Title

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Journal

Kidney360, 1(6)

ISSN

2641-7650

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Publication Date

2020-06-01

DOI

10.34067/kid.0000862019

Peer reviewed

Kidney360

US Trends in Prevalence of Sleep Problems and Associations with Chronic Kidney Disease and Mortality

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Abstract

Background To better understand the relation between sleep problems and CKD, we examined temporal trends in the prevalence of self-reported sleep problems in adults in the United States and their associations with CKD and all-cause mortality.

Methods Using data from 27,365 adult participants in five biannual National Health and Examination Surveys (2005–2006 through 2013–2014), we studied five self-reported sleep problems—trouble sleeping, sleep disorder, nocturia (urinating ≥2 times/night), inadequate sleep (<7 hours/night), and excessive sleep (>9 hours/night)—plus a composite index. We conducted three types of analysis: temporal trends in the prevalence of each sleep measure by CKD status, using model-based standardization; cross-sectional analysis of associations between four CKD measures and each sleep measure, using logistic regression; and survival analysis of the association between each sleep measure and mortality, using Cox regression.

Results The prevalence of trouble sleeping and sleep disorder increased over the five surveys by 4% and 3%, respectively, whereas the other sleep problems remained relatively stable. All sleep problems, except inadequate sleep, were more common during the study period among adults with CKD than without CKD (40% versus 21% for nocturia; 5% versus 2% for excessive sleep; 30% versus 25% for trouble sleeping; 12% versus 8% for sleep disorder). Both eGFR <30 ml/min per 1.73 m^2 and albuminuria were positively associated with nocturia and excessive sleep. Excessive sleep and nocturia were also associated with higher mortality (adjusted hazard ratio for >9 versus 7–9 hours/night=1.7; 95% CI, 1.3 to 2.1; and for nocturia=1.2; 95% CI, 1.1 to 1.4).

Conclusions The high prevalence of sleep problems among persons with CKD and their associations with mortality suggest their potential importance to clinical practice. Future work could examine the health effects of identifying and treating sleep problems in patients with CKD.

KIDNEY360 1: 458–468, 2020. doi: https://doi.org/10.34067/KID.0000862019

Introduction

Sleep abnormalities are associated with several health conditions including CKD and ESKD (1). The prevalence of sleep problems—including difficulty falling asleep, nightmares, restless legs syndrome, and sleep apnea—has been reported to range from 6% to 49% in older patients in the general population (2) and as high as 80% in patients with ESKD (1,2). In addition, 40%–85% of patients on dialysis and up to 85% of patients with CKD report poor sleep quality (3,4). Higher prevalences of inadequate sleep, frequent use of sleeping pills, restless legs syndrome, and nocturia were observed in individuals with CKD stages 1–2 than in individuals without CKD (*i.e.*, persons with versus without an albumin-creatinine ratio [ACR] ≥30 mg/g among those with an eGFR ≥60 ml/min per 1.73 m^2) (5).

The higher burden of sleep abnormalities in patients with kidney disease is important because sleep problems have been linked with all-cause mortality (6). Sleep disorders may be an important risk factor for mortality in the ESKD patient population (7). Although the prevalence of sleep disturbances has been shown to be increasing among adults in the United States (6), temporal trends in sleep-related problems have been suboptimally examined in adults with kidney disease

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in the United States. Moreover, few studies with large national samples have been conducted to document the frequency of sleep problems by CKD status in the United States or to examine their associations with morbidity and mortality (8).

Our study aims were first to describe the prevalence and temporal trends in the United States of five self-reported sleep problems (trouble sleeping, sleep disorder, nocturia, inadequate sleep, excessive sleep) plus a composite measure and, second, to examine the associations of those sleep problems with CKD prevalence and mortality by CKD status.

Materials and Methods

Data Source and Study Design

We used data on United States adults (aged ≥20 years) with and without CKD from five biennial National Health and Nutrition Examination Surveys (NHANESs), conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention between 2005–2006 and 2013–2014. A series of cross-sectional and longitudinal (trend) analyses were conducted to examine the prevalence of sleep problems and their associations with CKD. NHANES is designed to assess the health and nutritional status of adults and children in the United States (9). The surveys include demographic, socioeconomic, dietary, and health-related questions from a representative sample of noninstitutionalized United States residents, with oversampling of people 60 and older and black and Hispanic people. The analysis was limited to 27,365 NHANES participants during the 10-year study period (2005–2014) who were 20 years and older and not on RRT at the time of examination. All NHANES participants were required to give written informed consent as part of the NHANES study procedures. This study was deemed "nonregulated" by the Institutional Review Board at the University of Michigan, because NHANES provides publicly available deidentified data as part of the Centers for Disease Control and Prevention's CKD Surveillance System Contract with the University of Michigan.

Study Variables

We examined four self-reported sleep variables: (*1*) trouble sleeping, obtained from responses to the question, "Have you ever told a doctor or other health professional that you have trouble sleeping?"; (*2*) sleep disorder, obtained from responses to the question, "Have you ever been told by a doctor or other health professional that you have a sleep disorder?"; (*3*) nocturia, obtained from responses to the question, "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?"; and (*4*) total hours of sleep per night, obtained from responses to the question, "How much sleep do you usually get at night on weekdays or workdays?" Responses to the nocturia question were dichotomized as two or more times per night (nocturia) or less frequently, and responses to the sleep-duration question were categorized according to national and international guidelines (10) as <7 hours per night (inadequate sleep), 7–9 hours (recommended sleep), and >9 hours (excessive sleep). In addition, a composite sleep-problem index was created by first summing indicators of all five sleep problems. Because excessive sleep was nearly unrelated to the other sleep problems (and mutually exclusive with inadequate sleep), it was excluded from the index, resulting in a reliable composite measure that is internally consistent (Cronbach $\alpha = 0.57$).

Demographic information (age, sex, and race/ethnicity) was collected during the interview of each participant. Race/ethnicity was categorized into four groups: Hispanic, non-Hispanic white, non-Hispanic black, and non-Hispanic other race. Hypertension and diabetes were defined by any of three criteria: self-report of each condition as told by a health professional, self-reported use of condition-specific medications, and laboratory measurements (systolic and diastolic BP, hemoglobin level [A1c], and blood sugar). Obesity was defined as a body mass index ≥30 kg/m^2. Serum creatinine levels were corrected for different laboratory methods used in different years (11). Urine albumin was measured by a solid-phase fluorescein immunoassay and urine creatinine by the enzymatic method (12). Smoking status was defined as currently smoking on all or some days. Histories of cancer, cardiovascular disease (CVD), and chronic respiratory disease were based on self-reports as told by a health professional. Prescription medications were recorded by the interviewer from the bottles provided by the participant, and medications that affect drowsiness and cognition were extracted from these data and created indicators for sedatives, stimulants, and other drugs (Supplemental Table 1).

Because CKD is diagnosed on the basis of both reduced kidney function indicated by low eGFR and kidney damage indicated by a high urinary ACR or albuminuria, we used four measures of CKD in our analyses (13):

(*1*) CKD status (binary, CKD versus no CKD): eGFR <60 ml/min per 1.73 m^2 (using the CKD Epidemiology Collaboration equation (14)) and/or ACR ≥30 mg/g versus eGFR ≥60 ml/min per 1.73 m^2 and ACR <30 mg/g (reference group).

(*2*) eGFR category (ordinal): eGFR ≥60 ml/min per 1.73^2 (reference group), eGFR of 30–60 ml/min per 1.73^2, and eGFR <30 ml/min per 1.73^2.

(*3*) ACR category (ordinal): normal to mildly increased (ACR <30 mg/g, reference group), moderately increased (ACR of 30–300 mg/g), and severely increased (ACR >300 mg/g).

(*4*) CKD prognosis category defined in Kidney Disease Outcomes Quality Initiative (13) (ordinal, based on the combination of eGFR category and ACR category): low risk (no CKD, same reference group as in #*1*), moderate increased risk, high risk, and very high risk (see Supplemental Table 2 for details).

All-cause mortality data were available for 27,322 (99.8%) of the 27,365 participants. All five survey cohorts were followed from their baseline interviews (2005–2014) to the end of 2015. Thus, the follow-up duration of study participants could range from as little as 1 year to as much as 11 years; the median observed follow-up was 77 months. Vital status and date of death were ascertained from the National Death Index (NDI). The primary determination of

mortality status for participants was based on matching survey records to the NDI. If a source of mortality other than NDI was available, the participant was considered deceased. The publicly available records from the NDI were linked with NHANES by the National Center for Health Statistics. The linkage of NHANESs to the NDI involved identifying eligible participants from the NHANESs, creating base submission records plus any alternative records, merging base submission records with NDI data, executing the match process, reviewing match results, selecting matches, and determining vital status (15).

Statistical Analysis

Temporal trends in the prevalence of each sleep problem and the composite index were estimated across the five NHANESs, by CKD status (CKD versus no CKD). The crude and standardized prevalence of the five sleep problems were estimated for each 2-year survey (2005–2006–2013–2014). Weighted linear regression, as recommended by the Centers for Disease Control and Prevention (16), was used to directly standardize for age, sex, and race/ethnicity, using the 2000 United States population as the standard (17) and treating survey year as a nominal variable. The ACR was standardized to the covariate distribution of the 2005–2006 cohort. To test for a monotonic trend, we treated survey year as an interval variable (coded 1–5).

Cross-sectional associations of each CKD measure (predictor) with each sleep problem (outcome) were examined using data from all five NHANESs (2005–2014). Weighted logistic regression was used to estimate the adjusted prevalence odds ratios (ORs) and 95% confidence intervals (95% CIs). In this analysis, amount of sleep each night was treated as a three-category outcome, using multinomial logistic regression to estimate the effects of each CKD predictor on inadequate and excessive sleep versus normal sleep. These associations were adjusted for survey year, age, sex, race/ethnicity, diabetes, hypertension, obesity, and use of one or more medications thought to affect sleep problems. To examine age as a possible modifier of the associations between CKD measures and sleep variables, we stratified by age to compare adults who were 65 and older with those who were <65.

The association between each sleep problem as well as the composite index observed at baseline interviews in all five surveys (2005–2014) and all-cause mortality through 2015 was estimated in separate models using Cox regression. The hazard ratio (HR) and 95% CI for the effect of each sleep problem and composite index on time to death was adjusted for survey year, age, sex, race/ethnicity, CKD status, hypertension, diabetes, obesity, current smoking status, cancer, CVD, chronic respiratory disease, the selected medications, and the other sleep problems (excluding the composite index). To assess CKD status as a potential modifier of the effect of each sleep problem on mortality, product terms for each sleep variable and CKD status were added to the models. In addition, separate analyses were conducted for participants with and without CKD.

Multiple imputation was implemented to impute missing values of trouble sleeping (0.05% missing), sleep disorders (0.2% missing), nocturia (29% missing), sleep amount (0.2% missing), eGFR (7% missing), and ACR (3% missing), assuming data were missing at random (18). First, we imputed values for the missing data 25 times by sampling from the chained equations using PROC MI procedures within SAS software, which included auxiliary variables that may contain information about the missing data, variables and outcomes involved in the planned analysis, and variables accounting for the clusters and strata (19). From the complete variables and the imputed set, 25 complete data sets were created. Second, we analyzed the 25 complete data sets using SURVEY procedures within SAS. Finally, we combined the 25 parameter estimates and SEMs to calculate pooled estimates and SEMs using PROC MIANALYZE procedures within SAS, which reflect the variability of the imputation process along with the complex sampling design (20).

Because many participants in our survival analysis were followed for several years (from as early as January 1, 2005 to as late as December 31, 2015), the status of their sleep problems could have changed during follow-up, possibly leading to bias in effect estimation. Unfortunately, we did not have data on changing sleep problems after baseline interviews, so we could not treat each sleep problem as time dependent. Therefore, we conducted a sensitivity analysis by restricting the follow-up of each survey participant to no more than 1 year. Although changes in sleep problems could still occur over 1 year, the potential for bias would be reduced appreciably, and the number of deaths in 1 year yielded sufficient estimation precision.

All analyses were performed in SAS version 9.4 and account for the survey data structure including sampling weights, primary sampling units, and sample strata.

Results

Table 1 shows summary statistics for selected baseline variables in 27,365 participants. The mean age was 47 years; 48% were male and 68% were non-Hispanic white. Compared with participants without CKD, those with CKD were more likely to be older, female, have larger body mass indexes, have diabetes, hypertension, cancer, CVD, and worsening memory.

Time trends in the age-, sex-, and race-standardized prevalence of each sleep problem and the composite sleep-problem index during the study period are displayed in Figure 1 and Supplemental Table 3. Overall, there was a steady rise of 4% between 2005–2006 (24%) and 2013–2014 (28%) in the prevalence of reported trouble sleeping (P for trend <0.001; Figure 1A) and a sharper rise of 3% between 2009–2010 (7%) and 2013–2014 (10%) in the prevalence of reported sleep disorders (P for trend <0.001; Figure 1B). In contrast, there was an overall decrease of 3% in the prevalence of inadequate sleep between 2007–2008 (38%) and 2013–2014 (35%) (P for trend=0.53; Figure 1C). The other sleep problems remained fairly stable or varied inconsistently during the study period (Figure 1, D and E). The prevalences of all five sleep problems and the composite index were greater for persons with CKD than without CKD during most survey years (Supplemental Table 3). There was a steady increase of 3% between 2005–2006 (23%) and 2013–2014 (26%) in the prevalence of the composite index score greater than one (P for trend=0.04; Figure 1F). There

Table 1. Summary statistics of selected baseline variables by CKD status: total study population, 2005–2014

Measure	All (n=27,365)	No CKD (n=22,137)	CKD (n=5228)
Age, yr	47 (0.27)	45 (0.24)	60 (0.39)
20–34 (%)	28	31	12
35–49 (%)	29	31	17
50–64 (%)	26	26	23
65–74 (%)	10	8	19
>75 (%)	7	4	29
Male (%)	48	49	42
Race/ethnicity (%)			
Hispanic	14	14	11
Non-Hispanic white	68	68	70
Non-Hispanic black	11	11	13
Other non-Hispanic race	7	7	6
Body mass index, kg/m^2	28.8 (0.08)	28.6 (0.09)	29.9 (0.14)
<18.5 kg/m^2, underweight (%)	3	2	2
18.5 to <25 kg/m^2, normal weight (%)	29	30	25
25 to <30 kg/m^2, overweight (%)	33	34	30
≥30 kg/m^2, obese (%)	35	34	43
Diabetes (%)	11	7	28
Hypertension (%)	34	27	71
Smoking (%)	33	33	33
Cancer (%)	10	8	17
Cardiovascular disease (%)	8	6	24
Chronic respiratory disease (%)	18	18	21
Full-time job	38	38	37
Worsening confusion or memory loss in the past 12 mo[a]	15	12	21

Data are presented as weighted proportions (%) or weighted means (and SD).
[a]Only among people who were ≥60 years from 2011 to 2014.

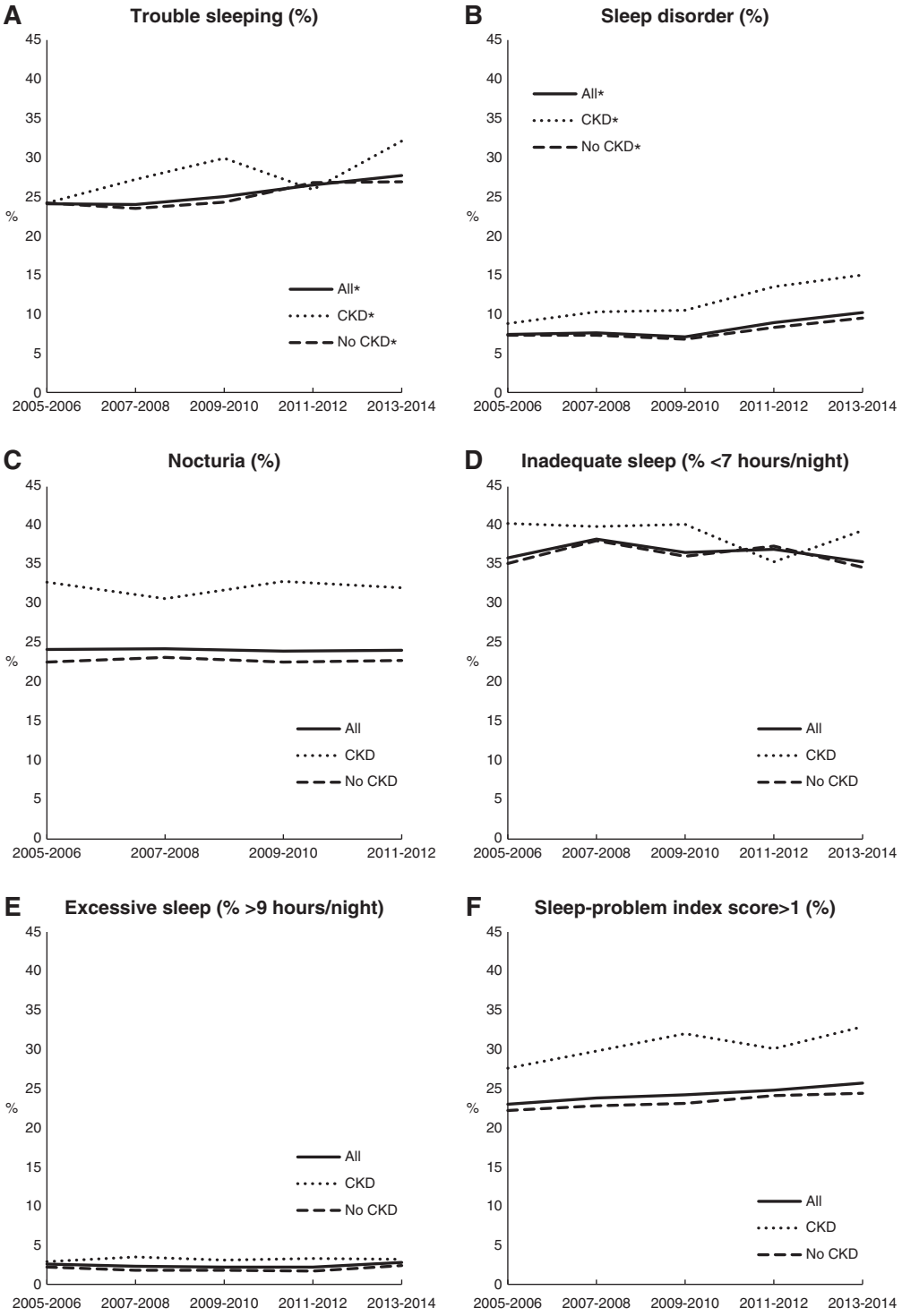
was a downward spike in 2011–2012 in the prevalences of trouble sleeping, inadequate sleep, and the composite index among patients with CKD, deviating from those overall trends. Because the sleep questions did not change for that one survey among any group, we cannot explain the unusual deviation.

Table 2 shows the cross-sectional associations between each of four CKD measures treated as predictors—CKD status, ACR category, eGFR category, and CKD prognostic category (based on both ACR and eGFR; refer to Supplemental Table 2 for the joint distribution of these two CKD measures)—and each sleep problem treated as the outcome. CKD status was most strongly associated with excessive sleep (OR=2.2; 95% CI, 1.8 to 2.5) and nocturia (OR=1.3; 95% CI, 1.1 to 1.4); it was inversely associated with trouble sleeping (OR=0.88; 95% CI, 0.78 to 0.99) but not associated with inadequate sleep or sleep disorder. ACR category was more strongly and positively associated with each sleep problem than was eGFR category, except for excessive sleep. Compared with eGFR ≥60 ml/min per 1.73 m^2, the adjusted OR for excessive sleep was 2.4 (95% CI, 1.9 to 3.1) for eGFR=30–59 ml/min per 1.73 m^2 and 5.8 (95% CI, 3.4 to 9.8) for eGFR <30 ml/min per 1.73 m^2. Compared with ACR <30 mg/g, the adjusted OR for nocturia was 1.2 (95% CI, 1.1 to 1.4) for ACR=30–300 mg/g and 1.6 (95% CI, 1.3 to 2.0) for ACR >300 mg/g. Positive monotonic associations were observed between CKD prognosis category and nocturia and between CKD prognosis category and excessive sleep (P for trend<0.001). Nocturia and excessive sleep were positively associated with CKD prevalence (P<0.001) and monotonically associated with the three polytomous measures of CKD (P for trend<0.001). Weighted and standardized prevalences of each of the five sleep problems are provided in Supplemental Tables 4 and 5.

The weighted prevalence of each sleep problem and the index score are shown in Table 3. The overall prevalences, in order from most to least common, were: inadequate sleep (37%), trouble sleeping (26%), nocturia (24%), sleep disorder (9%), and excessive sleep (2%). For all problems except inadequate sleep, the prevalence was greater in persons with CKD than without CKD. More than 60% of the study population had a sleep-problem index score greater than zero.

Crude and mutually adjusted HRs for the estimated effects of the five sleep problems on all-cause mortality, are shown in Table 4. Overall, the sleep problem with the strongest association with mortality was excessive sleep (>9 hours/night), which was reported less frequently (2%) than the other sleep problems (Table 3). Compared with recommended sleep (7–9 hours/night), the adjusted HR for excessive sleep was 1.7 (95% CI, 1.3 to 2.1) in the total study population. The crude association (HR=3.6) was reduced appreciably with covariate adjustment, and it was stronger for persons without CKD (P for interaction=0.08) but did not vary much by age (P for interaction=0.28; data not shown). A weaker overall association was found for nocturia (adjusted HR=1.2; 95% CI, 1.1 to 1.4) with little difference between age groups, and little or no association overall or by age was observed for trouble sleeping, sleep disorder, and inadequate sleep.

The associations of the sleep-problem index and excessive sleep with mortality, mutually adjusted for each other, are



[a]Standardized for age, sex, and race/ethnicity. Using 2000 US Census population as the standard population.
[b]The sleep-problem index ranging from 0 (no problems) to 4, was created by summing the number of problems (trouble sleeping, sleep disorder, nocturia, inadequate sleep) reported by each subject.
[c]NHANES, National Health and Nutrition Examination Survey.
[d]*P_{trend}<0.05.

Figure 1. | Trend in the standardized prevalence (%) of each sleep problem and sleep-problem index in 2005–2014 for the total study population, by NHANES survey years and CKD. (A) Trouble sleeping (%), (B) sleep disorder (%), (C) nocturia (%), (D) inadequate sleep (% <7 hours/night), (E) excessive sleep (% >9 hours/night), and (F) sleep-problem index score greater than one (%). [a]Standardized for age, sex, and race/ethnicity. Using 2000 United States Census population as the standard population. [b]The sleep-problem index ranging from zero (no problems) to four, was created by summing the number of problems (trouble sleeping, sleep disorder, nocturia, inadequate sleep) reported by each subject. NHANES, National Health and Nutrition Examination Survey. *P_{trend}<0.05.

Table 2. Estimated cross-sectional association between each CKD measure and each binary sleep problem (outcome) in 2005–2014 for the total study population

CKD Measure Category	Trouble Sleeping[a]	Sleep Disorder[a]	Nocturia[a]	Inadequate Sleep[b]	Excessive Sleep[b]
CKD status					
No CKD (reference)	1	1	1	1	1
CKD	0.88 (0.78 to 0.99)	1.0 (0.87 to 1.2)	1.3 (1.1 to 1.4)	0.98 (0.88 to 1.1)	2.2 (1.8,2.5)
P value	0.04	0.78	<0.001	0.29	<0.001
ACR category					
<30 mg/g (reference)	1	1	1	1	1
30–300 mg/g	0.89 (0.78 to 1.0)	1.1 (0.90 to 1.3)	1.2 (1.1 to 1.4)	1.1 (0.97 to 1.2)	1.7 (1.4 to 2.2)
>300 mg/g	1.2 (0.92 to 1.5)	1.3 (0.92 to 1.8)	1.6 (1.3 to 2.0)	1.2 (0.97 to 1.5)	2.7 (1.6 to 4.5)
P for trend[c]	0.65	0.11	<0.001	0.16	<0.001
eGFR category					
≥60 ml/min per 1.73 m^2 (reference)	1	1	1	1	1
30–60 ml/min per 1.73 m^2	0.82 (0.68 to 0.98)	0.89 (0.67 to 1.2)	1.1 (0.99 to 1.3)	0.81 (0.67 to 0.97)	2.4 (1.9 to 3.1)
<30 ml/min per 1.73 m^2	1.2 (0.79 to 1.8)	1.1 (0.71 to 1.8)	1.6 (1.0 to 2.4)	0.98 (0.70 to 1.4)	5.8 (3.4 to 9.8)
P for trend[d]	0.26	0.68	<0.001	0.003	<0.001
CKD prognostic category					
Low (reference)	1	1	1	1	1
Moderate increased	0.87 (0.76 to 1.0)	1.0 (0.85 to 1.2)	1.2 (1.1 to 1.3)	0.98 (0.86 to 1.1)	1.7 (1.4 to 2.2)
High	1.0 (0.83 to 1.3)	1.0 (0.76 to 1.4)	1.3 (1.1 to 1.7)	1.0 (0.84 to 1.2)	3.0 (2.1 to 4.4)
Very high	0.86 (0.62 to 1.2)	1.2 (0.80 to 1.7)	1.5 (1.1 to 1.9)	0.92 (0.70 to 1.2)	5.2 (3.5 to 7.8)
P for trend[e]	0.19	0.52	<0.001	0.18	<0.001

Data are presented as adjusted odds ratios and 95% CIs. Data adjusted for survey year, age, sex, race/ethnicity, diabetes, hypertension, obesity, and medications that affect drowsiness and cognition (sedatives, stimulants, and other drugs). ACR, albumin-creatinine ratio.
[a]Using weighted ordinary binary logistic regression.
[b]Using weighted multinomial logistic regression, where inadequate sleep (<7 hours/night) and excessive sleep (>9 hours/night) are compared with recommended sleep (7–9 hours/night).
[c]ACR category were considered as an interval variable (1–3) to test for a monotonic trend.
[d]eGFR categories were considered as an interval variable (1–3) to test for a monotonic trend.
[e]CKD prognostic category were considered as an interval variable (1–4) to test for a monotonic trend.

shown in Table 5. A positive monotonic association in the total population was observed for the index score (*P* for trend=0.01), and a moderate association was observed for excessive sleep (adjusted HR=1.7; 95%CI, 1.3 to 2.1). Although the association with the index score was slightly stronger in persons with CKD, the association with excessive sleep was stronger in persons without CKD.

Results of the sensitivity analysis in which follow-up for mortality was limited to 1 year are shown in Table 6. The HR estimates are similar to the estimates in the main analysis with full follow-up to the end of 2015 (Table 4), but with wider confidence intervals. These results suggest little bias resulting from unmeasured changes in the prevalence of sleep problems during follow-up in the main analysis.

Table 3. Weighted prevalence (%) of each binary sleep problem and category of the sleep-problem index, by CKD status: total study population, 2005–2014

Prevalence (%)	All (*n*=27,322)	No CKD (*n*=22,100)	CKD (*n*=5222)
Trouble sleeping	25.9	25.2	30.0
Sleep disorder	8.5	7.9	11.6
Nocturia	24.3	21.4	40.3
Inadequate sleep	36.5	36.7	35.5
Excessive sleep	2.4	1.9	5.0
Sleep-problem index score[a]			
0	39.0	40.6	30.1
1	36.2	36.2	36.4
2–4	24.8	23.2	33.5

[a]Sleep-problem index was created by summing the number of problems (trouble sleeping, sleep disorder, nocturia, inadequate sleep) reported by each subjects.

Discussion

Our analysis of data from a series of contemporary, nationally representative surveys over the past decade shows that the prevalence of self-reported sleep problems—trouble sleeping, sleep disorders, nocturia, inadequate sleep, and excessive sleep—were generally higher in adults with CKD than those without CKD in the United States. We observed monotonic associations between severity of CKD (based on ACR, eGFR, and CKD prognostic categories) and sleep problems adjusting for potential confounders. The sleep problems most strongly and consistently associated with all CKD measures were excessive sleep and, to a lesser extent, nocturia. All measured sleep problems, except trouble sleeping among patients with CKD, were positively associated with mortality, and we found a dose-response association between the number of sleep problems and mortality. The sleep problem with the strongest association with mortality was the one with the lowest prevalence, excessive sleep, which likely reflects the influence of major chronic health problems. These findings highlight the

Table 4. Estimated association between each sleep problem and all-cause mortality, by CKD status: total study population, 2005–2014

Sleep Problem	All (*n*=27,322)		No CKD (*n*=22,100)		CKD (*n*=5222)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Trouble sleeping	1.4 (1.2 to 1.5)	1.0 (0.88 to 1.2)	1.4 (1.1 to 1.6)	1.1 (0.89 to 1.4)	1.2 (1.0 to 1.4)	0.97 (0.81 to 1.2)
Sleep disorder	1.6 (1.4 to 1.9)	1.2 (0.97 to 1.5)	1.6 (1.2 to 2.1)	1.1 (0.86 to 1.5)	1.2 (0.97 to 1.6)	1.2 (0.93 to 1.7)
Nocturia	2.9 (2.6 to 3.3)	1.2 (1.1 to 1.4)	2.5 (2.2 to 2.9)	1.3 (1.1 to 1.5)	1.8 (1.6 to 2.2)	1.2 (0.99 to 1.5)
Sleep duration						
Inadequate	1.0 (0.91 to 1.1)	1.1 (0.95 to 1.2)	0.99 (0.84 to 1.2)	0.99 (0.83 to 1.2)	1.0 (0.89 to 1.2)	1.2 (1.0 to 1.4)
Recommended	1	1	1	1	1	1
Excessive	3.6 (3.0 to 4.4)	1.7 (1.3 to 2.1)	2.7 (1.8 to 3.9)	2.3 (1.5 to 3.6)	2.6 (2.0 to 3.3)	1.5 (1.1 to 2.0)

Data are presented as crude and adjusted hazard ratios and 95% CIs. Data adjusted for survey year, age, sex, race/ethnicity, diabetes, hypertension, obesity, smoking, cardiovascular disease, chronic respiratory disease, cancer, other sleep problems, and medications that affect drowsiness and cognition (sedatives, stimulants, and other drugs). Additional adjustment of CKD status for the analysis for "all". HR, hazard ratio.

importance of remaining alert to the presence of sleep problems among those with CKD both by primary care and by specialist providers.

The prevalence of reported sleep disorders, especially trouble sleeping and sleep disorder, has risen over the past 10 years and almost doubled among persons with CKD. These findings are supported by evidence in the general population of the increasing prevalence of sleep-disordered breathing including obstructive sleep apnea (OSA), purportedly due in part to the obesity epidemic and an aging society (2,21). Thus, the increasing prevalence of self-reported sleep disorders in this study may not only reflect an artifactual increase in reporting.

The increasing prevalence of self-reported insomnia and excessive daytime sleepiness among the United States population from 2002 to 2012 was reported by Ford *et al.* (22). Moreover, sleep duration has been declining over the years in the United States and reached an average of 7.2 hours per night in 2012 (23). According to Knutson *et al.* (24), who compiled time-diary data from eight national studies conducted between 1975 and 2006, the percentage of United States adults having <6 hours sleep per night ("short sleepers") fluctuated inconsistently from a low of 8% in 1992–1994 to a high of 12% in 1998–1999; the prevalence in 2006 was 9%. In contrast, we found the prevalence of <6 hours sleep per night in 2005–2006 to be 13% and this was relatively stable through 2013–2014 (data not shown for <6 hours/night). This inconsistency may be due to the different methods used to measure sleep duration, *i.e.*, time diaries used by Knutson *et al.* (24) versus recall-based self-reports used in our study.

We found that the low eGFR category was associated, as expected, with higher prevalences of nocturia and excessive sleep, but not with the other sleep problems; in fact, the high eGFR category was associated with inadequate sleep, which may, at least in part, potentially reflect longer work hours (23) or other factors (*e.g.*, stress, anxiety, depression). We

Table 5. Estimated associations of excessive sleep and category of the sleep-problem index score with all-cause mortality, by CKD status: total study population, 2005–2014

Association	All (*n*=27,322)		No CKD (*n*=22,100)		CKD (*n*=5222)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Excessive sleep versus recommended sleep[a]	3.6 (3.0 to 4.4)	1.7 (1.3 to 2.1)	2.7 (1.8 to 3.9)	2.3 (1.5 to 3.6)	2.6 (2.0 to 3.3)	1.5 (1.1 to 2.0)
Sleep-problem index score[b]						
0	1	1	1	1	1	1
1	1.6 (1.4 to 1.8)	1.1 (0.98 to 1.3)	1.4 (1.1 to 1.7)	1.1 (0.85 to 1.4)	1.5 (1.2 to 1.8)	1.2 (1.0 to 1.5)
2–4	2.2 (1.9 to 2.5)	1.2 (1.1 to 1.5)	1.9 (1.5 to 2.4)	1.2 (0.95 to 1.6)	1.6 (1.3 to 2.0)	1.3 (1.0 to 1.6)
P for trend[c]	<0.001	0.01	<0.001	0.11	<0.001	0.02

Sleep-problem index was created by summing the number of problems (trouble sleeping, sleep disorder, nocturia, inadequate sleep) reported by each subjects. Data are presented as crude and adjusted hazard ratios and 95% CIs. HR, hazard ratio.
[a]Adjusted for survey year, age, sex, race/ethnicity, diabetes, hypertension, obesity, smoking cardiovascular disease, chronic respiratory disease, cancer, sleep problem index, and medications that affect drowsiness (sedatives, stimulants, and other drugs). Additional adjustment of CKD status for the analysis for "all".
[b]Adjusted for excessive sleep, survey year, age, sex, race/ethnicity, diabetes, hypertension, obesity, smoking, cardiovascular disease, chronic respiratory disease, and cancer. Additional adjustment of CKD status for the analysis for "all".
[c]Sleep-problem index was considered as an interval variable (0–4) to test for a monotonic trend.

Table 6. Estimated association between each sleep problem and all-cause mortality, overall and by CKD status in 2005–2014 for the total study population

Sleep Characteristics	All (n=27,322)		No CKD (n=22,100)		CKD (n=5222)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Trouble sleeping	1.6 (1.1 to 2.3)	1.4 (0.89 to 2.1)	1.5 (0.89 to 2.5)	1.3 (0.76 to 2.4)	1.5 (0.97 to 2.3)	1.4 (0.77 to 2.4)
Sleep disorder	1.9 (1.2 to 3.0)	1.3 (0.79 to 2.2)	2.2 (1.0 to 4.8)	1.7 (0.74 to 3.9)	1.2 (0.68 to 2.2)	1.1 (0.50 to 2.3)
Nocturia	3.2 (2.5 to 4.3)	1.3 (0.96 to 1.8)	2.7 (1.8 to 4.0)	1.4 (0.83 to 2.4)	2.1 (1.4 to 3.3)	1.3 (0.77 to 2.3)
Sleep duration						
Inadequate sleep	1.0 (0.76 to 1.5)	0.95 (0.63 to 1.4)	0.83 (0.54 to 1.3)	0.70 (0.41 to 1.2)	1.4 (0.86 to 2.1)	1.3 (0.75 to 2.3)
Recommended	1	1	1	1	1	1
Excessive sleep	4.7 (3.1 to 7.4)	2.1 (1.3 to 3.5)	3.1 (1.3 to 7.3)	2.5 (1.0 to 6.2)	3.6 (2.0 to 6.4)	2.2 (1.2 to 4.3)

Sensitivity analysis of all participants in the study population where follow-up is limited to 1 year. Adjusted for survey year, age, sex, race/ethnicity, diabetes, hypertension, obesity, smoking, other sleep problems, cardiovascular disease, chronic respiratory disease, cancer, and medications that affect drowsiness and cognition (sedatives, stimulants, and other drugs). Additional adjustment of CKD status for the analysis for "all". Data are presented as crude and adjusted hazard ratios and 95% CIs. HR, hazard ratio.

were not, however, able to assess the influence of employment status or work hours on the associations with eGFR.

Plantinga *et al.* (5) found a higher prevalence of sleep disorders and inadequate sleep (≤6 hours/night) for persons with CKD stages 1 and 2, but not for stages 3 and 4, relative to persons without CKD. We found a similar but very weak association with inadequate sleep (<7 hours/night) but little or no association with sleep disorder (Table 2). Similar to Plantinga *et al.* (5), we found that nocturia was strongly associated with CKD, regardless of the method used to characterize CKD. It is possible that people with lower eGFR tend to be more often on multiple medications, be more fatigued, and therefore have longer sleep duration (which may clinically be [mis]interpreted as "good sleep"). Because GFR has a weaker association with obesity than do the other CKD measures (25), another possible explanation is that patients with lower eGFR may not be getting the requisite sleep diagnostic workup as frequently, due either to low index of suspicion by the clinician, or greater attention to kidney-specific complications in the setting of having to deal with multiple clinical domains (*e.g.*, BP control, management of anemia, bone and mineral metabolism and fluid-electrolyte abnormalities, CKD progression) in the limited time typically available for an average clinical encounter. This could result in the patient not receiving a sleep study, and thus not being aware of the presence of a sleep disorder.

Although only 2% of participants reported excessive sleep, this problem was most strongly associated with all four CKD measures (Table 2) and all-cause mortality in the total sample (Table 4). For the associations between sleep duration and all-cause mortality, a positive monotonic association was found in participants without CKD, indicating that more sleep is associated with mortality; but a U- or J-shaped association was observed among those with CKD, indicating that both inadequate and excessive sleep are associated with mortality (Table 4). A similar U-shaped association has been reported in previous studies (6,26–28). Sleep fragmentation, immune dysfunction, photoperiodic abnormalities, depression, underlying disease process such as sleep apnea, heart disease, or failing health are potential mechanisms linking excessive sleep duration with mortality (29). The prevalence of sleeping >9 hours a night in the United States varied a little across studies: 5% reported excessive sleep in 2006 in Patel *et al.* (30), 4% in 2014 according to Liu *et al.* (31), and 2% in our study.

Unlike the association between inadequate sleep and mortality, the underlying mechanisms for the association between excessive sleep and mortality are yet to be fully investigated. This association could be confounded by other unmeasured risk factors for mortality such as comorbidities (32). Comorbidities such as chronic respiratory disease, cancer, and CVD were adjusted for in the study, but they were self-reported; thus, their misclassification may have limited control for confounding. Furthermore, excessive sleep could simply be a marker of poor sleep quality, chronic pain, increased duration of rapid-eye-movement sleep, or soporific side effects of medications (33).

Short sleep duration has also been found in several systematic reviews to be associated with a number of adverse health outcomes including mortality (6,27,28,34–36). Possible mechanisms for the health effects of inadequate sleep are endocrinologic, immunologic, and metabolic factors such as increased ghrelin and decreased leptin (37,38), chronic inflammation, altered cortisol secretion and growth hormone metabolism (39,40), the development of hypertension from increased sympathetic nervous system activity, and changes in circadian rhythm (41). In our study, however, we found little positive association between inadequate sleep and CKD or mortality. That apparent discrepancy might be due to our data being derived from self-reports, rather than more objective methods such as actigraphy or polysomnography, which may not strongly correlate with self-reports from surveys (32).

We found that nocturia was strongly associated with CKD and mortality regardless of the method used to characterize CKD. Nocturia is one of the most common symptoms in patients with CKD (42), with a prevalence of 40% in our study. A trend of increased mortality with increased number of voiding episodes in the general population was also reported in NHANES III participants (43). Król *et al.* (44) reported that nocturia was associated with albuminuria,

which is consistent with our finding of a dose-response association with ACR (Table 2). Studies have showed that osmotic diuresis rather than water diuresis or urea excretion is the main mechanism of nocturia in CKD (45). Possible mechanisms of nocturia include an overall increase in urine production (secondary to diminished ability to concentrate urine by a poorly functioning kidney), resulting in continued higher volume of urine production even at night, a reduced bladder capacity, or any sleep disorder (46). Aside from urologic conditions, nocturia may also reflect multiple underlying renal or systemic diseases (47). In addition, it is linked to urinary urgency, prostate cancer, obstructive sleep apnea, depression, and the metabolic syndrome (48,49).

An important limitation of this study concerns the measurement of sleep problems. First, self-reports may be inaccurate, possibly resulting in bias in estimating the prevalence of the sleep problems or their associations with CKD or mortality. Second, detailed information was lacking on reported sleep problems, especially relevant for trouble sleeping and sleep disorder. For trouble sleeping, we did not know the frequency, duration, or timing of reported problems. For sleep disorder, we did not know the type or nature of the disorder that a doctor presumably told the patient he or she had. Third, persons with CKD, especially advanced CKD, are generally more likely than those without CKD to be seeing a physician on a regular basis. Therefore, they may have been more likely to report communicating with their doctors about sleep problems and specific sleep disorders, even if those two problems were not more frequent or severe. Finally, although our composite sleep index was an *ad hoc* measure, there is evidence of its construct validity in Table 5, where it was monotonically associated with mortality, consistent with our hypothesis; and we found the index to have good reliability with Cronbach α of 0.57.

Another limitation is the cross-sectional design for estimating associations between CKD and sleep problems. Thus, we cannot determine whether associations may have been due to the effects of CKD on sleep problems, as hypothesized, or to the possible effects of sleep problems on CKD (50). Finally, a limitation of this study is residual confounding due to unmeasured risk factors for the outcomes in our analyses (sleep problems or mortality). We adjusted for several demographic and clinical risk factors, but we were not able to adjust for others such as benign prostatic hyperplasia, socioeconomic status, cognitive impairment, and mental-health status. In the analyses of mortality, unmeasured confounders may have exaggerated the positive associations with certain sleep problems, particularly excessive sleep. The fact that our adjusted associations tended to be noticeably weaker than the corresponding crude associations suggests that it was not possible, with the available data, to fully control for confounding. On the other hand, some covariates we adjusted for may have been mediators in causal pathways linking sleep problems with mortality, which could have resulted in underestimates of the effects of interest.

Several unique aspects, strengths of our study, and advantages over previous NHANES studies of sleep problems in the United States, merit attention (5,28,43). The fact that we analyzed a large, randomly selected, contemporary, representative sample of the United States population of persons with and without CKD from several biennial surveys, the use of sampling weights to reflect the complex survey designs, and the use of comparable data collection methods across surveys enhanced our ability to make reliable statistical inferences about the adult population in the United States. We measured five sleep problems, a composite sleep-problem index, and four complementary measures of CKD (5,28); we adjusted for several potential confounders; and we used a state-of-the-art method, multiple imputation, to handle missing data—all of which helped to enhance causal inference.

In conclusion, the relatively high prevalence of sleep problems among persons with CKD in the United States and the associations of those sleep problems with mortality underscore their potential clinical importance of addressing this topic by both primary care providers as well as by specialists. Future work could address the feasibility of early identification, objective characterization, and management of sleep problems among patients with CKD and ESKD by studying the effects of those proactive practices on patient health, disease progression, and other clinically relevant outcomes.

Author Contributions

J. Bragg-Gresham, H. Morgenstern, and M. Shieu were responsible for methodology; J. Bragg-Gresham and M. Shieu were responsible for data curation; H. Morgenstern was responsible for visualization; H. Morgenstern and R. Saran provided supervision; H. Morgenstern, R. Saran, and M. Shieu conceptualized the study and were responsible for resources; H. Morgenstern and M. Shieu wrote the original draft; R. Saran was responsible for funding acquisition; M. Shieu was responsible for formal analysis, investigation, project administration, software, and validation; and all authors reviewed and edited the manuscript.

Disclosures

H. Morgenstern has been a consultant at Arbor Research Collaborative for Health. All remaining authors have nothing to disclose.

Funding

This study was done under the auspices of the Supporting, Maintaining and Improving the Surveillance System for Chronic Kidney Disease in the U.S., Cooperative Agreement Number, U58 DP006254, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

Supplemental Material

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000862019/-/DCSupplemental.

Supplemental Table 1. List of medications that affect drowsiness and cognition included in the study.

Supplemental Table 2. Number of participants, by joint and marginal categories of eGFR and albuminuria; total study population, 2005–2014.

Supplemental Table 3. Standardized prevalence (%) of each sleep problem and sleep-problem index, by CKD status; total study population, 2005–2014.

Supplemental Table 4. Weighted prevalence (% and 95% CI) of each sleep problem, by category of CKD prognosis; total study population, 2005–2014.

Supplemental Table 5. Crude prevalence (% and 95% CI) of each sleep problem (A–E), by joint and marginal categories of eGFR and albuminuria; total study population, 2005–2014.

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Received: December 3, 2019 **Accepted:** April 24, 2020

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