

Association of Sleep Duration, Symptoms, and Disorders With Mortality in Adults With Chronic Kidney Disease

Ana C. Ricardo^{1,5}, Vivien Goh^{1,5}, Jinsong Chen¹, Esteban Cedillo-Couvert¹, Mary Kapella², Bharati Prasad^{1,4}, Sharmila Parvathaneni², Kristen Knutson³ and James P. Lash¹

¹Department of Medicine, University of Illinois, Chicago, IL, USA; ²Department of Biobehavioral Health Science, College of Nursing, University of Illinois, Chicago, IL, USA; ³Department of Medicine, University of Chicago, Chicago, IL, USA; and ⁴Jesse Brown VA Medical Center, Chicago, IL, USA

Introduction: In general populations, short and long sleep duration, poor sleep quality, and sleep disorders have been associated with increased risk of death. We evaluated these associations in individuals with CKD.

Methods: This was a prospective cohort study of 1452 NHANES 2005 to 2008 participants with CKD. CKD was defined by estimated glomerular filtration rate <60 ml/min per 1.73 m² or urine albumin-to-creatinine ratio ≥30 mg/g. Sleep duration, sleep symptoms (difficulty falling asleep, difficulty staying asleep, daytime sleepiness, and nonrestorative sleep), and sleep disorders (restless legs syndrome and sleep apnea) were self-reported. Vital status was determined using NHANES mortality linkage through December 31, 2011.

Results: In this cohort, the mean age was 61 years, 58% were women, and 75% non-Hispanic white. During 4.4 years of median follow-up, we observed 234 deaths, of which 75 were due to cardiovascular causes. In multivariable analyses, compared with individuals who reported 7 to 8 hours of sleep, HR (95% CI) for all-cause mortality for sleep duration <7 hours and >8 hours were 1.50 (1.08–2.10) and 1.36 (0.89–2.08), respectively. The corresponding HR (95% CI) for cardiovascular mortality were 1.56 (0.72–3.37) and 1.56 (0.66–3.65). Nonrestorative sleep and restless legs syndrome were associated with increased risk for all-cause mortality (HR, 1.63 [95% CI, 1.13–2.35], and HR, 1.69 [95% CI, 1.04–2.75], respectively).

Discussion: In adults with CKD, short sleep duration, nonrestorative sleep, and restless legs syndrome are associated with increased risk of death. These findings underscore the importance of promoting adequate sleep in patients with CKD, and the need for future studies evaluating the impact of sleep interventions in this population.

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KEYWORDS: chronic kidney disease; mortality; sleep

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Sleep is an essential state of rest for the well-being of the mind and body, but sleep curtailment has become a common, often voluntary behavior in modern society.¹ In general populations, impaired sleep has been found to be associated with poor health outcomes including death.^{2,3} In addition, there is increasing evidence for an association between both short and long duration of habitual sleep, as well as impaired sleep quality, with prevalence and severity of major chronic

diseases, including hypertension, diabetes, and cardiovascular disease.⁴⁻⁷

It is estimated that among people with chronic kidney disease (CKD), the prevalence of sleep disturbances can be as high as 80%.⁸ In an analysis of the National Health and Nutrition Examination Survey (NHANES) 2005 to 2008, Plantinga *et al.*⁹ found that the prevalence of inadequate sleep (defined as ≤6 hours per night) was higher in individuals with mild CKD than in those with no CKD. However, the impact of sleep duration and sleep quality on clinical outcomes in individuals with CKD is not well understood. For this reason, we conducted a study to assess the association of sleep duration, sleep symptoms, and disorders with all-cause and cardiovascular mortality in U.S. adults with CKD using data from NHANES 2005 to 2008.

Correspondence: Ana C. Ricardo, MD, MPH, University of Illinois at Chicago, Department of Medicine, Division of Nephrology, 820 S. Wood Street 418W CSN, MC 793, Chicago, IL 60612-7315, USA. E-mail: aricar2@uic.edu

⁵Shared first authors.

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MATERIALS AND METHODS

Study Population

NHANES is a stratified, clustered, multistage probability sample survey of the civilian, noninstitutionalized U.S. population, conducted by the National Center for Health Statistics (NCHS) of the U.S. Centers for Disease Control and Prevention, with oversampling of non-Hispanic black and Mexican American persons.¹⁰ The survey consists of a standardized in-home interview followed by physical examination, as well as blood and urine collection at a mobile examination center. Survey protocol was approved by the NCHS Institutional Review Board and is adherent to the Declaration of Helsinki. All participants provided informed consent. This analysis was limited to NHANES 2005 to 2008 participants who met the inclusion criteria (18 years or older, nonpregnant, and had available serum creatinine and urine albumin and creatinine measurements) and the study definition of CKD.

Measurements and Definitions

Chronic Kidney Disease

Serum and urine creatinine were measured using the modified kinetic Jaffé method. Urine albumin was measured using a solid-phase fluorescent immunoassay. Urine albumin and creatinine concentrations were measured in 1 random urine sample. CKD was defined by either an estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m², using the CKD Epidemiology Collaboration creatinine equation¹¹ or the presence of albuminuria (urine albumin-to-creatinine ratio ≥ 30 mg/g).

Sleep

During the home interview, through a computer-assisted personal interviewing system, NHANES 2005 to 2008 participants answered questions regarding sleep habits and sleep-related problems from 2 validated instruments: the Sleep Heart Health Study Sleep Habits Questionnaire¹² and the Functional Outcomes of Sleep Questionnaire.^{13,14} For this study, we used selected questions as described herein. Sleep duration was ascertained using the following question: "How much sleep do you usually get at night on weekdays or workdays?" We classified total hours of sleep as <7 , 7 to 8 or >8 .² The items used to ascertain the presence of sleep symptoms were the following: (i) difficulty falling asleep, "In the past month, how often did you have trouble falling asleep?"; (ii) difficulty staying asleep, "In the past month, how often did you wake up during the night and had trouble getting back to sleep?"; (iii) daytime sleepiness, "In the past month, how often did you feel excessively or overly sleepy during the day?"; and (iv) nonrestorative sleep, "In the past month, how

often did you feel unrested during the day, no matter how many hours of sleep you had?" Participants were asked to choose from among the following options: Never, rarely (1 time a month); sometimes (2–4 times a month); often (5–15 times a month); almost always (16–30 times a month); refused; or "don't know." Sleep symptoms were considered to be present if reported "often" or more (at least 5 times a month). The presence of restless legs was also self-reported using the questions: "Have you ever been told by a doctor or other health professional that you have a sleep disorder?" if yes, "What was the sleep disorder?" The possible answers were "sleep apnea," "insomnia," "restless legs," "other," "refused," and "don't know."

Covariates

Race or ethnicity was categorized as non-Hispanic white, non-Hispanic black, Mexican American, or other. In these analyses, income was classified as annual family income $<20,000$ or $\geq 20,000$ U.S. dollars, and educational attainment as less than high school or high school or beyond. Participants were considered to have health insurance if they self-reported coverage by any health insurance plan. Participants were classified as current or past or never smoker based on responses to the questions "Have you smoked at least 100 cigarettes during your entire life?" and "Do you smoke cigarettes now?" Participants had 3 blood pressure (BP) measurements at the mobile examination center in the sitting position, after 5 minutes of rest, using a standardized protocol.¹⁵ The averages of all systolic BP available readings are reported here. Hypertension was defined as systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg or the self-reported use of antihypertensive medications. Diabetes was defined as a history of diabetes, self-reported use of insulin or other medication to treat diabetes, a fasting blood glucose ≥ 126 mg/dl, or a random blood glucose ≥ 200 mg/dl. The presence of congestive heart failure was ascertained using the following question: "Has a doctor or other health professional ever told you that you had congestive heart failure?" The use of medications for sleep was ascertained using the following question: "In the past month, how often did you take sleeping pills or other medication to help you sleep?" The possible answers were never, rarely (1 time per month), sometimes (2–4 times per month), often (5–15 times per month), or almost always (16–30 times per month); participants who answered ≥ 5 times per month were classified as sleeping pills users. Height and weight were measured by trained NHANES staff. Body mass index was calculated as weight in kilograms divided by height in meters squared. The presence of depressive symptoms was defined as a Patient Health Questionnaire (PHQ-9) ≥ 10 .¹⁶

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