sleep duration³²; 9 hours or more also was examined separately as above the range for optimal sleep (7-8 hours).^{33,34} Sleep-onset latency was categorized as 30 or fewer or 30 or more minutes in primary analyses; 5 minutes or less also was examined as an indicator of severe sleep deprivation.³⁵ Snoring and stopping breathing were considered habitual if reported at least once per week. Sleep problems were considered frequent if reported "often" or more (at least 5 times/mo). Nocturia was defined as reported urination 2 times or more per night. Functional Outcomes of Sleep Questionnaire items^{29,30} were summarized using mean scores.

Chronic Kidney Disease

CKD was defined as either decreased kidney function or elevated albuminuria. eGFR was calculated according to the isotope-dilution mass spectrometry-traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.³⁶ Serum creatinine levels were corrected for different analyzers in different years.^{37,38} Albuminuria was defined as a single urinary albumin-creatinine ratio ≥ 30 mg/g (microalbuminuria). Definitions of CKD stages³⁹ were modified as no CKD, eGFR ≥ 60 mL/min/1.73 m² and no albuminuria; stages 1 and 2 (mild CKD), eGFR ≥ 60 mL/min/1.73 m² and the presence of albuminuria; and stages 3 and 4 (moderate to severe CKD), eGFR of 15-59 mL/min/1.73 m².

Other Definitions

Self-reported diseases were defined as answers of yes to the question, "Have you ever been told by a doctor or other health professional that you have [disease or condition]?" Self-reported CVD was defined as an answer of yes to any of coronary artery disease, angina, myocardial infarction, stroke, or congestive heart failure. Hypertension was defined using self-report or measured systolic or diastolic blood pressure ≥ 140 or ≥ 90 mm Hg, respectively. Obesity was defined as a measured body mass index ≥ 30 kg/m². Depressive symptoms were defined as at least 5 positive responses on the Patient Health Questionnaire-9, including the items "little or no interest or pleasure in doing things" and "feeling down/depressed, or hopeless," along with at least some reported functional impairment.

Statistical Methods

Selected participant characteristics were compared across CKD categories using χ^2 and analysis of variance for categorical and continuous variables, respectively. Excluded participants also were compared with those included in the study by these characteristics. Unadjusted and adjusted prevalences of

Table 1. Sleep Survey Items, NHANES 2005-2008

Measure	Item	Possible Responses
Total hours of sleep	"How much sleep do you usually get at night on weekdays or workdays?"	Any no. of h, with upper limit of 12
Sleep onset	"How long does it usually take you to fall asleep at bedtime?"	Any no. of min, with upper limit of 60
Snoring	"In the past 12 months, how often did you snore while you were sleeping?"	Never, rarely (1-2 nights/wk), occasionally (3-4 nights/wk), frequently (≥ 5 nights/wk)
Apnea	"In the past 12 months, how often did you snort, gasp, or stop breathing while you were sleeping?"	Yes, no
Diagnosed trouble sleeping	"Have you ever been told by a doctor or other health professional that you have trouble sleeping?"	
Diagnosed sleep disorder	"Have you ever been told by a doctor or other health professional that you have a sleep disorder?"	Yes, no
	"What was the sleep disorder?"	Sleep apnea, insomnia, restless legs, other
Trouble falling asleep	"In the past month, how often have you had trouble falling asleep?"	
Waking up at night	"In the past month, how often did you wake up at night and have trouble getting back to sleep?"	
Waking too early	"In the past month, how often did you wake up too early in the morning and were unable to get back to sleep?"	
Daytime unrest	"In the past month, how often did you feel unrested during the day, no matter how many hours of sleep you had?"	
Daytime sleepiness	"In the past month, how often did you feel excessively or overly sleepy during the day?"	Never; rarely ($1 \times / \text{mo}$); sometimes ($2-4 \times / \text{mo}$); often ($5-15 \times / \text{mo}$); almost always ($16-30 \times / \text{mo}$)
Insufficient sleep	"In the past month, how often did you not get enough sleep?"	
Sleeping pill use	"In the past month, how often did you take sleeping pills or other medication to help you sleep?"	
Leg jerks	"In the past month, how often did you have leg jerks while trying to sleep?"	
Leg cramps	"In the past month, how often did you have leg cramps while trying to sleep?"	
Nocturia ^a	"During the past 30 days, how many times per night did you most typically get up to urinate, from the time you went to bed at night until the time you got up in the morning?"	0-4 or ≥ 5
Sleep-related difficulty with concentration ^b	Sleep-related difficulty with concentration ^b	
Sleep-related difficulty with memory ^b	"Do you have difficulty remembering things because you are sleepy or tired?"	
Sleep-related difficulty with eating ^b	"Do you have difficulty finishing a meal because you become sleepy or tired?"	
Sleep-related difficulty with hobby ^b	"Do you have difficulty working on a hobby, for example, sewing, collecting, gardening, because you are sleepy or tired?"	Do not do this activity for other reasons; no difficulty; yes, a little difficulty; yes, moderate difficulty; yes, extreme difficulty
Sleep-related difficulty with transportation ^b	"Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation?"	
Sleep-related difficulty with finances ^b	"Do you have difficulty taking care of financial affairs and doing paperwork (for example, paying bills or keeping financial records) because you are sleepy or tired?"	
Sleep-related difficulty with work ^b	"Do you have difficulty performing employed or volunteer work because you are sleepy or tired?"	
Sleep-related difficulty with telephone ^b	"Do you have difficulty maintaining a telephone conversation because you become sleepy or tired?"	

Abbreviation: NHANES, National Health and Nutrition Examination Survey.

Adapted from the NHANES sleep questionnaire.²⁷

^aFrom kidney and urological conditions survey.

^bFunctional Outcomes of Sleep Questionnaire²⁹ preface: "The purpose of this next set of questions is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. When the words 'sleepy' and 'tired' are used, it means the feeling that you can't keep your eyes open, your head is droopy, that you want to 'nod off' or that you feel the urge to take a nap. The words do not refer to the tired or fatigued feeling you may have after you have exercised."²⁷

sleep-related problems were calculated by CKD category, and variance of proportions was estimated using Taylor series linearization. Adjusted odds ratios, prevalence estimates, and *P* values were calculated using multivariable logistic regression and predictive margin estimation,⁴⁰ with adjustment for covariates that were chosen for both evidence of confounding and for parsimony. Sensitivity analyses with further covariates (depres-

sion, alcohol intake, and use of diuretics or psychotropics) and CKD defined by GFR estimated using the CKD-EPI (CKD Epidemiology Collaboration) equation⁴¹ also were performed. All analyses were performed using the *svy* commands in Stata, version 10.0 (www.stata.com), to account for study design weights, strata, and primary sampling units. Statistical significance was set at *P* < 0.05.

Table 2. Characteristics of 2005-2008 US Population Sample by CKD Status

Characteristic	Total (N = 9,110)	No CKD (n = 7,305)	CKD Stage 1 or 2 (n = 875)	CKD Stage 3 or 4 (n = 930)	P ^a
% of total	100	84.6 (83.1-85.9)	7.3 (6.6-8.0)	8.2 (7.1-9.4)	—
Demographics					
Age (y)	47.2 (46.3-48.0)	44.7 (44.0-45.4)	52.3 (50.8-53.7)	68.4 (66.5-70.4)	<0.001
Sex					<0.001
Men	49.8 (48.9-50.7)	51.3 (50.3-52.4)	45.2 (40.5-49.9)	38.4 (34.3-42.5)	
Women	50.2 (49.3-51.1)	48.7 (47.6-49.7)	54.8 (50.1-59.5)	61.6 (57.5-65.7)	
Race/ethnicity ^b					<0.001
Non-Hispanic white	71.7 (66.9-76.1)	71.1 (66.3-75.5)	62.4 (54.9-69.2)	86.1 (82.0-89.3)	
Non-Hispanic black	10.6 (8.2-13.5)	10.6 (8.2-13.6)	14.7 (11.5-18.6)	6.6 (4.6-9.4)	
Mexican-American	8.1 (6.4-10.2)	8.4 (6.6-10.6)	10.1 (8.1-12.6)	2.5 (1.6-3.8)	
Socioeconomic status					
Education					<0.001
<High school	18.8 (16.7-21.2)	17.7 (15.4-20.2)	27.5 (24.4-30.8)	23.1 (19.4-27.2)	
>High school	81.2 (78.9-83.3)	82.3 (79.8-84.6)	72.6 (69.2-75.6)	77.0 (72.8-80.6)	
Household income					<0.001
<\$20,000	15.1 (13.6-16.9)	13.6 (12.1-15.4)	22.9 (20.2-25.7)	24.2 (20.3-28.5)	
\$20-\$44,999	27.7 (25.3-30.3)	26.7 (24.2-29.4)	33.9 (29.7-38.4)	32.8 (29.2-36.7)	
\$45-\$74,999	24.2 (22.5-25.9)	24.5 (22.7-26.5)	20.7 (16.4-25.8)	23.4 (19.7-27.5)	
>\$75,000	33.0 (29.8-36.3)	35.1 (31.8-38.6)	22.5 (18.5-27.1)	19.6 (15.3-24.9)	
Insurance					<0.001
Not insured	18.8 (16.8-21.0)	20.3 (18.2-22.7)	16.7 (13.5-20.5)	5.2 (3.4-7.7)	
Insured	81.2 (79.0-83.2)	79.7 (77.3-81.8)	83.3 (79.5-86.5)	94.8 (92.3-96.5)	
Clinical status					
Smoking					0.001
Every day	19.9 (18.0-22.0)	20.7 (18.5-23.1)	22.7 (19.5-26.3)	9.4 (7.2-12.1)	
Sometimes/not at all	80.1 (78.0-82.0)	79.3 (76.9-81.5)	77.3 (73.7-80.5)	90.6 (87.8-92.8)	
Body mass index					<0.001
≥30 kg/m ²	33.8 (31.9-35.7)	32.5 (30.5-34.7)	45.1 (39.6-50.8)	36.6 (33.7-39.6)	
<30 kg/m ²	66.2 (64.3-68.1)	67.5 (65.3-69.5)	54.9 (49.2-60.5)	63.4 (60.4-66.3)	
Diabetes (self-reported)					<0.001
Yes	8.3 (7.4-9.2)	5.6 (4.9-6.5)	25.6 (22.0-29.5)	20.3 (16.7-24.5)	
No	91.7 (90.8-92.6)	94.4 (93.5-95.1)	74.5 (70.5-78.1)	79.7 (75.6-83.3)	
Hypertension ^c					<0.001
Yes	42.0 (40.1-44.0)	37.3 (35.1-39.5)	61.2 (57.6-64.7)	74.2 (70.4-77.6)	
No	58.0 (56.0-59.9)	62.7 (60.5-64.9)	38.8 (35.3-42.4)	25.9 (22.4-29.6)	
CVD (self-reported)					<0.001
Yes	8.5 (7.6-9.5)	5.8 (5.1-6.6)	15.2 (12.4-18.6)	30.4 (25.6-35.6)	
No	91.5 (90.5-92.4)	94.2 (93.4-94.9)	84.8 (81.4-87.6)	69.6 (64.4-74.4)	
Current health status (self-reported)					<0.001
Good/fair/poor	51.0 (48.6-53.4)	48.6 (46.0-51.1)	67.8 (63.3-72.0)	61.4 (57.0-65.6)	
Very good or excellent	49.0 (46.6-51.4)	51.4 (48.9-54.0)	32.2 (28.0-36.8)	38.6 (34.4-43.0)	
Depression					0.006
Symptomatic by PHQ-9	5.2 (4.5-6.0)	5.0 (4.3-5.8)	8.0 (5.8-10.9)	4.4 (3.1-6.2)	
Not symptomatic by PHQ-9	94.8 (94.0-95.5)	95.0 (94.2-95.7)	92.0 (89.1-94.2)	95.6 (93.8-96.9)	
No. of alcoholic drinks/wk	3.9 (3.6-4.3)	4.1 (3.7-4.5)	3.5 (2.6-4.5)	2.0 (1.7-2.4)	<0.001
Diuretic use					<0.001
Yes	6.1 (5.4-6.9)	5.2 (4.4-6.2)	6.3 (4.7-8.4)	14.5 (12.0-17.5)	
No	93.9 (93.1-94.7)	94.8 (93.8-95.6)	93.8 (91.6-95.4)	85.5 (82.5-88.0)	
Psychotropic use					0.03
Yes	3.0 (2.5-3.4)	2.7 (2.3-3.2)	3.5 (2.2-5.5)	4.8 (3.0-7.5)	
No	97.0 (96.6-97.5)	97.3 (96.8-97.7)	96.5 (94.5-97.8)	95.2 (92.5-97.0)	
Laboratory Parameters					
eGFR (mL/min/1.73 m ²)	87.9 (86.5-89.3)	91.2 (90.1-92.3)	92.1 (89.7-94.6)	49.6 (48.6-50.5)	<0.001
Serum creatinine (mg/dL)	0.88 (0.87-0.89)	0.85 (0.84-0.85)	0.82 (0.80-0.84)	1.29 (1.26-1.31)	<0.001
UACR (mg/g)	35.6 (29.9-41.3)	8.1 (7.8-8.3)	213.9 (171.5-256.4)	162.5 (108.4-216.7)	<0.001

Note: Values shown are percentage or mean (95% confidence interval). Conversion factors for unit: eGFR in mL/min/1.73 m², ×0.01667; serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; PHQ-9, Patient Health Questionnaire 9; UACR, urine albumin-creatinine ratio.

^aAcross CKD severity categories, by χ^2 (categorical variables) and analysis of variance (continuous variables) tests.

^bOther race/ethnicity not shown due to small sample sizes, but individuals in "other" category are included in all analyses.

^cSelf-reported or measured blood pressure ≥140/≥90 mm Hg.

Table 3. Crude Prevalence of Sleep-Related Problems by CKD Status

Sleep-Related Problem	No CKD (n = 7,305)	CKD Stage 1 or 2 (n = 875)	CKD Stage 3 or 4 (n = 930)	P ^a
Total sleep time				0.001
≥7 h	62.6 (60.3-64.9)	57.1 (52.1-61.9)	69.1 (65.0-73.0)	
≤6 h	37.4 (35.1-39.7)	43.0 (38.2-47.9)	30.9 (27.0-35.1)	
Sleep onset				0.2
<30 min	64.3 (62.3-66.2)	62.3 (57.9-66.5)	67.6 (63.4-71.5)	
≥30 min	35.7 (33.8-37.7)	37.7 (33.5-42.1)	32.4 (28.5-36.6)	
Snoring				0.6
Never	28.4 (26.5-30.3)	26.7 (22.6-31.3)	29.5 (26.0-33.3)	
≥1×/wk	71.6 (69.7-73.5)	73.3 (68.7-77.4)	70.5 (66.7-74.0)	
Stop breathing				0.04
Never	79.1 (77.7-80.4)	75.9 (71.8-79.6)	80.9 (77.7-83.9)	
≥1×/wk	20.9 (19.6-22.3)	24.1 (20.4-28.2)	19.1 (16.2-22.3)	
Ever told by physician: trouble sleeping				0.002
No	24.0 (22.9-25.1)	30.0 (25.4-35.0)	28.3 (25.5-31.4)	
Yes	76.0 (74.9-77.1)	70.0 (65.0-74.6)	71.7 (68.7-74.5)	
Ever told by physician: sleep disorder				0.02
No	92.5 (91.9-93.2)	89.1 (85.3-92.0)	92.3 (90.3-94.0)	
Yes	7.5 (6.8-8.2)	10.9 (8.0-14.7)	7.7 (6.0-9.7)	
Apnea	4.5 (4.0-5.2)	7.6 (5.2-11.1)	5.8 (4.3-7.9)	0.01
Insomnia	1.4 (1.1-1.7)	0.8 (0.4-1.6) ^b	1.1 (0.6-1.9)	0.3
Restless legs	0.3 (0.2-0.5)	0.5 (0.2-1.4) ^b	0.3 (0.0-1.1) ^b	0.6
Other	1.2 (1.0-1.5)	1.9 (1.0-3.5)	0.7 (0.2-1.9) ^b	0.2
Trouble falling asleep				0.5
<5×/mo	82.6 (81.5-83.7)	80.8 (77.4-83.8)	83.1 (80.3-85.5)	
≥5×/mo	17.4 (16.3-18.5)	19.2 (16.2-22.7)	16.9 (14.5-19.8)	
Waking at night				0.3
<5×/mo	79.7 (78.6-80.8)	77.5 (73.6-81.0)	77.9 (74.9-80.7)	
≥5×/mo	20.3 (19.2-21.4)	22.5 (19.0-26.4)	22.1 (19.3-25.1)	
Waking early				0.9
<5×/mo	83.1 (82.0-84.2)	82.2 (78.0-85.7)	82.9 (78.8-86.4)	
≥5×/mo	16.9 (15.8-18.0)	17.8 (14.3-22.0)	17.1 (13.7-21.2)	
Feeling unrested during day				0.2
<5×/mo	73.2 (71.8-74.5)	70.4 (65.4-74.9)	75.5 (71.6-79.0)	
≥5×/mo	26.8 (25.5-28.2)	29.6 (25.1-34.6)	24.5 (21.0-28.4)	
Feeling sleepy during day				0.2
<5×/mo	82.2 (80.9-83.5)	78.7 (73.9-82.8)	80.7 (77.3-83.6)	
≥5×/mo	17.8 (16.5-19.1)	21.3 (17.2-26.1)	19.3 (16.4-22.7)	
Not getting enough sleep				0.004
<5×/mo	73.3 (71.8-74.6)	73.8 (69.5-77.7)	80.6 (76.9-83.8)	
≥5×/mo	26.7 (25.4-28.2)	26.2 (22.3-30.5)	19.5 (16.3-23.1)	
Taking sleeping pills				<0.001
<5×/mo	91.6 (90.6-92.5)	90.2 (87.1-92.6)	83.4 (79.3-86.9)	
≥5×/mo	8.4 (7.5-9.4)	9.9 (7.4-12.9)	16.6 (13.2-20.7)	
Leg jerks				0.2
Never	77.5 (76.2-78.7)	74.3 (70.5-77.8)	76.5 (73.1-79.6)	
≥1×/wk	22.5 (21.3-23.8)	25.7 (22.2-29.5)	23.5 (20.3-26.9)	
Leg cramps				<0.001
Never	70.6 (68.5-72.7)	60.4 (55.8-64.8)	56.3 (51.8-60.6)	
≥1×/wk	29.4 (27.3-31.5)	39.6 (35.2-44.2)	43.7 (39.4-48.2)	

(Continued)

Table 3 (Cont'd). Crude Prevalence of Sleep-Related Problems by CKD Status

Sleep-Related Problem	No CKD (n = 7,305)	CKD Stage 1 or 2 (n = 875)	CKD Stage 3 or 4 (n = 930)	P ^a
Combined leg symptoms ^c				<0.001
No	60.8 (58.9-62.8)	52.0 (48.1-55.9)	49.1 (44.9-53.3)	
Yes	39.2 (37.2-41.1)	48.0 (44.1-51.9)	50.9 (46.7-55.1)	
Nocturia				<0.001
Urinate 0-1×/night	79.1 (77.1-80.9)	64.8 (61.1-68.3)	56.4 (52.2-60.5)	
Urinate ≥2×/night	20.9 (19.1-22.9)	35.2 (31.7-38.9)	43.6 (39.5-47.8)	
Mean FOSQ score ^d				0.04
<0.5	88.2 (87.2-89.2)	84.2 (81.3-86.8)	88.7 (85.2-91.5)	
≥0.5	11.8 (10.8-12.8)	15.8 (13.2-18.7)	11.3 (8.5-14.8)	

Note: Values shown are percentage reporting sleep-related problem (95% confidence interval). Based on National Health and Nutrition Examination Survey 2005-2008.

Abbreviations: CKD, chronic kidney disease; FOSQ, Functional Outcomes of Sleep Questionnaire.

^aBy χ^2 test (categorical variables).

^bUnreliable estimate: relative standard error $\geq 30\%$.

^cDiagnosed restless legs syndrome or leg cramps or jerks at least once per month.

^dScore represents mean of all completed items as listed in Table 1. Scores are on a 0-3 scale, with 0 = no difficulty, 1 = a little difficulty, 2 = moderate difficulty, and 3 = severe difficulty; all other responses excluded.

RESULTS

Characteristics of Study Population by CKD

As listed in Table 2, patients with CKD stages 3 and 4 were older and more likely to be women, have insurance, and be nonsmokers than those without CKD. Patients with CKD stages 1 and 2 were more likely to be non-Hispanic black than those without CKD and with CKD stages 3 and 4. Education and income levels and body mass index were higher in patients without CKD than those with CKD regardless of severity. Diabetes, hypertension, and CVD were more frequent with greater CKD severity. Depressive symptoms did not differ by CKD severity (Table 2).

Patients included in the study were older and more likely to be men and have higher income ($P < 0.05$ for all) relative to those excluded from the study due to missing sleep questionnaire or CKD measurements, eGFR < 15 mL/min/1.73 m², or pregnancy. There were no statistically significant differences between included and excluded samples by body mass index, smoking status, or other clinical characteristic.

Prevalence of Sleep-Related Problems by CKD

Table 3 lists crude prevalences of sleep-related problems by survey item and CKD. Patients with CKD stages 1 and 2 had higher levels of inadequate sleep (≤ 6 hours per night) and prolonged sleep-onset latency (≥ 30 minutes to fall asleep; not statistically significant) than those with no CKD or CKD stages 3 and 4. Notably, in those who reported 7 or more hours of sleep per night, those with CKD also were more likely to report sleeping 9 or more hours per night (6.8% for stages 1 and 2 and 6.9% for stages 3 and 4 compared with 2.8% in those without CKD; $P = 0.04$;

not shown in table). Mean sleep durations were 6.8, 6.7, and 7.2 hours for no CKD, stages 1 and 2, and stages 3 and 4 ($P < 0.001$ by analysis of variance). The prevalence of sleep-onset latency of 5 minutes or less (characteristic of severe sleep deprivation) was high, but did not differ by CKD status (29.0%, 30.4%, and 27.5% for no CKD, stages 1 and 2, and stages 3 and 4, respectively; not shown in table).

Frequent daytime sleepiness and frequent sleeping pill use were more frequent in those with CKD (Table 3). Frequent sleeping pill use also was associated with shorter sleep duration: 63.4% of patients not reporting frequent sleeping pill use reported sleeping 7 or more hours per night compared with 55.7% of those reporting frequent use ($P = 0.002$; not shown in table). Combined leg symptoms (leg jerks, leg cramps, or diagnosed restless legs syndrome) and nocturia were more frequent with increasing CKD severity. There were no significant differences in crude prevalences of any other reported sleep-related problems by CKD status (Table 3).

Table 4 compares unadjusted prevalences of selected sleep-related problems overall with the prevalence adjusted to US population distributions of the given covariates (models 1 and 2). Age-, sex-, and race/ethnicity-adjusted prevalences (model 1) of inadequate sleep, daytime sleepiness, leg-related symptoms, and nocturia were higher in those with CKD stages 1 and 2 and stages 3 and 4 relative to no CKD. Adjusted total sleep duration was higher in those with CKD stages 3 and 4 (7.1 hours; $P < 0.001$) relative to no CKD. Sleeping pill use was no longer statistically significantly different by CKD status after this adjustment. Further adjustment for common comorbid conditions (obesity, diabetes, and CVD; model 2) showed

Table 4. Odds Ratios for Selected Sleep-Related Problems by CKD Status

Model	CKD Stages 1 & 2	CKD Stages 3 & 4
Inadequate Sleep (≤ 6 h sleep per night)		
Unadjusted	1.26 (1.05-1.51)	0.75 (0.60-0.93)
Model 1	1.26 (1.04-1.52)	0.81 (0.62-1.05)
Model 2	1.17 (0.96-1.42)	0.75 (0.58-0.98)
+ Depression	1.15 (0.95-1.41)	0.76 (0.58-0.98)
+ Alcohol use	1.14 (0.93-1.39)	0.76 (0.58-1.00)
+ Diuretics	1.17 (0.96-1.42)	0.75 (0.58-0.98)
+ Psychotropics	1.17 (0.96-1.42)	0.75 (0.58-0.98)
Model 2, CKD-EPI ^a	1.17 (0.97-1.41)	0.73 (0.55-0.96)
Daytime Sleepiness (feeling sleepy during the day > 5 x/mo)		
Unadjusted	1.25 (0.95-1.65)	1.11 (0.89-1.39)
Model 1	1.36 (1.02-1.81)	1.34 (1.06-1.70)
Model 2	1.20 (0.89-1.63)	1.22 (0.95-1.57)
+ Depression	1.16 (0.86-1.55)	1.26 (0.98-1.60)
+ Alcohol use	1.22 (0.86-1.73)	1.35 (0.97-1.88)
+ Diuretics	1.21 (0.89-1.63)	1.22 (0.94-1.57)
+ Psychotropics	1.20 (0.89-1.62)	1.22 (0.94-1.58)
Model 2, CKD-EPI ^a	1.20 (0.89-1.61)	1.23 (0.96-1.56)
Frequent Use of Sleep Medications (taking sleeping pills > 5 x/mo)		
Unadjusted	1.19 (0.86-1.65)	2.16 (1.73-2.70)
Model 1	1.00 (0.71-1.38)	1.18 (0.92-1.51)
Model 2	0.90 (0.65-1.24)	1.06 (0.82-1.35)
+ Depression	0.86 (0.62-1.19)	1.07 (0.84-1.36)
+ Alcohol use	1.07 (0.76-1.49)	1.13 (0.86-1.47)
+ Diuretics	0.90 (0.65-1.24)	1.05 (0.82-1.35)
+ Psychotropics	0.90 (0.65-1.24)	1.06 (0.83-1.35)
Model 2, CKD-EPI ^a	0.91 (0.65-1.28)	0.84 (0.64-1.11)
Combined Leg-Related Sleep Symptoms (leg cramps or jerks > 1 x/mo or diagnosed RLS)		
Unadjusted	1.43 (1.23-1.66)	1.61 (1.39-1.86)
Model 1	1.30 (1.10-1.54)	1.17 (1.00-1.35)
Model 2	1.17 (0.99-1.39)	1.10 (0.94-1.29)
+ Depression	1.15 (0.97-1.37)	1.11 (0.95-1.30)
+ Alcohol use	1.20 (0.98-1.46)	1.01 (0.81-1.26)
+ Diuretics	1.17 (0.99-1.39)	1.10 (0.94-1.29)
+ Psychotropics	1.17 (0.99-1.39)	1.10 (0.93-1.30)
Model 2, CKD-EPI ^a	1.17 (0.98-1.40)	1.15 (0.97-1.27)
Nocturia (reported urinations > 5 x/night)		
Unadjusted	2.06 (1.71-2.47)	2.92 (2.45-3.49)
Model 1	1.54 (1.28-1.86)	1.27 (1.06-1.54)
Model 2	1.30 (1.07-1.57)	1.13 (0.94-1.35)
+ Depression	1.26 (1.05-1.52)	1.14 (0.95-1.36)
+ Alcohol use	1.32 (1.07-1.62)	1.21 (0.99-1.49)
+ Diuretics	1.30 (1.07-1.57)	1.12 (0.94-1.35)
+ Psychotropics	1.30 (1.07-1.57)	1.13 (0.94-1.35)
Model 2, CKD-EPI ^a	1.31 (1.09-1.58)	1.22 (1.02-1.45)

Note: Values shown are odds ratio (95% confidence interval); reference group is no CKD. Based on National Health and Nutrition Examination Survey 2005-2008. Model 1, age, sex, and race/ethnicity; model 2, model 1 + obesity, diabetes, and cardiovascular disease. Obesity defined as body mass index ≥ 30 kg/m², and diabetes and cardiovascular disease defined by self-report.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; RLS, restless legs syndrome.

^aCKD status based on estimated glomerular filtration rates calculated using the CKD-EPI equation instead of the isotope-dilution mass spectrometry-traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.

that frequent daytime sleepiness and sleeping pill use were no longer statistically significant by CKD status; the prevalence of inadequate sleep was statistically significantly lower in patients with CKD stages 3 and 4 relative to no CKD, whereas leg symptoms ($P = 0.06$) and nocturia ($P = 0.01$) remained higher in patients with CKD stages 1 and 2 compared with those with no CKD.

Further adjustment for depression, alcohol intake, diuretic use, and psychotropic use did not change results (Table 4; vs Model 2). Additionally, the prevalence of all sleep-related problems by CKD estimated using the CKD-EPI equation⁴¹ did not substantially differ (Table 4).

Due to possible effects of sleeping pill use on symptoms (confounding by indication), we examined the prevalence of inadequate sleep, leg-related sleep symptoms, and nocturia by CKD in those reporting and not reporting regular sleeping pill use (Table 5). The associations of sleep-related problems in this subpopulation were not substantially different from those in the overall population; however, results for inadequate sleep and daytime sleepiness were most robust in the frequent sleeping pill users, whereas results for leg symptoms and nocturia were most robust in nonfrequent users (Table 5).

Reported Use of Sleep-Inducing and Sleep-Disrupting Medications by CKD

Although 9.2% (Fig 1A) of the overall study population reported using sleeping pills 5 or more times a month, only 17.4% of these frequent users reported having a prescription for sleep medication, and this prevalence did not differ by CKD status (17.9%, 13.8%, and 16.1% for no CKD, stages 1 and 2, and stages 3 and 4; Fig 1B). Of note, 11.8% and 7.1% of patients with CKD stages 1 and 2 and stages 3 and 4 had prescriptions for sleep medications specifically contraindicated for those with known kidney problems, respectively (ramelteon, zaleplon, and zolpidem; Fig 1B). These proportions represent 70.6% (CKD stages 1 and 2) and 39.2% (CKD stages 3 and 4) of patients with CKD who had a prescription sleep medication. As shown in Fig 1C, reported prescription diuretics and psychotropics, which can disrupt sleep, were more frequent in those with CKD stage 3 or 4 compared with either no CKD or CKD stage 1 or 2 (not statistically significant).

DISCUSSION

The prevalence of sleep-related problems in the US population generally was high. Many of the sleep symptoms examined, including prolonged sleep-onset latency/trouble falling asleep, frequent waking at night or too early, sleep-disordered breathing, snoring, diag-

Table 5. Adjusted Odds Ratios for Selected Sleep-Related Problems by CKD Status and Sleeping Pill Use

	<5 Sleeping Pills/mo			≥5 Sleeping Pills/mo		
	No CKD	Stages 1 & 2	Stages 3 & 4	No CKD	Stages 1 & 2	Stages 3 & 4
Inadequate sleep	1.00 (ref)	1.13 (0.90-1.41)	0.79 (0.60-1.03)	1.00 (ref)	1.93 (1.19-3.11)	0.60 (0.34-1.07)
Frequent daytime sleepiness	1.00 (ref)	1.14 (0.79-1.64)	1.31 (0.96-1.79)	1.00 (ref)	1.98 (1.04-3.77)	0.95 (0.61-1.46)
Combined leg-related symptoms	1.00 (ref)	1.21 (1.01-1.46)	1.05 (0.88-1.24)	1.00 (ref)	1.04 (0.68-1.58)	1.46 (0.88-2.40)
Nocturia	1.00 (ref)	1.27 (1.07-1.51)	1.11 (0.93-1.33)	1.00 (ref)	1.57 (0.75-3.27)	1.18 (0.67-2.06)

Note: Values shown are adjusted odds ratio (95% confidence interval). Based on National Health and Nutrition Examination Survey 2005-2008. Odds ratios adjusted for age, sex, race/ethnicity, obesity, diabetes, and cardiovascular disease. Obesity defined as body mass index ≥ 30 kg/m², and diabetes and cardiovascular disease defined by self-report.

Abbreviations: CKD, chronic kidney disease; ref, reference.

nosed sleep disorders, and functional outcomes of sleep, did not differ by CKD severity. However, prevalence estimates for inadequate sleep, frequent daytime sleepiness, reported use of sleeping pills, leg symptoms, and nocturia were found to be higher in patients with early-stage CKD than in those without CKD. These patterns persisted for inadequate sleep, leg symptoms, and nocturia after adjustment for demographics, but were not always statistically significant after adjustment for common comorbid conditions (obesity, diabetes, and CVD).

We did not find CKD status to be associated with a higher prevalence of sleep-disordered breathing or sleep apnea. Sim et al¹⁵ found that coded sleep apnea was associated with severity of CKD in a patient cohort. Coded sleep apnea likely is a specific but not necessarily sensitive marker. Additionally, providers who frequently measure CKD status may be more likely to test and code for sleep apnea. Here, both diagnosed sleep apnea and sleep-disordered breathing were self-reported, and many patients with sleep apnea may be unaware of their condition.

In our study, with the exception of inadequate sleep, decreased sleep quality in patients with CKD was explained largely by age, obesity, diabetes, and CVD. Several previous studies^{13,14,16,42} have shown a high prevalence of sleep problems in patients with moderate to severe CKD. These studies predominantly were of patients with higher stage or diagnosed CKD, which may explain some differences. Additionally, they used questionnaire items that differ from those used in NHANES.

We found that inadequate sleep was associated with mild CKD, but not moderate to severe CKD, relative to those with no CKD, a pattern that was not explained by the increased age of the population with moderate to severe CKD. It is possible that early stages of kidney damage may have more effect on sleep than subsequently decreased kidney function, or perhaps more severe CKD leads to more pronounced

fatigue, more frequent use of sleeping pills, and/or greater total hours of sleep regardless of the quality of the sleep. We found that reported sleep duration of 9 or more hours was increasingly common with CKD severity. Additionally, further examination of actual numbers of sleep hours showed that sleep duration was shorter in patients with CKD stages 1 and 2, but longer in those with CKD stages 3 and 4 relative to no CKD.

Both leg symptoms⁹ and nocturia⁴³ have been shown to be associated with lower health-related quality of life. We found that leg symptoms and nocturia were reported more frequently by patients with CKD, which was explained largely by age and comorbid conditions in patients with moderate to severe and mild CKD versus no CKD. Greater mortality in patients with sleep-related problems in the early stages of CKD may contribute to the slightly (but not statistically significantly) higher prevalence of these symptoms in patients with mild versus moderate to severe CKD.¹⁵ It also is possible that as disease progresses, persons with CKD become inured to these symptoms and less likely to report them. The finding that 45% of patients with CKD stages 3 and 4 report urinating 2 or more times per night, but 23% report frequently waking at night, suggests possible unreliability of self-report data and/or adaptation to sleep disturbances. Finally, it is possible that older individuals with moderate to severe CKD are more likely to attribute such symptoms (particularly nocturia) to their age and thus less likely to recognize and report abnormal symptoms relative to individuals with mild or no CKD.

A large proportion (~9%) of the US population reported using sleeping pills 5 or more times per month, although few of these reported having a prescription sleep aid, indicating that most sleeping aids used were available over the counter. Patients with moderate to severe CKD reported more frequent sleeping pill use than those without CKD, explained largely

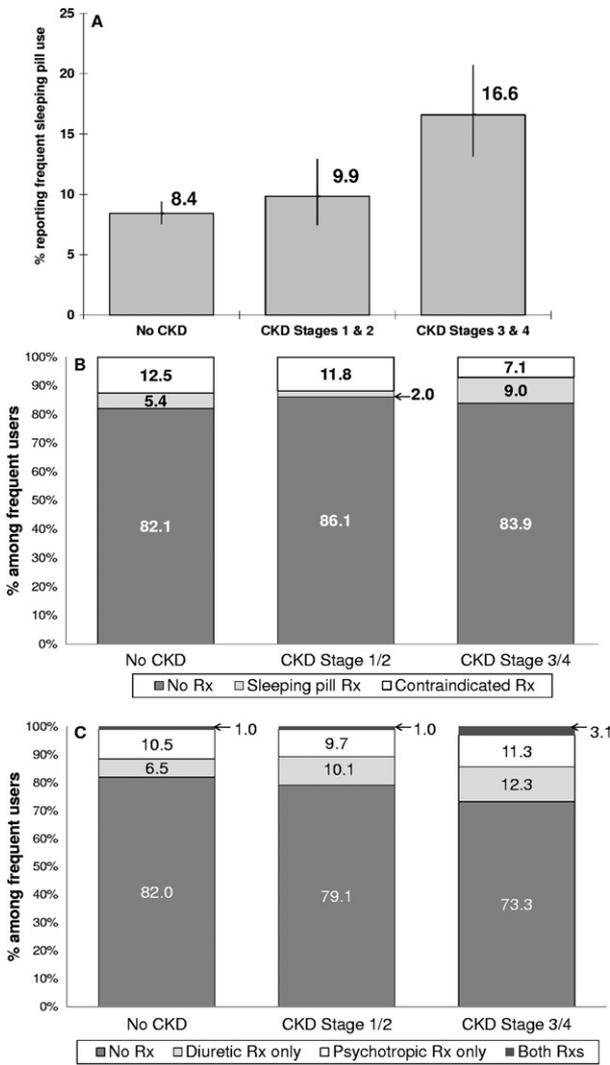


Figure 1. (A) Reported frequent use (≥ 5 times per month) of sleeping pills by chronic kidney disease (CKD) status ($P < 0.001$) and, in reported frequent sleeping pill users, reported current prescriptions for (B) sleep medications and (C) drugs that interfere with sleep. National Health and Nutrition Examination Survey 2005-2008. P values by χ^2 test, not statistically significant for B ($P = 0.13$) and C ($P = 0.28$). Contraindicated sleep medications: contraindicated in the presence of kidney disease (from warning labels), ramelteon, zaleplon, and zolpidem; psychotropic medications, benzodiazepines, theophylline, fluoxetine, and bupropion.

by obesity, diabetes, CVD, and other sequelae of increasing age. In those with moderate to severe CKD who used a prescription sleep aid, nearly 25% were using medications contraindicated for kidney disease, likely because they and their physicians were unaware of their disease. Although diuretics commonly were used, they were not statistically significantly associated with CKD status or nocturia after adjustment for hypertension.

Although we found several significant associations between CKD and sleep, most markers of sleep quality examined in this study did not differ by CKD

status, including prolonged sleep-onset latency/trouble falling asleep, frequent waking at night or too early, sleep-disordered breathing, snoring, and diagnosed sleep disorders. This contradictory evidence relative to some previous reports may reflect no true association, differences in ascertainment, and/or self-report bias. Sleep-disordered breathing and snoring likely are under-recognized and may not be reliable by self-report; most (up to 95%) sleep disorders frequently may be undiagnosed⁴⁴ as well. Additionally, functional outcomes of sleep generally did not differ by CKD status, suggesting that regardless of CKD status, effects of dysfunctional sleep on daytime functioning likely are similar between those with and without CKD.

There are several limitations of this study that should be noted. The cross-sectional design precludes causal inference about CKD and sleep symptoms. Data from only 2 surveys are available, limiting adjusted and stratified analyses. Sleep symptoms were self-reported and thus may be over- or under-reported, depending on the presence of a sleep partner, individual variation in detecting sleep issues, and possible recall bias. Although we adjusted for confounders, we know that patients included in the study were more likely to be older, men, non-Hispanic white, and wealthier than those excluded because of missing measurements. Thus, our estimates of the prevalence of sleep-related problems may not be representative of the entire CKD population. Data for specific kidney issues, such as pruritis and chronic pain⁴⁵ and caffeine use, all of which might affect sleep, were not available in this survey. Measures of leg symptoms may have lacked some sensitivity given that patients with CKD may have sensations in legs (eg, “creepy-crawly”) that are not attributable to leg cramps or jerks or are not recognized as restless legs syndrome, but which nonetheless may interfere with sleep. Over-the-counter, off-label, and herbal drugs for sleep were not tracked. The high prevalence of many sleep problems in the general population may make it difficult to determine a CKD-specific effect. Finally, misclassification of CKD due to single measurements of eGFR and albuminuria is possible.

However, our study also has several important advantages over previous studies. It is a large nationally representative study examining a comprehensive range of sleep-related problems in patients with CKD before ESRD. CKD was defined regardless of whether the disease is recognized, diagnosed, or treated, all of which may affect sleep symptoms. Additionally, we were able to compare prevalence with that in similar persons without CKD to determine whether CKD had an independent effect on sleep after adjustment for

other factors strongly related to both CKD and sleep, including age, sex, obesity, diabetes, and CVD.

Although the association between CKD and sleep-related problems in the United States might not be as strong as previously thought after adjustment for age and comorbid conditions common in patients with CKD, we note that inadequate sleep, leg symptoms, and nocturia were reported more frequently by patients with CKD in its early stages than in those without CKD. Primary care providers, who are most likely to identify and treat early-stage CKD, should be aware that sleep-related problems likely are common in all their patients and certain sleep symptoms may be even more prevalent in their patients with CKD. Providers also should be aware that many patients with CKD report using unprescribed sleep aids and should query patients about their use of herbal, off-label, and over-the-counter drugs for sleep to ensure their safety and prevent kidney-related complications.

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