DR. KRISTEN L. KNUTSON (Orcid ID : 0000-0002-2751-6168)

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Title: Habitual Sleep and Kidney Function in Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study

Concise Title: Sleep and Kidney Function in CKD

Authors: Kristen L Knutson, PhD[1], James Lash, MD[2], Ana C Ricardo, MD[2], James Herdegen, MD[3], J. Daryl Thornton, MD, [4] Mahboob Rahman, MD[4], Nicolas Turek[1], Janet Cohan[2], Lawrence J Appel, MD[5], Lydia A Bazzano, MD PhD[6], Manjula Kurella Tamura, MD[7], Susan P Steigerwalt, MD[8], Matthew R Weir, MD[9] , Eve Van Cauter, PhD[1] and CRIC Study Investigators*

1. Department of Medicine, University of Chicago, Chicago, IL
2. Department of Medicine, University of Illinois, Chicago
3. Rush University Medical Center, Chicago, IL
4. School of Medicine, Case Western Reserve University
5. Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD
6. Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA
7. Geriatric Research and Education Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA
8. Internal Medicine, University of Michigan, Ann Arbor
9. Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD

* CRIC Study Group investigators include: Harold I. Feldman, MD, MSCE, Alan S. Go, MD, Jiang He, MD, PhD, John W. Kusek, PhD, Akinlolu Ojo, MD, PhD, Raymond R. Townsend, MD

Corresponding Author:

Kristen L Knutson, PhD
Department of Medicine
University of Chicago
5841 S Maryland Ave, MC6076
Chicago, IL 60637
Tel: 773-834-1973
Email: kknutson@medicine.bsd.uchicago.edu
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Summary

Physiologic evidence suggests that sleep modulates kidney function. Our objective was to examine the cross-sectional association between kidney function and objectively-estimated habitual sleep duration, quality and timing in a cohort of patients with mild to moderate chronic kidney disease. This study involved 2 U.S. clinical centers of the Chronic Renal Insufficiency Cohort (CRIC) Study including 432 participants in a CRIC ancillary sleep study. Habitual sleep duration, quality and timing were measured using wrist actigraphy for 5-7 days. Validated sleep questionnaires assessed subjective sleep quality, daytime sleepiness and risk of sleep apnea. Kidney function was assessed with the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation, and the urinary protein to creatinine ratio (PCR). Lower eGFR was associated with shorter sleep duration (-1.1 ml/min/1.73m^2 per hour less sleep, p=.03), greater sleep fragmentation (-2.6 ml/min/1.73m^2 per 10% higher fragmentation, p<.001), and later timing of sleep (-0.9 ml/min/1.73m^2 per hour later, p=.05). Higher PCR was also associated with greater sleep fragmentation (approximately 28% higher per 10% higher fragmentation, p<.001). Subjective sleep quality, sleepiness, and persistent snoring were not associated with eGFR or PCR. Thus, worse objective sleep quality was associated with lower eGFR and higher PCR. Shorter sleep duration and later sleep timing were also associated with lower eGFR. Physicians treating chronic kidney disease patients should consider inquiring about sleep and

possibly sending for clinical sleep assessment. Longitudinal and interventional trials are needed to understand causal direction.

Key Words: circadian rhythms, nephrology, renal, proteinuria

Introduction

Over 20 million adults (approximately 10% of the adult U.S. population) have chronic kidney disease (CKD) (Eckardt et al., 2013, Coresh et al., 2007). Impaired kidney function is associated with increased risk of cardiovascular disease, and age-adjusted mortality and, as kidney function worsens, these risks increase (Eckardt et al., 2013, Gansevoort et al., 2013). Thus, identification of novel, modifiable risk factors associated with the progression of CKD would increase our understanding of the pathophysiology of CKD and potentially lead to new therapies to prevent or delay end-stage renal disease and reduce the health burden associated with CKD.

One novel risk factor may be inadequate sleep, including insufficient sleep, poor sleep quality and later sleep timing. Under normal conditions, sleep profoundly modulates the key hormones involved in the control of kidney function, particularly those of the renin-angiotensin-aldosterone system, which exhibit large diurnal variations that are dependent on sleep (Brandenberger et al., 1994, Charloux et al., 1999, Turek et al., 2012, Hurwitz et al., 2004). Normal sleep suppresses urinary sodium excretion (Rubin et al., 1978) and acute total sleep deprivation reduces the normal nocturnal increases in plasma renin activity (PRA) and aldosterone (Charloux et al., 2001). Sleep quality, independently of sleep duration, may also play an important role in kidney function because during normal sleep, the REM-nonREM cycle drives a robust ultradian oscillation of PRA and aldosterone (Brandenberger et al., 1994, Brandenberger et al., 1988). Experimental studies that manipulated sleep or the circadian system have observed significant changes in several physiological systems that could affect kidney function, including increased sympathetic nervous system activity (Spiegel et al., 2004, Spiegel et al., 1999, Buxton et al., 2010, Tasali et al., 2008, Stamatakis and Punjabi, 2010), alterations in the 24-hour profiles of growth hormone and cortisol (Spiegel et al., 2000, Spiegel et al., 1999, Buxton et al., 2010), increased blood pressure (Tochikubo et al., 1996, Sayk et al., 2010, Scheer et al., 2009) and impaired glucose tolerance (Spiegel et al., 1999, Nedeltcheva et al., 2009, Buxton et al., 2010, Tasali et al., 2008, Stamatakis and Punjabi, 2010, Leproult et al., 2014, Scheer et al., 2009). Given these established associations between sleep, circadian alignment and several physiological systems that affect kidney function, it is possible that habitual sleep patterns could influence the risk and severity of CKD.

Previous research has found that self-reported habitual sleep duration is associated with prevalent and incident CKD (Turek et al., 2012). Studies have found that the prevalence of kidney disease or renal hyperfiltration was higher in those reporting short sleep durations as well as in those reporting long sleep durations compared to those sleeping 7-8 hours/night (Salifu et al., 2014, Lin et al., 2017, Cheungpasitporn et

al., 2016, Kim et al., 2017), although one study only observed this association in women (Choi et al., 2017). Further, the incidence of proteinuria was greater among people reporting shorter sleep duration (≤5 hours/night) in a sample of employees of Osaka University in Japan (Yamamoto et al., 2012). Finally, a study of Japanese type 2 diabetic patients without CKD found that both self-reported short and long sleep durations were significantly associated with higher urinary albumin-creatinine ratios (Ohkuma et al., 2013). Whether or not sleep characteristics are associated with kidney function among people who already have kidney disease remains to be determined.

The aim of the present study was to examine the association between sleep and kidney function, as assessed by both the estimated glomerular filtration rate (eGFR) and the urine protein to creatinine ratio (PCR) in patients with mild to moderate CKD. Habitual sleep duration, quality and timing were objectively assessed via actigraphy and self-reports of sleep quality, daytime sleepiness and risk of sleep apnea were obtained via questionnaires. Our hypothesis was that inadequate sleep, defined as shorter sleep duration, poorer sleep quality, later sleep timing or greater daytime sleepiness, would be associated with worse kidney function.

Methods

CRIC and HCRIC Cohorts

The Chronic Renal Insufficiency Cohort (CRIC) Study is a prospective observational study of over 3,000 subjects with CKD (Feldman et al., 2003). The CRIC Study was established in order to improve our understanding of CKD and its relationship with cardiovascular disease and other complications of CKD. At enrollment, participants were aged 21-74 years, had an estimated GFR value above 20 ml/min/1.73m^2 and below 50-70 ml/min/1.73m^2, depending on age, and approximately 50% had type 2 diabetes mellitus. Exclusion criteria included being institutionalized; having previously undergone dialysis for longer than 1 month; having a previous diagnosis of polycystic kidney disease; having had an organ or bone marrow transplant; having been on immunosuppressive drugs for kidney disease in the past 6 months; cancer chemotherapy within 2 years; current participation in another research study including clinical trials; having New York Heart Association Class III or IV heart failure, cirrhosis, HIV infection or AIDS, multiple myeloma, or renal cell carcinoma (Yaffe et al., 2010). CRIC participants were recruited at seven sites across the United States. This sleep ancillary study recruited subjects from two of these sites: University of Illinois, Chicago, Illinois and Case Western Reserve University, including the University Hospital, the affiliated MetroHealth System, and Cleveland Clinic, in Cleveland, Ohio. A second cohort, the Hispanic CRIC (HCRIC) cohort, was created to increase the number of Hispanics in the study (Fischer et al., 2011). The inclusion/exclusion criteria and the clinical evaluations for HCRIC were identical to CRIC; however, HCRIC involved only one site, the University of Illinois, Chicago. Participants in the CRIC and HCRIC studies participated in annual clinical examinations. We used the clinical data that were obtained closest to the sleep assessment in our analyses. The

interval between the clinical examination and the sleep assessment was 21 days on average; 63% of the sample had the two assessments within 90 days of each other and 92% within 180 days.

Institutional review boards at the University of Chicago, University of Illinois, Chicago and all three sites of Case Western Reserve University approved the protocol. All participants provided written informed consent.

Measurements

Outcome measures

Kidney function was assessed using eGFR and PCR because of their well-established and complementary roles in staging CKD and predicting outcomes. Fasting blood samples were drawn at each clinical examination and serum creatinine was assayed. A 24 hour urine collection was also collected at each clinical examination and protein and creatinine levels were measured. The eGFR (ml/min/1.73m^2) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009). This equation includes log serum creatinine (modeled as a 2-slope linear spline with sex-specific knots), sex, race, and age on the natural scale (Levey et al., 2009). The urine protein-to-creatinine ratio (PCR, mcg/mg) was also calculated.

Sleep

This study included both objective estimates of habitual sleep patterns using wrist activity monitoring and subjective estimates of sleep quality and daytime sleepiness. We also used a validated screening instrument to identify participants likely to have sleep apnea due to snoring symptoms.

Participants wore a wrist activity monitor (Actiwatch-16 in CRIC and Actiwatch-2 in HCRIC, Philips/Respironics, Bend OR) continuously for 5-7 days to estimate habitual sleep duration and quality (n=405). Participants in the CRIC Study were also asked to wear an activity monitor (Actiwatch-64, Philips/Respironics, Bend OR) on one foot at night only for up to 3 nights in order to estimate periodic leg movements and a subset complied and had valid data. In addition, both CRIC and HCRIC participants completed a series of validated questionnaires to estimate risk of sleep apnea, daytime sleepiness and subjective sleep quality.

The activity monitors contain highly sensitive omnidirectional accelerometers that counted movements in 30-second epochs. Wrist actigraphy has been validated against polysomnography, demonstrating a correlation for sleep duration between .82 in insomniacs and .97 in healthy subjects (Jean-Louis et al., 1997). We calculated several measures of sleep using the associated Actiware software. **Sleep duration** is the amount of time that is spent sleeping between sleep onset and final awakening. **Sleep fragmentation** is a marker of sleep quality and is an index of restlessness expressed as a percentage. It is calculated by summing the

percentage of the sleep period that is spent moving (a 30-second epoch with more than 2 activity counts is considered moving) and the percentage of the number of immobile phases (consecutive 30-second epochs with no movement) that last only one minute or less. **Sleep start time** is the time of sleep onset and a marker of the timing of the sleep period. Sleep start time is calculated by the software as the beginning of the first 10-minute period in which no more than one 30-second epoch is scored as mobile. From the foot actigraphy, we estimated the periodic leg movement index (**PLMI**), which is the number of leg movements per hour of sleep, using the Actiware-PLM software. We then dichotomized this variable into <15 and ≥15 movements/hour.

We administered three validated questionnaires: the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS) and the Berlin questionnaire. The PSQI is a validated 19-item questionnaire assessing **subjective sleep quality** over the past month (Buysse et al., 1989). Scores range from 0 to 21 and a score greater than 5 indicates poor subjective sleep quality. The ESS is an 8-item questionnaire assessing **daytime sleepiness** (Johns, 1991, Johns, 1992). Scores range from 0 to 24 and a score greater than 10 indicates excessive daytime sleepiness. Finally, the Berlin questionnaire is a validated screening tool for sleep **apnea** (Netzer et al., 1999). Typically, a participant is identified as highly likely to have sleep apnea if two of three conditions were met: (1) persistent snoring symptoms, (2) persistent daytime dysfunction or sleepiness, or (3) obesity or hypertension. However, since hypertension was present in 95% of this sample , we used only the "persistent snoring symptoms" as an indicator of sleep apnea risk.

Covariates

Covariates used in these analyses include age, sex, race/ethnicity, body mass index, current smoker, alcohol use, and fasting glucose level or presence of diabetes. Four racial/ethnic groups were examined: non-Hispanic white, non-Hispanic black, Hispanic/Latino and other race or ethnicity. Body mass index (kg/m^2) was calculated using measured height and weight. Participants were asked if they were a current smoker (yes/no) and if they consumed alcohol (yes/no). Fasting blood samples were obtained at the clinic examination and levels of glucose were measured. Presence of diabetes was defined as fasting glucose ≥126 mg/dl, random glucose ≥200 mg/dl, or use of insulin or antidiabetic medication.

Statistical Analysis

For descriptive analyses, we calculated means and standard deviations for continuous variables and the percentages for the categorical variables. We examined the distribution of our outcome measures and PCR was log transformed due to a skewed distribution. Thus, the regression coefficients are interpreted as percent change per unit increase in the sleep measure. To test for associations between the sleep measures and the outcome measures, eGFR and PCR, we used separate linear regression models for each outcome and each sleep measure. Covariates in these initial models included age, race, sex, BMI, study site (Chicago or Ohio), systolic blood

pressure and fasting glucose. In addition, since there have been reports of a U-shaped association between renal function and sleep duration (Lin et al., 2017), we added a quadratic term for sleep duration to the sleep duration models. For the illustrations, we calculated the quartiles for sleep duration, sleep fragmentation and sleep start time and calculated the marginal means for eGFR and PCR for each quartile from regression models that included the covariates. The mean PCR in these figures was back-transformed from the natural log used in the regression models. Finally, we created interaction terms between the presence of diabetes and each sleep measure as continuous variables and between sex and each sleep measure to see if the associations between sleep and kidney function varied either between those with and without diabetes or between men and women. All analyses were conducted using Stata SE v14 (StatCorp, College Station, TX).

Results

{Figure 1 here}

Sixty-eight participants developed ESRD prior to the sleep assessment and therefore were excluded from these analyses (Figure 1). In addition, we excluded participants missing key data and who had an eGFR<10 or >80 ml/min/1.73m^2. Our final sample size was 432 patients. The description of the sample is presented in Table 1. Average age was approximately 60 years and 61% of the sample was obese (BMI≥30 kg/m^2). Almost half of the participants were women, and half of the sample had diabetes. On average, these patients slept for 6.5 hours per night, but this ranged from about 2 hours per night to 10 hours per night. Patients went to bed at 11:30pm on average. Of those with foot actigraphy, 20% had a PLMI at or above 15 movements/hour. Nearly two-thirds of the participants had PSQI scores above the clinical threshold for poor sleep quality (score >5) and more than 25% had Epworth scores above the clinical threshold for excessive daytime sleepiness. Approximately one quarter of the sample had persistent snoring. Furthermore, 80% of participants qualified for at least one of the following: poor subjective sleep quality (PSQI>5), excessive daytime sleepiness (Epworth>10) or persistent snoring.

{Table 1 here}

Many of the sleep measures were correlated, albeit only weakly or modestly. For example, shorter sleep duration was associated with greater sleep fragmentation (r= -.39, p<.001) and later sleep start time (r= -.36, p<.001). Higher PLMI was associated with greater sleep fragmentation (r= .28, p<.001). Higher PSQI scores were associated with greater sleep fragmentation (r= .16, p=.001) but not with sleep duration or sleep timing (both p>.05). Greater subjective sleepiness was associated shorter sleep duration (r= -.30, p<.001), greater sleep fragmentation (r= .16, p<.001) and later sleep timing (r= .13, p=.006).

Association between sleep and eGFR

{Figure 2 here}

Figure 2 presents the adjusted means of eGFR for the quartiles of sleep duration, sleep fragmentation and sleep timing. Results from multivariable linear regression analyses predicting eGFR are presented in Table 2. Lower eGFR was associated with shorter sleep duration (1.1 ml/min/1.73m^2 per hour less sleep), greater sleep fragmentation (-2.6 ml/min/1.73m^2 per 10% higher sleep fragmentation) and later sleep timing (-0.9 ml/min/1.73m^2 per hour later). Subjective sleep quality, subjective sleepiness, PLMI and persistent snoring were not associated with eGFR. The quadratic term for sleep duration was not significant (p=.30), indicating the absence of a U-shaped association between sleep duration and eGFR.

{Table 2 here}

Association between sleep and PCR

Figure 2 also presents the unadjusted associations between the distribution of PCR and the quartiles of sleep duration, sleep fragmentation and sleep timing. Median PCR was significantly higher in those with greater sleep fragmentation, but there was no significant association between PCR and sleep duration or sleep timing quartiles. In the linear regression models (Table 2), PCR was only associated with greater sleep fragmentation (approximately 28% higher PCR per 10% higher sleep fragmentation). Habitual sleep duration, the quadratic term for sleep duration, sleep start time, PLMI, subjective sleep quality, sleepiness and persistent snoring were not associated with PCR.

We examined whether the associations between the measures of sleep and the measures of kidney function varied by diabetes status or sex by testing interaction terms in each of the models. The interaction term between diabetes and PLMI was considered significantly associated with eGFR and lnPCR (p<.10). Thus, stratified analyses were performed for these models. Among CKD patients without diabetes, having a PLMI≥15 events/hour was associated with lower eGFR (beta = -3.8 ml/min/1.73m^2, p=.2, n=154) and a higher PCR (approximately 28% higher, p=.36, n=141), although neither association was significant. Among CKD patients with diabetes, having a PLMI≥15 events/hour was associated with higher eGFR (beta=4.0 ml/min/1.73m^2, p=.1, n=136) and lower PCR (approximately 63% lower, p=.07, n=126), but neither association reached statistical significance. The diabetes interaction terms in all other models were not significant and none of the interaction terms with sex were significant (all p>.10).

Discussion

In this sample of patients with pre-dialysis CKD, greater sleep fragmentation was associated with worse kidney function, as represented by both estimated glomerular filtration rate and the ratio of urine protein to creatinine. Shorter sleep duration and later sleep timing were also associated with lower eGFR but not PCR. Subjective sleep quality, sleepiness and persistent snoring (a symptom of sleep apnea) were not associated with the kidney function measures.

Our study found that reduced sleep quality, as represented by greater sleep fragmentation, was associated with reduced estimated GFR and increased PCR. Experimentally induced sleep fragmentation in young healthy adults significantly reduced insulin sensitivity, impaired glucose metabolism and attenuated nocturnal blood pressure dipping (Tasali et al., 2008, Stamatakis and Punjabi, 2010, Sayk et al., 2010), which are risk factors for the development of diabetes and hypertension. Diabetes and hypertension are, in turn, major risk factors for the development of CKD (Centers for Disease and Prevention, 2007). Further, experimental sleep fragmentation led to a 14% increase in cardiac sympathovagal balance, suggesting a shift toward higher sympathetic activity (Tasali et al., 2008). If sympathetic nervous activity is elevated due to habitual sleep fragmentation, then this could impair kidney function (Masuo et al., 2010). Unfortunately, previous experimental studies that manipulated sleep duration or quality have not examined effects on kidney function measures. One other observational study did use actigraphy and estimated sleep fragmentation (Agarwal and Light, 2011). They found no association between sleep fragmentation and eGFR, however this analysis included only 27 patients with CKD.

A bidirectional relationship between sleep duration and quality and kidney function is possible. Only a few studies have documented sleep quality and duration in CKD prior to kidney failure. Evidence suggests that sleep disturbances in CKD could be a precursor of the more severe sleep disturbances described in ESRD (Turek et al., 2012). Studies that used actigraphy reported that individuals with ESRD had more disturbed sleep than individuals with CKD (Barmar et al., 2009, Agarwal and Light, 2011). Elevated sympathetic nervous system activity can lead to fragmented sleep, and conversely, fragmented sleep is associated with activation of the sympathetic nervous system. This bidirectional relationship could constitute a vicious circle where sleep problems and reduced kidney function enhance one another.

The finding that later sleep timing is associated with kidney function is a novel discovery and it may be related to circadian rhythms. A possible explanation for the association between sleep timing and kidney function is circadian misalignment between endogenous clocks. Circadian misalignment can arise when behaviors such as sleep and meals occur at times that are not in synchrony with our endogenous clocks and therefore key organ systems do not respond properly or work efficiently. Circadian clocks in renal cells seem to play an important role in the regulation of fluid levels and blood pressure homeostasis (Tokonami et al., 2014), thus if there is desynchrony between the circadian rhythms in the kidney and behaviors such as sleep, it is possible that disturbances in kidney function could occur. An additional possible explanation for the association between later sleep timing and worse kidney function involves melatonin release. Melatonin is a hormone secreted predominantly by the pineal gland and this secretion is inhibited by light. People who stay up later will be exposed to artificial light at night, and since light suppresses melatonin, melatonin levels may be lower in later sleepers. Melatonin has antioxidant properties and administration of melatonin protected kidney allografts from ischemia/reperfusion injury-induced renal dysfunction and tubular injury in an animal model (Li

et al., 2009). A recent study in obese mice (Ob/Ob) found that melatonin administration was associated with beneficial changes in the renal proximal convoluted tubules, which suggests that melatonin may be protective against renal morphological damage and dysfunction due to obesity (Stacchiotti et al., 2014).

The strengths of this study include the objective estimates of sleep duration, quality and timing, the large and ethnically diverse sample. There are a few limitations to note, however. This study did not have an objective measure of obstructive sleep apnea (OSA) and OSA may be associated with worse kidney function in patients with CKD (Pierratos and Hanly, 2011), although not all studies have observed these associations (Fornadi et al., 2014). While we did use a validated screening tool to identify patients with persistent snoring, a major symptom of sleep apnea, it is possible that the prevalence of apnea was underestimated. Previous epidemiologic data suggested that year-to-year variability in sleep duration and quality is quite low in middle-aged adults (Knutson et al., 2007), although the stability of sleep habits in CKD patients has not been examined. Finally, the study design is cross-sectional, and the direction of effect cannot be determined.

Our study found significant associations between worse sleep quality, as indicated by greater sleep fragmentation and reduced kidney function (either lower eGFR or higher PCR). Shorter sleep duration and later sleep timing were also associated with worse kidney function as indicated by lower eGFR. Future research should employ longitudinal and interventional designs in order to determine whether poor sleep quality or circadian disruption can impair kidney function. Physicians treating patients with CKD should consider inquiring about sleep and possibly sending for clinical sleep assessment. Importantly, future research should examine whether improving sleep quality and/or optimizing circadian rhythms in CKD patients can slow CKD progression.

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Table 1: Description of Key Characteristics among CRIC Sleep Study Cohort

Variable	**Total n**	**Mean (Standard Deviation) or n (%)**	**Range**
DEMOGRAPHICS			
Age (years)	432	59.7 (10.4)	23-79
BMI (kg/m2)	432	33.7 (9.2)	17.6-111.8
Women (n, %)	432	208 (48.2%)	
Race/Ethnicity	432		
Non-Hispanic White (n, %)		152 (35.2%)	
Non-Hispanic Black (n, %)		137 (31.7%)	
Hispanic/Latino (n, %)		135 (31.3%)	
Other (n, %)		8 (1.9%)	
Current smoker (n, %)	432	57 (13.2%)	
Alcohol use (n, %)	432	226 (52.3%)	
Diabetes (n, %)	432	218 (50.5%)	
Fasting glucose (mg/dL)	432	119.9 (57.7)	49-538
Recruited at Chicago site (n, %)	432	255 (59.0%)	
KIDNEY FUNCTION, GLUCOSE & BLOOD PRESSURE			
eGFR (ml/min/1.73m^2)	432	38.3 (14.5)	10.8-79.0
PCR (mcg/mg; median; IQR)	399	0.20 (0.07, 0.81)	0.01-15.6
Systolic Blood Pressure (mmHg)	432	130.5 (20.1)	71-200.7
Diastolic Blood Pressure (mmHg)	432	70.6 (12.0)	37.7-121.3
SLEEP VARIABLES			
Sleep Duration (hours)	432	6.5 (1.4)	1.7-11.2
Sleep Fragmentation (% of sleep period)	432	21.1 (9.8)	3.4-82.8

Sleep Start (hh:mm)	432	23:32 (1:37)	19:32-8:26
PLMI >15 events/hour	290	59 (20.3%)	
PSQI Score	388	8.1 (4.5)	0-21
PSQI >5 (poor sleep quality) (n, %)		256 (66.0%)	
Epworth Sleepiness Score	420	7.9 (4.9)	0-24
Epworth >10 (excessive sleepiness) (n, %)		110 (26.2%)	
Persistent Snoring (n, %)	364	90 (24.7%)	

Abbreviations: BMI body mass index; eGFR estimated glomerular filtration rate; PCR protein to creatinine ratio; PLMI periodic leg movement index; PSQI Pittsburgh Sleep Quality Index;

Table 2. Results from 7 separate linear regression models predicting eGFR (ml/min/1.73m^2 ; n=405) and PCR.*

	eGFR (ml/min/1.73m^2)	**ln(PCR)**
	Beta (95% CI, p value)	Beta (95% CI, p value)
1. Sleep Duration (per hour of sleep)	**1.1** **(95% CI: 0.1, 2.2, p=.03)**	-0.07 (95% CI: -.18, .04, p=.2)
2. Sleep Fragmentation (per 10%)	**-2.6** **(95% CI: -4.0, -1.1, p<.001)**	**0.28** **(95% CI: 0.13, 0.44, p<.001)**
3. Sleep start time (per hour later)	**-0.9** **(95% CI: -1.7, -0.01, p=.05)**	0.04 (95% CI: -.05, 0.13, p=.4)
4. PLMI ≥15 events/hour	-0.1 [a] (95% CI: -4.1, 3.9, p=.9)	-0.21 [b] (95% CI: -0.65, 0.23, p=.4)
5. PSQI Score	-0.03 [c] (95% CI: -0.4, 0.3, p=.9)	.005 [d] (95% CI: -0.03, 0.04, p=.8)
6. Epworth Sleepiness Score	0.06 [e] (95% CI: -0.2, 0.3, p=.7)	0.02 [f] (95% CI: -0.01, 0.05, p=.2)
7. Persistent Snoring	1.7 [g] (95% CI: -1.5, 4.9, p=.3)	.14 [h] (95% CI: -0.19, 0.47, p=.4)

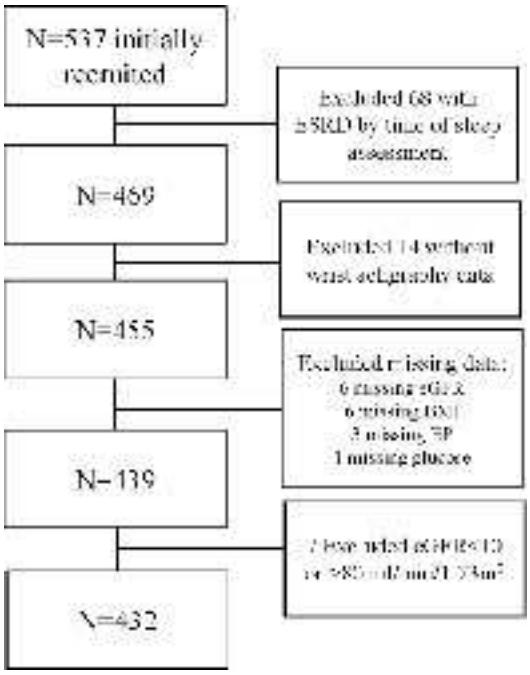
*Adjusting for age, race, sex, BMI, current smoking, alcohol use (yes/no), systolic BP, fasting glucose & study site.

[a] n=290; [b] n=267, [c] n=388; [d] n= 356, [e] n=420; [f] n= 387; [g] n=336; [h] n= 322

Figure Legends.

Figure 1. Consort diagram.

Figure 2. Mean eGFR and PCR levels over the quartiles of sleep duration, sleep fragmentation and sleep timing adjusted for age, race, sex, BMI, study site, systolic blood pressure and fasting glucose. PCR values have been back-transformed from ln(PCR) used in regression analyses. Error bars represent 95% CI from the regression analysis.



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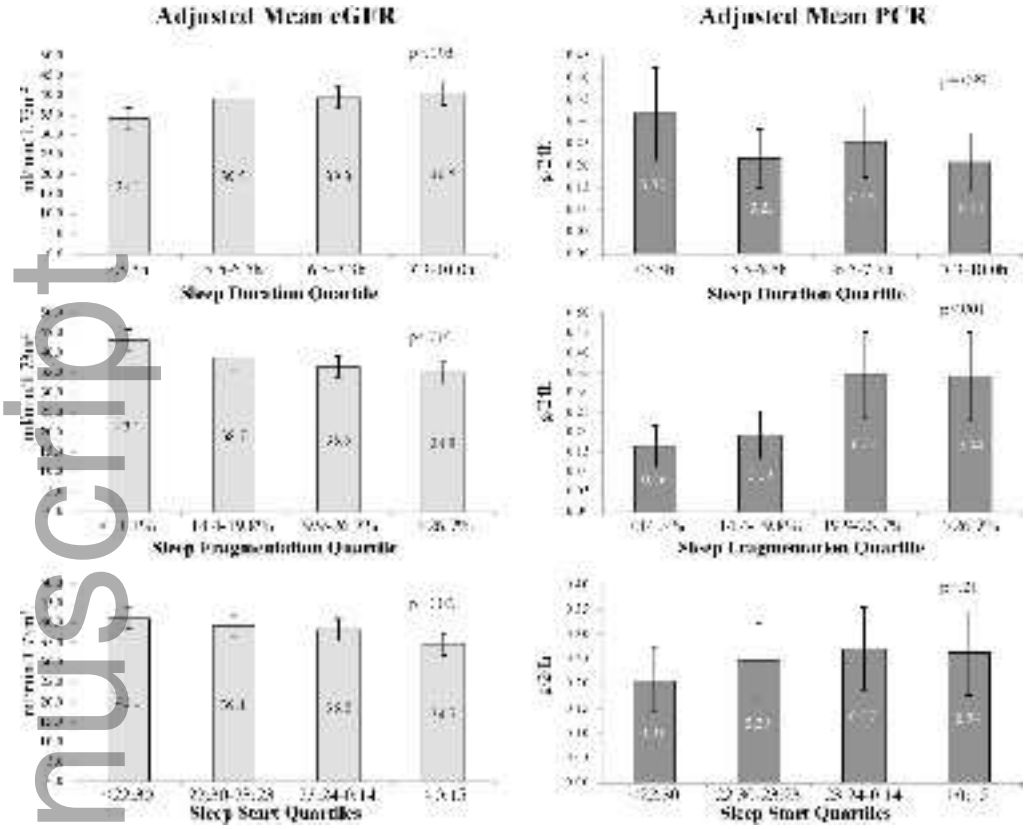

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