The Association of Sleep Duration and Quality with CKD Progression

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ABSTRACT

Evidence suggests that sleep disorders are common in individuals with CKD, but the influence of sleep duration and quality on CKD progression is unknown. We examined the association of habitual sleep duration and quality with CKD progression in 431 Chronic Renal Insufficiency Cohort (CRIC) Study participants, of whom 48% were women and 50% had diabetes (mean age of 60 years old, mean eGFR =38 ml/min per 1.73 m^2, and median urine protein-to-creatinine ratio [UPCR] =0.20 g/g). We assessed sleep duration and quality by 5–7 days of wrist actigraphy and self-report. Primary outcomes were incident ESRD, eGFR slope, log-transformed UPCR slope, and all-cause death. Participants slept an average of 6.5 hours per night; mean sleep fragmentation was 21%. Over a median follow-up of 5 years, we observed 70 ESRD events and 48 deaths. In adjusted analyses, greater sleep fragmentation associated with increased ESRD risk (hazard ratio, 1.04; 95% confidence interval, 1.01 to 1.07 per 1% increase in fragmentation). In adjusted mixed effects regression models, shorter sleep duration (per hour less) and greater sleep fragmentation (per 1% more) each associated with greater eGFR decline (−1.12 and −0.18 ml/min per 1.73 m^2 per year, respectively; P=0.02 and $P<0.01$, respectively) and greater log UPCR slope (0.06/yr and 0.01/yr, respectively; P=0.02 and $P<0.001$, respectively). Self-reported daytime sleepiness associated with increased risk for all-cause death (hazard ratio, 1.11; 95% confidence interval, 1.02 to 1.20 per one-point increase in the Epworth Sleepiness Scale score). These findings suggest that short and poor-quality sleep are unrecognized risk factors for CKD progression.

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Given the steady increase in the prevalence of CKD and ESRD and the high mortality rate for patients with CKD,[1] it is important to identify risk factors for the progression of CKD. There is increasing evidence for an association between sleep duration and/or quality and the prevalence and severity of hypertension and diabetes, which are among the best documented risk factors for the progression of CKD.[2–4]

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Decreases in sleep duration and/or quality have been shown to be associated with deleterious effects on cardiac vagal tone, levels of proinflammatory cytokines, insulin resistance, glucose tolerance, and hormonal regulation of appetite.[5–10] Furthermore, there is evidence to suggest that sleep disturbances may have an adverse effect on kidney function. Sleep is a major modulator of kidney function, because urinary and sodium output is suppressed during normal sleep. Moreover, the hormones of the renin-angiotensin-aldosterone system exhibit large diurnal variations that are dependent on sleep.[11–13] Thus, insufficient or impaired sleep in CKD could increase the risk of specific comorbidities or accelerate its progression. This study evaluates the role of habitual objectively assessed sleep duration and quality as risk factors for progression of CKD and death in individuals enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study and the Hispanic CRIC Study.

RESULTS

Baseline Demographic and Clinical Characteristics

Of the 537 participants enrolled, 68 were excluded due to the development of ESRD before the sleep assessment; 14 were excluded due to incomplete actigraphy data; 16 were excluded due to incomplete data on eGFR, body mass index (BMI), BP, or glucose; seven were excluded due to eGFR<10 or >80 ml/min per 1.73 m^2; and one was excluded due to completion of the sleep study after the follow-up period ended (Figure 1). The baseline characteristics of the remaining 431 participants are summarized in Table 1 overall and by ESRD status at the end of follow-up. The overall mean age was 60 years old, 48% were women, 35% were non-Hispanic white, 32% were non-Hispanic black, and 31% were Hispanic. The mean BMI was 34 kg/m^2, 50% were diabetic, the mean eGFR was 38 ml/min per 1.73 m^2, and the median urine protein-to-creatinine ratio (UPCR) was 0.20 g/g. Compared with individuals who did not develop ESRD during follow-up, those who progressed to ESRD were more likely to be older (60 versus 57 years old), were more likely to be non-Hispanic black (60% versus 26%), had higher systolic BP (137 versus 129 mm Hg), had lower baseline eGFR (25 versus 41 ml/min per 1.73 m^2), and had higher UPCR (1.28 versus 0.15 g/g).

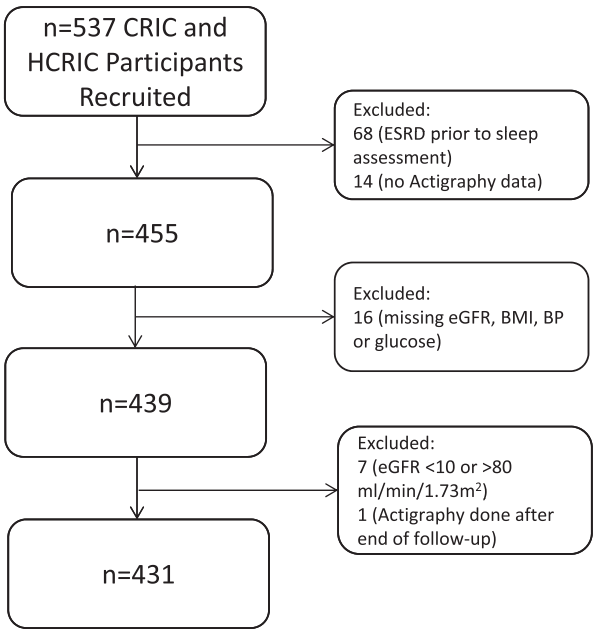

Figure 1. Participants included and excluded from this study. HCRIC, Hispanic Chronic Renal Insufficiency Cohort.

Sleep Measures

The overall mean sleep duration was 6.5 hours, the mean sleep fragmentation was 21%, and the mean sleep start time was 11:32 post meridian (p.m.). The mean (SD) Pittsburgh Sleep Quality Index (PSQI) score was 8.1 (4.5), and 26% had an Epworth Sleepiness Scale (ESS) score greater than ten. Compared with individuals who did not develop ESRD during follow-up, participants who progressed to ESRD were more likely to have shorter sleep duration (5.8 versus 6.6 hours), higher sleep fragmentation (26% versus 20%), and later sleep start time (11:59 p.m. versus 11:27 p.m.) (Table 1).

Outcomes

The median (interquartile range [IQR]) follow-up times were 5.2 (IQR, 1.4–5.9) years for ESRD and 5.4 (IQR, 1.5–6.0) years for all-cause mortality. We observed 70 ESRD events and 48 deaths. Event rates per 100 person-years of follow-up for the entire cohort are shown in Figure 2, and Table 2 shows these rates stratified by level of eGFR at study entry (above versus below the mean of 38 ml/min per 1.73 m^2).

Renal Outcomes

In multivariate-adjusted Cox proportional hazards models, greater sleep fragmentation was associated with a 4% increased risk of ESRD (hazard ratio [HR], 1.04; 95% confidence interval [95% CI], 1.01 to 1.07 per 1% higher fragmentation) (Table 2). There was no significant association between any of the other evaluated predictors and ESRD.

In mixed effects regression models of eGFR slope, shorter sleep duration (per 1 hour less) was associated with a greater decline in eGFR over time (−1.12 ml/min per 1.73 m^2 per year; P=0.02), and each 1% higher sleep fragmentation was associated with a greater decline in eGFR over time (−0.18 ml/min per 1.73 m^2 per year; P<0.01) (Table 3). There was no significant association between sleep start time or self-reported sleep measures and eGFR slope (Table 3). In mixed effects regression models of log-transformed UPCR, each hour shorter sleep duration was associated with increased protein excretion over time (β-coefficient =0.06/yr; P=0.02), and each 1% higher sleep fragmentation was associated with increased protein excretion over time (β-coefficient =0.01/yr; P<0.001).

Table 1. Baseline characteristics

Variables	Overall, *n*=431	ESRD during Follow-Up		*P* Value
		Yes, *n*=70	No, *n*=361	
Demographics				
Age, yr	59.7 (10.4)	56. 9 (11.2)	60.3 (10.1)	0.01
Women	208 (48.3%)	37 (52.9%)	171 (47.4%)	0.40
Race/ethnicity				<0.01
Non-Hispanic white	152 (35.3%)	16 (22.9%)	136 (37.7%)	
Non-Hispanic black	137 (31.8%)	42 (60.0%)	95 (26.3%)	
Hispanic	134 (31.1%)	8 (11.4%)	126 (34.9%)	
Other	8 (1.9%)	4 (5.7%)	4 (1.1%)	
Annual household income <$20,000	186 (42.3)	36 (51.4%)	150 (41.6%)	0.13
High school graduate	306 (71.0%)	52 (74.3%)	254 (70.4%)	0.51
Married	62 (14.4%)	15 (21.4%)	47 (13.0%)	0.07
Clinical history/laboratory				
Current smoking	57 (13.2%)	14 (20.0%)	43 (11.9%)	0.07
Hypertension	408 (94.7%)	68 (97.1%)	340 (94.2%)	0.31
Diabetes	217 (50.3%)	37 (52.9%)	180 (49.9%)	0.65
Cardiovascular disease	162 (37.6%)	31 (44.3%)	131 (36.3%)	0.21
MI or revascularization	110 (25.5%)	18 (25.7%)	92 (25.5%)	0.97
Heart failure	43 (10.0%)	7 (10%)	36 (10.0%)	0.99
Stroke	52 (12.0%)	13 (18.6%)	39 (10.8%)	0.07
Peripheral arterial disease	28 (6.5%)	9 (12.9%)	19 (5.3%)	0.02
Chronic obstructive pulmonary disease	34 (8.0%)	6 (8.7%)	28 (7.8%)	0.81
Family history of coronary heart disease	78 (18.1%)	13 (18.6%)	65 (18.0%)	0.91
ACE inhibitor or ARB use	287 (66.9%)	42 (60.9%)	245 (68.1%)	0.25
Medication for sleep ≥1/wk	18 (14.6%)	0 (0%)	18 (15.5%)	0.26
BMI, kg/m^2	33.7 (9.2)	34.2 (10.5)	33.6 (8.9)	0.59
Waist circumference, cm	107.7 (17.2)	108.4 (18.2)	107.5 (17.0)	0.69
Systolic BP, mm Hg	130 (20)	137 (20)	129 (20)	0.004
Diastolic BP, mm Hg	71 (12)	71 (12)	70 (12)	0.64
Total cholesterol, mg/dl	172.4 (40.5)	173.5 (40.7)	172.2 (40.6)	0.83
LDL cholesterol, mg/dl	93.8 (30.4)	94.8 (31.4)	93.6 (30.2)	0.78
HDL cholesterol, mg/dl	45.6 (14.9)	44.5 (14.0)	45.9 (15.1)	0.52
Hemoglobin, g/dl	12.3 (1.8)	11.2 (1.7)	12.5 (1.7)	<0.001
Urine sodium, mmol/L	78.1 (31.1)	71.0 (22.9)	79.5 (32.3)	0.04
Kidney function				
Serum creatinine, mg/dl	1.98 (0.83)	2.96 (1.07)	1.79 (0.61)	<0.001
eGFR, ml/min per 1.73 m^2	38.3 (14.5)	24.8 (10.6)	40.9 (13.7)	<0.001
eGFR category				<0.01
<30	124 (28.8%)	51 (72.9%)	73 (20.2)	
30–39	128 (29.7%)	11 (15.7%)	117 (32.4%)	
40–49	89 (20.6%)	7 (10.0%)	82 (22.7%)	
50–59	50 (11.6%)	1 (1.4%)	49 (13.6%)	
>60	40 (9.3%)	0 (0%)	11.1 (31.4%)	
UPCR, g/g, median (IQR)	0.20 (0.07–0.81)	1.28 (0.45–3.02)	0.15 (0.06–0.52)	
Sleep variables				
Sleep duration, h	6.5 (1.4)	5.9 (1.3)	6.6 (1.3)	<0.001
Sleep fragmentation, %	21.1 (9.8)	26.0 (12.6)	20.2 (8.8)	<0.001
Sleep start (hh:mm)	23:32 (1:37)	23:59 (1:44)	23:27 (1:35)	0.01
PSQI	8.1 (4.5)	8.5 (4.2)	8.1 (4.5)	0.51
ESS score	7.9 (4.9)	8.3 (5.0)	7.9 (4.9)	0.47
ESS>10	110 (26.3%)	21 (31.8%)	89 (25.2)	0.26

Values are mean (SD) or n (%) unless otherwise indicated. MI, Myocardial infarction; ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; hh:mm, hours:minutes.

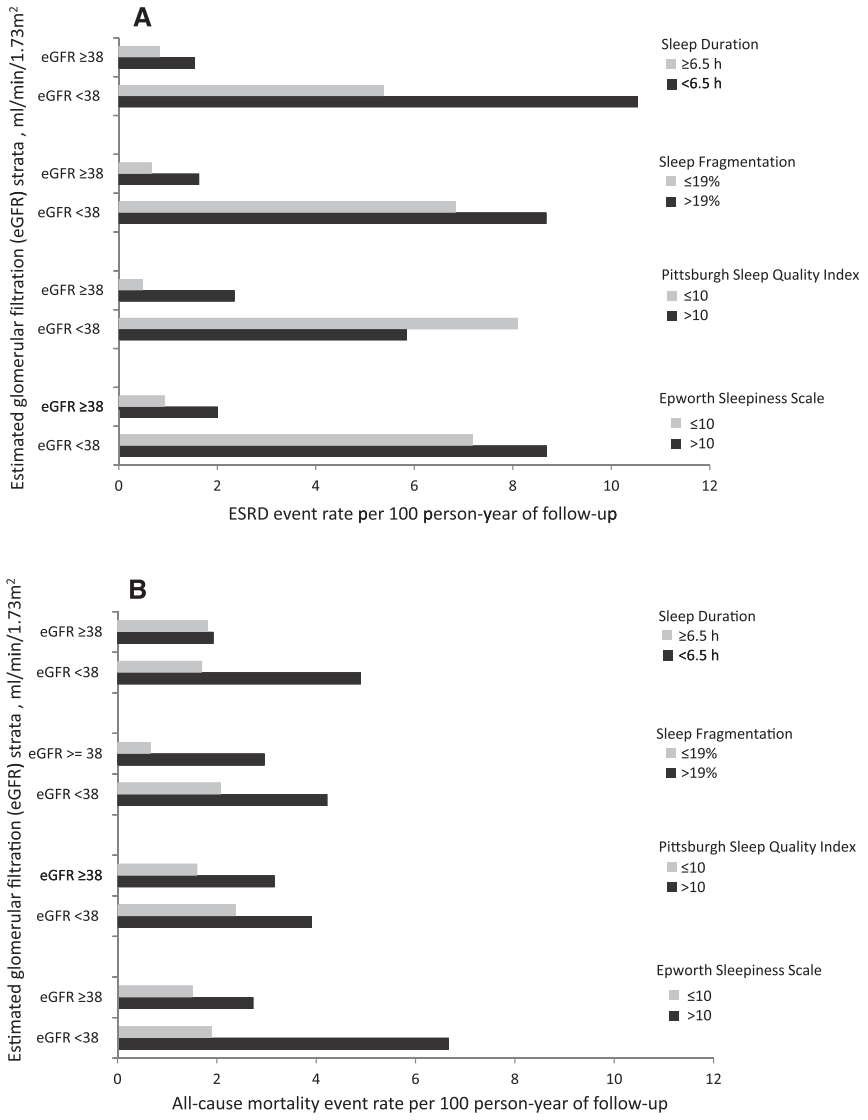

Figure 2. Individuals with short sleep duration, high sleep fragmentation, and daytime sleepiness experienced higher rates of ESRD and all-cause mortality. Event rates per 100 person-years stratified by level of estimated glomerular filtration rate (eGFR above or below the mean of 38 ml/min per 1.73 m^2) for each sleep predictor variable, for the outcomes (A) end-stage renal disease (ESRD) and (B) all-cause mortality.

All-Cause Mortality

Every 1% higher sleep fragmentation was associated with a 4% higher risk for all-cause death in multivariable analyses adjusted for demographic factors (HR, 1.04; 95% CI, 1.01 to 1.06). However, this association was attenuated and no longer significant after adjustment for clinical characteristics and laboratory measurements (HR, 1.03; 95% CI, 1.00 to 1.07). Sleepiness, as measured by the ESS, was associated with an 11% increased risk for all-cause death in the fully adjusted model (HR, 1.11; 95% CI, 1.02 to 1.20 per one score point higher). We found no significant association with self-reported sleep quality over the past month (PSQI) or sleep start time.

We found no evidence of a U-shaped association between the sleep duration and the outcomes evaluated. Furthermore, there was no evidence of effect modification by diabetes status.

DISCUSSION

In this large prospective cohort study of adults with predialysis CKD, we report important associations of objective measures of sleep duration and quality with CKD progression. We found that high sleep fragmentation was associated with a higher risk for incident ESRD. In addition, higher sleep fragmentation and shorter sleep duration were each associated with steeper decline in eGFR and increase in proteinuria over time. Furthermore, subjectively measured daytime sleepiness was associated with heightened risk of death from any cause. To the best of our knowledge, this is the first study to show a significant association between objective measures of disordered sleep and loss of kidney function among patients with CKD.

Sleep disturbances (notably sleep disordered breathing, restless legs syndrome, insomnia, and excessive daytime sleepiness) are common in patients with ESRD and associated with impairment of quality of life and increased mortality.[14] Less is known about the implications of sleep disturbances in CKD before ESRD. Indeed, to date, there are little data regarding the association of objective sleep duration and quality with CKD outcomes. We found that each 1 hour of shorter sleep duration was significantly associated with a modest decline in eGFR over time. Our results are in concordance with some but not all other studies in non-CKD populations. A Japanese study and a recent analysis from the Nurses' Health Study each reported that short self-reported sleep duration was associated with rapid decline in renal function.[15,16] In contrast, in the Coronary Artery Risk Development in Young Adults (CARDIA) Study,[17] which is a community-based cohort of young to middle-aged black and white adults without CKD, shorter sleep duration was associated with a modest increase in eGFR over time. These discordant findings could be related to differences in population characteristics and ascertainment of the exposure.

There are several potential explanations for the association between short sleep and faster decline in eGFR. Experimental sleep deprivation has been shown to cause acute increases in BP and heart rate,[18] activation of the sympathetic nervous system, increased salt retention,[19,20] and alterations of glucose metabolism.[8] Indeed, in general populations, short sleep duration (<5–7 hours) has been associated with increased risk for adverse outcomes, including incident hypertension,[21] type 2

Table 2. Results from Cox proportional hazards regression models

Predictors and Outcomes	Model 1[a]	*P* Value	Model 2[b]	*P* Value	Model 3[c]	*P* Value
ESRD (dialysis or transplantation)						
Event, *n*	70					
Follow-up time median (IQR)	5.19 (1.38–5.88)					
Event rate, 100 person-yr	4.17					
Sleep duration, per 1 h lower, *n*=397	1.29 (1.08 to 1.55)	<0.01	1.30 (1.06 to 1.58)	0.01	1.15 (0.91 to 1.46)	0.25
Sleep fragmentation, per 1% higher, *n*=397	1.04 (1.02 to 1.06)	<0.001	1.05 (1.03 to 1.07)	<0.001	1.04 (1.01 to 1.07)	0.01
Sleep start time, per 1 h later, *n*=397	1.09 (0.96 to 1.24)	0.20	1.10 (0.94 to 1.27)	0.23	1.13 (0.92 to 1.38)	0.25
PSQI, per one score point higher, *n*=354	0.99 (0.93 to 1.06)	0.83	0.99 (0.92 to 1.06)	0.82	0.98 (0.90 to 1.07)	0.68
ESS, per one score point higher, *n*=385	1.00 (0.95 to 1.05)	0.99	1.02 (0.96 to 1.07)	0.51	1.04 (0.98 to 1.11)	0.21
All-cause mortality						
Event, *n*	48					
Follow-up time median (IQR)	5.42 (1.52–6.03)					
Event rate, 100 person-yr	2.61					
Sleep duration, per 1 h lower, *n*=397	1.15 (0.94 to 1.42)	0.17	1.13 (0.90 to 1.42)	0.31	1.02 (0.79 to 1.31)	0.88
Sleep fragmentation, per 1% higher, *n*=397	1.04 (1.01 to 1.06)	0.004	1.03 (1.00 to 1.07)	0.08	1.03 (0.99 to 1.06)	0.18
Sleep start time, per 1 h later, *n*=397	0.94 (0.78 to 1.15)	0.56	0.94 (0.75 to 1.18)	0.59	0.95 (0.75 to 1.21)	0.68
PSQI, per one score point higher, *n*=354	1.06 (0.99 to 1.14)	0.10	1.07 (0.98 to 1.17)	0.12	1.05 (0.95 to 1.16)	0.34
ESS, per one score point higher, *n*=385	1.12 (1.05 to 1.19)	<0.001	1.14 (1.06 to 1.23)	<0.001	1.11 (1.02 to 1.20)	0.01

Sample sizes presented correspond to the final model.
[a]Model 1: adjusted for clinical site, age, sex, and education.
[b]Model 2: adjusted for variables in model 1 plus smoking, time-updated systolic BP, diabetes, BMI, cardiovascular disease, and urine sodium (millimoles per liter).
[c]Model 3: adjusted for variables in model 2 plus log UPCR and eGFR.

diabetes mellitus,[22,23] and coronary artery disease, all of which are CKD risk factors. Similar to sleep restriction, sleep fragmentation has been associated with increased BP, impaired glucose tolerance, and alterations in cortisol secretion.[7,24,25] We found that fragmented sleep was associated with both the development of ESRD and the steeper decline of eGFR over time. In a prior study of non-CKD participants, there was no independent association between sleep fragmentation and change in eGFR over time.[17] Our findings suggest that individuals with CKD may be particularly vulnerable to the deleterious effects of impaired sleep. Interventions to improve sleep hygiene and avoid short sleep duration need to be evaluated in patients with CKD, with the goal of slowing the progression of CKD.

The association of sleep duration and quality with change in proteinuria over time has not been previously studied. Although this association was statistically significant, the magnitude was modest, and its clinical significance needs to be further evaluated. Nevertheless, changes in proteinuria over time have been shown to predict renal outcomes in CKD.[26,27]

Although we found a significant association between daytime sleepiness and all-cause death, we did not find an association between daytime sleepiness or other self-reported sleep quality measures and CKD progression. In contrast, a recent

Table 3. Results from mixed effects regression models predicting eGFR and log UPCR slope

Sleep Variable	Model 1[a]	*P* Value	Model 2[b]	*P* Value	Model 3[c]	*P* Value
Regression coefficient (SEM) for eGFR slope, ml/min per 1.73 m^2 per yr						
Sleep duration, per 1 h lower, *n*=398	−1.07 (0.52)	0.04	−1.27 (0.53)	0.02	−1.12 (0.50)	0.02
Sleep fragmentation, per 1% higher, *n*=398	−0.22 (0.07)	0.002	−0.23 (0.07)	0.001	−0.18 (0.07)	<0.01
Sleep start time, per 1 h later, *n*=398	−0.74 (0.44)	0.10	−0.89 (0.44)	0.05	−0.62 (0.41)	0.13
PSQI, per one score point higher, *n*=355	0.05 (0.17)	0.78	0.00 (0.17)	0.98	−0.10 (0.16)	0.54
ESS, per one score point higher, *n*=386	0.11 (0.14)	0.43	0.06 (0.14)	0.64	0.06 (0.13)	0.65
Regression coefficient (SEM) for slope of log-transformed UPCR, g/g per yr						
Sleep duration, per 1 h lower, *n*=429	0.09 (0.05)	0.09	0.08 (0.05)	0.07	0.06 (0.02)	0.02
Sleep fragmentation, per 1% higher, *n*=429	0.02 (0.01)	0.001	0.02 (0.01)	0.001	0.01 (0.00)	<0.001
Sleep start time, per 1 h later, *n*=429	0.06 (0.04)	0.14	0.05 (0.04)	0.16	0.01 (0.02)	0.68
PSQI, per one score point higher, *n*=385	0.01 (0.02)	0.59	0.00 (0.01)	0.77	0.01 (0.01)	0.14
ESS, per one score point higher, *n*=417	0.01 (0.01)	0.44	0.01 (0.01)	0.67	−0.00 (0.01)	0.76

Sample sizes presented correspond to the final model.
[a]Model 1: adjusted for clinical site, age, sex, and education.
[b]Model 2: adjusted for variables in model 1 plus smoking, time-updated systolic BP, diabetes, BMI, cardiovascular disease, and urine sodium (millimoles per liter).
[c]Model 3: In addition to the variables in model 2, eGFR slope models are adjusted for baseline log UPCR, and log UPCR models are adjusted for baseline eGFR.

analysis from the CARDIA Study reported that lower self-reported sleep quality was significantly associated with increase in eGFR over time.[17] These heterogeneous findings are probably due to differences in study population, particularly the presence of CKD in our study participants.

Our study has several strengths, including the prospective design, objective measure of the exposure, long-term follow-up, detailed characterization of a wide range of patient features, and systematic ascertainment of the outcomes. However, our study had several limitations. First, the study included a volunteer cohort rather than a representative population-based sample, which may affect generalizability. Second, we did not have an objective estimate of obstructive sleep apnea, a common sleep disorder that may be associated with worse kidney function. Third, given that we measured sleep only once, we were not able to evaluate the effect of kidney function decline on sleep. Fourth, our analyses only included night-time sleep; therefore, we were not able to include an evaluation of daytime naps in our study.

In this prospective cohort study of adults with predialysis CKD, we report that short sleep duration and poor quality are associated with CKD progression. To the best of our knowledge, this is the first study to show a significant association between objective measures of disordered sleep and loss of kidney function among patients with CKD. These findings suggest that impaired sleep is an unrecognized and clinically significant risk factor for CKD progression. Future work is needed to evaluate interventions to improve sleep habits in patients with CKD and assess whether the observed relationship with CKD progression is causal.

CONCISE METHODS

Study Population

The CRIC Study and the Hispanic CRIC Study are ongoing multicenter, prospective, observational studies of risk factors for progression of CKD and cardiovascular disease. The design, methods, and baseline characteristics of study participants have been previously published.[28–30] In brief, the CRIC included 170 Hispanics and 3289 non-Hispanics recruited at seven clinical centers across the United States from May of 2003 to March of 2007, whereas the Hispanic CRIC included 327 Hispanics recruited at the University of Illinois at Chicago and in the Chicago metropolitan area from October of 2005 to June of 2008. Main inclusion criteria were ages 21–74 years old and eGFR=20–70 ml/min per 1.73 m^2. Exclusion criteria were inability to consent, institutionalization, pregnancy, dialysis treatment for longer than 1 month, polycystic kidney disease, organ or bone marrow transplant, immunosuppressive drugs for kidney disease in the past 6 months, chemotherapy within 2 years, current participation in another research study, New York Heart Association class 3 or 4 heart failure, cirrhosis, HIV infection, multiple myeloma, or renal cell carcinoma. For this sleep ancillary study, 537 participants were recruited from two CRIC Study sites (the University of Illinois at Chicago [Chicago, IL] and Case Western Reserve University, including the University Hospital, MetroHealth System, and Cleveland Clinic [Cleveland, OH]). The study protocol was approved by the institutional review boards of all participating centers and is in accordance with the Declaration of Helsinki. All participants provided informed consent.

Sleep Variables

Participants were asked to wear an activity monitor (Actiwatch-16 in the CRIC and Actiwatch-2 in the Hispanic CRIC; Philips/Respironics, Bend, OR) on their wrist continuously for 5–7 days to estimate sleep duration and quality. These activity monitors contain highly sensitive omnidirectional accelerometers that count movements in 30-second epochs. Wrist actigraphy has been validated against polysomnography as a measure of sleep duration.[31] Validated computer software algorithms provided by the manufacturer were used to calculate sleep duration, sleep quality, and sleep timing. Sleep duration was defined as the amount of time between sleep onset and final awakening that is spent sleeping (excludes all awakenings after sleep onset). Sleep fragmentation is a marker of sleep quality and an index of restlessness. It is calculated by summing the percentage of the sleep period that is spent moving (an epoch with more than two activity counts is considered moving) and the percentage of the number of immobile phases (consecutive epochs with no movement) that last only 1 minute or less. Sleep start time is the time of sleep onset, and it is an indicator of the timing of the sleep period.

In addition, participants completed the PSQI and the ESS. The PSQI is a validated 21-item questionnaire to assess subjective sleep quality over the past month.[32] Scores range from zero to 21, and a score greater than five indicates poor subjective sleep quality. The ESS is an eight-item questionnaire that assesses daytime sleepiness.[33,34] Scores range from zero to 24, and a score greater than ten indicates excessive daytime sleepiness.

In these analyses, we used the clinical data from the CRIC Study visit closest to the sleep assessment (index visit), which was done between April of 2006 and October of 2012. On average, there were 21 days between the clinical examination and the sleep assessment. Sixty-eight participants developed ESRD before the sleep assessment and therefore, were excluded from these analyses (Figure 1).

Covariates

Information on sociodemographics, medical history, and medications was obtained at baseline by self-reported questionnaires.[29] Four racial/ethnic groups were examined: non-Hispanic white, non-Hispanic black, Hispanic, and other race or ethnicity. BMI (kilograms per square meter) was calculated using measured height and weight. Diabetes mellitus was defined by a fasting glucose $\geq$126 mg/dl or use of insulin or oral hypoglycemic medications; hypertension was defined by a systolic BP $\geq$140 mm Hg, a diastolic BP $\geq$90 mm Hg, or use of antihypertensive medications. Prior cardiovascular disease was assessed by self-reported history of heart failure, myocardial infarction, coronary revascularization, cerebrovascular accident, peripheral artery revascularization, or amputation. Twenty-four–hour urine samples were collected at the index visit to measure sodium excretion.

Outcomes

We evaluated the following outcomes: (*1*) occurrence of ESRD (defined as receipt of chronic dialysis therapy or kidney transplantation),

(*2*) rate of decline in kidney function (slope of the eGFR over time), (*3*) change in urine protein excretion over time, and (*4*) death from any cause. Ascertainment of ESRD was done through semiannual surveillance by the CRIC Study personnel supplemented by cross-linkage with the US Renal Data System, leading to no missing data for this outcome. GFR was estimated annually during the follow-up period using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[35] UPCR was calculated at each annual clinic visit using a random spot urine sample or at selected visits, a 24-hour urine collection. Deaths were ascertained from reports by next of kin, death certificates, hospital records, and linkage with the Social Security Death Master File. Participants were followed until the occurrence of death, withdrawal from the study, or March of 2013, when the database was locked for analysis.

Statistical Analyses

Descriptive statistics were summarized as mean (SD) or median (IQR) for continuous variables and frequency (proportion) for categorical variables. Chi-squared and ANOVA tests were used to compare categorical and continuous variables, respectively. Because of its skewed distribution, UPCR was log transformed for regression analyses. Event rates (per 100 person-years) for time to event outcomes were calculated as the ratio of the number of participants reaching the event to the total person-years of follow-up before an event or until censoring by using Poisson regression. In addition to the overall event rates, we estimated event rates of ESRD and all-cause mortality associated with categories of sleep duration and quality ($<$6.5 versus $\geq$6.5 hours; sleep fragmentation $>$19% versus $\leq$19%; PSQI$>$10 versus $\leq$10; ESS$>$10 versus $\leq$10) stratified by baseline eGFR (above versus below the mean of 38 ml/min per 1.73 m^2). In computations of event rates and in failure time regression analyses, follow-up times were censored at time of death or end of the follow-up period (March 31, 2013). For slope analyses, follow-up times were censored at the time of ESRD, death, or end of follow-up. In all regression models, we evaluated sleep duration, sleep fragmentation, sleep start time, and PSQI and ESS scores as continuous variables. Cox proportional hazards models were used to examine the association between sleep variables and outcomes. For each outcome, we fitted three nested Cox proportional hazards models, whereby covariates from each prior model are retained as follows. Model 1 included demographic characteristics (clinical site, age, sex, and education). Model 2 added clinical characteristics and laboratory measurements (smoking, diabetes, BMI, systolic BP, cardiovascular disease, and urine sodium excretion), and Model 3 added measures of kidney function (log urine protein excretion per 24 hours and eGFR). These covariates were ascertained at the time of the index visit except for systolic BP, which was time updated on an annual basis. All covariates were chosen on the basis of known clinical importance in prior literature. For slope analyses, linear mixed effects models were used to assess the association between the difference in mean annual change in each continuous outcome (*i.e.*, eGFR or log-transformed UPCR) and each sleep variable after adjusting for covariates. Estimations of GFR after development of ESRD were not taken into account for these analyses. We constructed three nested models as described for failure time analyses. To evaluate the presence of a U-shaped association between sleep duration and outcomes, we added a quadratic term to the final regression model for each outcome. We explored effect modification by diabetes status at baseline by adding an interaction terms between each sleep variable and diabetes to the final regression model. All tests were two sided, and $P<0.05$ was considered significant for hypothesis testing. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

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DISCLOSURES

None.

REFERENCES

1. United States Renal Data System: 2015 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States, 2015. Available at: http://www.usrds.org/2015/view/v2_01.aspx. Accessed December 21, 2015

2. Knutson KL: Sleep duration and cardiometabolic risk: A review of the epidemiologic evidence. *Best Pract Res Clin Endocrinol Metab* 24: 731–743, 2010
3. St-Onge M-P, Grandner MA, Brown D, Conroy MB, Jean-Louis G, Coons M, Bhatt DL; American Heart Association Obesity, Behavior Change, Diabetes, and Nutrition Committees of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council: Sleep duration and quality: Impact on lifestyle behaviors and cardiometabolic health: A scientific statement from the American heart association. *Circulation* 134: e367–e386, 2016
4. Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A: Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis. *Sleep Med Rev* 30: 11–24, 2016
5. Benca RM, Quintas J: Sleep and host defenses: A review. *Sleep* 20: 1027–1037, 1997
6. Krueger JM, Obál FJ, Fang J, Kubota T, Taishi P: The role of cytokines in physiological sleep regulation. *Ann N Y Acad Sci* 933: 211–221, 2001
7. Spiegel K, Leproult R, Van Cauter E: Impact of sleep debt on metabolic and endocrine function. *Lancet* 354: 1435–1439, 1999
8. Spiegel K, Leproult R, L'hermite-Balériaux M, Copinschi G, Penev PD, Van Cauter E: Leptin levels are dependent on sleep duration: Relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J Clin Endocrinol Metab* 89: 5762–5771, 2004
9. Spiegel K, Tasali E, Penev P, Van Cauter E: Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 141: 846–850, 2004
10. Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, Mullington JM: Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol* 43: 678–683, 2004
11. Brandenberger G, Follenius M, Goichot B, Saini J, Spiegel K, Ehrhart J, Simon C: Twenty-four-hour profiles of plasma renin activity in relation to the sleep-wake cycle. *J Hypertens* 12: 277–283, 1994
12. Luthringer R, Brandenberger G, Schaltenbrand N, Muller G, Spiegel K, Macher JP, Muzet A, Follénius M: Slow wave electroencephalic activity parallels renin oscillations during sleep in humans. *Electroencephalogr Clin Neurophysiol* 95: 318–322, 1995
13. Charloux A, Gronfier C, Lonsdorfer-Wolf E, Piquard F, Brandenberger G: Aldosterone release during the sleep-wake cycle in humans. *Am J Physiol* 276: E43–E49, 1999
14. Perl J, Unruh ML, Chan CT: Sleep disorders in end-stage renal disease: 'Markers of inadequate dialysis'? *Kidney Int* 70: 1687–1693, 2006
15. McMullan CJ, Curhan GC, Schernhammer ES, Forman JP: Association of nocturnal melatonin secretion with insulin resistance in nondiabetic young women. *Am J Epidemiol* 178: 231–238, 2013
16. Yamamoto R, Nagasawa Y, Iwatani H, Shinzawa M, Obi Y, Teranishi J, Ishigami T, Yamauchi-Takihara K, Nishida M, Rakugi H, Isaka Y, Moriyama T: Self-reported sleep duration and prediction of proteinuria: A retrospective cohort study. *Am J Kidney Dis* 59: 343–355, 2012
17. Petrov ME, Kim Y, Lauderdale DS, Lewis CE, Reis JP, Carnethon MR, Knutson KL, Glasser SP: Objective sleep, a novel risk factor for alterations in kidney function: The CARDIA study. *Sleep Med* 15: 1140–1146, 2014
18. Grimaldi D, Carter JR, Van Cauter E, Leproult R: Adverse impact of sleep restriction and circadian misalignment on autonomic function in healthy young adults. *Hypertension* 68: 243–250, 2016
19. Lusardi P, Mugellini A, Preti P, Zoppi A, Derosa G, Fogari R: Effects of a restricted sleep regimen on ambulatory blood pressure monitoring in normotensive subjects. *Am J Hypertens* 9: 503–505, 1996
20. Tochikubo O, Ikeda A, Miyajima E, Ishii M: Effects of insufficient sleep on blood pressure monitored by a new multibiomedical recorder. *Hypertension* 27: 1318–1324, 1996
21. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK, Malaspina D: Short sleep duration as a risk factor for hypertension: Analyses of the first national health and nutrition examination survey. *Hypertension* 47: 833–839, 2006
22. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA: Quantity and quality of sleep and incidence of type 2 diabetes: A systematic review and meta-analysis. *Diabetes Care* 33: 414–420, 2010
23. Knutson KL, Ryden AM, Mander BA, Van Cauter E: Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. *Arch Intern Med* 166: 1768–1774, 2006
24. Knutson KL, Van Cauter E, Rathouz PJ, Yan LL, Hulley SB, Liu K, Lauderdale DS: Association between sleep and blood pressure in midlife: The CARDIA sleep study. *Arch Intern Med* 169: 1055–1061, 2009
25. Spiegel K, Leproult R, Colecchia EF, L'Hermite-Balériaux M, Nie Z, Copinschi G, Van Cauter E: Adaptation of the 24-h growth hormone profile to a state of sleep debt. *Am J Physiol Regul Integr Comp Physiol* 279: R874–R883, 2000
26. de Zeeuw D, Remuzzi G, Parving H-H, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. *Kidney Int* 65: 2309–2320, 2004
27. Heerspink HJL, Kröpelin TF, Hoekman J, de Zeeuw D; Reducing Albuminuria as Surrogate Endpoint (REASSURE) Consortium: Drug-induced reduction in albuminuria is associated with subsequent renoprotection: A meta-analysis. *J Am Soc Nephrol* 26: 2055–2064, 2015
28. Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, Fink JC, Franklin-Becker ED, Go AS, Hamm LL, He J, Hostetter T, Hsu C-Y, Jamerson K, Joffe M, Kusek JW, Landis JR, Lash JP, Miller ER, Mohler ER 3rd, Muntner P, Ojo AO, Rahman M, Townsend RR, Wright JT; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators: The Chronic Renal Insufficiency Cohort (CRIC) study: Design and methods. *J Am Soc Nephrol* 14[Suppl 2]: S148–S153, 2003
29. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rahman M, Townsend RR, Xie D, Cifelli D, Cohan J, Fink JC, Fischer MJ, Gadegbeku C, Hamm LL, Kusek JW, Landis JR, Narva A, Robinson N, Teal V, Feldman HI; Chronic Renal Insufficiency Cohort (CRIC) Study Group: Chronic Renal Insufficiency Cohort (CRIC) study: Baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 4: 1302–1311, 2009
30. Fischer MJ, Go AS, Lora CM, Ackerson L, Cohan J, Kusek JW, Mercado A, Ojo A, Ricardo AC, Rosen LK, Tao K, Xie D, Feldman HI, Lash JP: CRIC and H-CRIC Study Groups: CKD in Hispanics: Baseline characteristics from the CRIC (Chronic Renal Insufficiency Cohort) and Hispanic-CRIC studies. *Am J Kidney Dis* 58: 214–227, 2011
31. Jean-Louis G, von Gizycki H, Zizi F, Spielman A, Hauri P, Taub H: The actigraph data analysis software. I. A novel approach to scoring and interpreting sleep-wake activity. *Percept Mot Skills* 85: 207–216, 1997
32. 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* 28: 193–213, 1989
33. Johns MW: A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* 14: 540–545, 1991
34. Johns MW: Reliability and factor analysis of the Epworth sleepiness scale. *Sleep* 15: 376–381, 1992
35. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators: Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 367: 20–29, 2012