Impact of Sleep Duration on Mortality and Quality of Life in Chronic Kidney Disease: Results from the 2007–2015 KNHANES

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Keywords

Sleep duration · Mortality · Quality of life · Chronic kidney disease

Abstract

Introduction: In the general population, short and long sleep durations have been associated with adverse health outcomes. However, this association remains unclear in patients with chronic kidney disease (CKD). We examined the relationship of sleep duration to mortality and health-related quality of life (HRQOL) in individuals with CKD. **Methods:** A total of 1,783 adults with CKD who participated in the 2007–2015 Korea National Health and Nutrition Examination Survey were analyzed. CKD was defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m². Participants were categorized into 3 groups according to self-reported sleep duration: <6 h (short sleepers), 6–8 h, and >8 h (long sleepers). The outcome variables were all-cause mortality and HRQOL. HRQOL was assessed using the European Quality of Life-5 Dimensions (EQ-5D) index. **Results:** During a median of 6.4 years, 481 (27%) deaths occurred. In unadjusted Cox regression analysis, long sleepers with CKD had an increased risk of death (hazard ratio [HR], 1.62; 95% con-

fidence interval [CI]: 1.26–2.09). This significant association remained after adjusting for age, sex, and BMI (HR, 1.36; 95% CI: 1.05–1.75); however, it was lost after adjusting for CKD stage, social and lifestyle factors, and presence of comorbidities (HR, 1.15; 95% CI: 0.89–1.49). Compared with 6- to 8-h sleepers with CKD, long sleepers with CKD had significantly worse HRQOL in multivariable linear regression models. The adjusted means of the EQ-5D index were 0.80 (95% CI: 0.77–0.82) for short sleepers, 0.81 (95% CI: 0.80–0.82) for 6- to 8-h sleepers, and 0.76 (95% CI: 0.73–0.79) for long sleepers ($p = 0.01$). **Discussion/Conclusion:** Long sleep duration is associated with poor HRQOL in Korean adults with CKD. The weak association between long sleep duration and mortality was attenuated after multivariable adjustment in this study.

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Introduction

Chronic kidney disease (CKD) is a major public health issue, affecting approximately 10% of adult populations worldwide, including in Korea [1–3]. CKD is associated with various chronic diseases such as hypertension, type 2 diabetes, and cardiovascular disease [1], resulting in

worse health-related quality of life (HRQOL) [4, 5] and increased mortality [6, 7]. An effective means of preventing the development and progression of CKD is identifying the lifestyle-related risk factors of an individual [8].

Sleep is essential for optimal health and HRQOL [9]. Substantial evidence suggesting the association between sleep duration and adverse health outcomes in the general population has been accumulating [8, 10]. Short and long sleep durations have been associated with an increased risk of hypertension, type 2 diabetes, and cardiovascular disease, leading to poor HRQOL and mortality [11–13].

Sleep duration may be a modifiable risk factor for the development and progression of CKD [14]. Previous studies have reported that inadequate sleep duration is associated with an increased risk of CKD development [15–18] and progression to end-stage renal disease (ESRD) [19, 20]. In addition, several sleep interventions have been applied to enhance HRQOL by improving both the duration and quality of sleep among individuals with CKD [21, 22]. To improve the understanding of the relationships between sleep duration and adverse health outcomes, especially HRQOL and mortality, in adults with CKD, we conducted this study using data from the Korea National Health and Nutrition Examination Survey (KNHANES) IV to VI.

Materials and Methods

Study Design and Participants

This study was based on the KNHANES-linked Cause of Death data (version 1.1). The KNHANES is a nationally representative cross-sectional survey of noninstitutionalized Korean citizens residing in Korea, conducted by the Korea Centers for Disease Control and Prevention (KCDC). The KNHANES is composed of 3-component surveys: health interview, health examination, and nutritional survey. The methodology of the KNHANES has been published in detail [23]. All participants provided written informed consent. The study protocol for the survey was approved by the institutional review board of the KCDC. The current study has been granted an exemption from requiring ethical approval by the Institutional Review Board of the Seoul National University Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki. Among the KNHANES 2007–2015 participants, we enrolled adults (≥ 19 years old) with CKD, which was defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min per 1.73 m^2 . Participants who did not agree to the link to death certificate data were excluded.

Variables and Their Definitions

Habitual total sleep duration, including daytime naps, was determined with the following question: “How many hours a day do you usually sleep?” Sleep duration was categorized as < 6 , 6–8, and

> 8 h. Short sleepers were defined as those who sleep < 6 h per day, and long sleepers were defined as those who sleep > 8 h per day. The eGFR was calculated using the 4-variable Chronic Kidney Disease Epidemiology Collaboration equation, and the categories of glomerular filtration rate were based on the Kidney Disease Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of CKD [24].

The covariates for this study included age, sex, BMI, eGFR, CKD stage, history of tobacco smoking, education, income, living with a spouse, occupation, regular exercise, and comorbidities (e.g., anemia, hypertension, diabetes, cardiovascular disease, cancer, and depression). However, the presence of comorbid sleep disorders, including obstructive sleep apnea (OSA), was not assessed in our study because these data were not collected in the KNHANES. Smokers including former or current smokers were defined as individuals who had smoked ≥ 100 cigarettes during their lifetime. Education level was classified as middle school or lower and high school or higher. In the KNHANES 2007–2013, regular exercise was defined as ≥ 30 min of moderate-intensity physical activity for ≥ 5 days a week or ≥ 20 min of vigorous-intensity physical activity for ≥ 3 days a week. In the KNHANES 2014–2015, regular exercise was defined as ≥ 150 min of moderate-intensity physical activity per week or ≥ 75 min of vigorous-intensity physical activity per week or an equivalent combination of moderate- and vigorous-intensity physical activity (1 min of vigorous-intensity physical activity = 2 min of moderate-intensity physical activity). Data on income (lowest quartile or not), living with a spouse (yes or no), and occupation (yes or no) were also collected.

Anemia was defined as hemoglobin < 12 g/dL for nonpregnant women, hemoglobin < 11 g/dL for pregnant women, and hemoglobin < 13 g/dL for men. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or the use of blood pressure-lowering medication. Diabetes was defined as serum fasting glucose level ≥ 126 mg/dL or hemoglobin A1c $\geq 6.5\%$, or use of antidiabetic medications, or a previous diagnosis of diabetes made by a physician. Cardiovascular disease was defined as angina, myocardial infarction, or stroke as diagnosed by a physician. Participants were considered to have cancer if they had malignant tumors in either of the 6 major organs (stomach, liver, colon, breast, cervix, or lung) diagnosed by a physician. A self-reported diagnosis (made by a physician) of depression was also recorded.

Outcome Variables

The outcome variables were death of any cause and HRQOL. The dates and causes of death were collected from Statistics Korea. The follow-up duration was calculated from the month and year of the KNHANES to the month and year of death or December 2018, whichever occurred first.

The European Quality of Life-5 Dimensions (EQ-5D) was used to assess HRQOL in the KNHANES. The EQ-5D is a brief, self-completed instrument for describing and evaluating the quality of health states and is one of the most widely used instruments for measuring HRQOL [25]. The EQ-5D descriptive system comprises 5 dimensions: (i) mobility, (ii) self-care, (iii) usual activities, (iv) pain/discomfort, and (v) anxiety/depressive mood. For each dimension, participants were asked to select one of the 3 levels of perceived problems (no problems, some problems, and extreme problems) to indicate the most appropriate statement for their health state on the day of the interview. This descriptive profile

Table 1. Characteristics of adults with CKD according to sleep duration

Characteristic	Sleep duration, h/day				<i>p</i> value
	all (<i>n</i> = 1,783)	<6 (<i>n</i> = 448)	6–8 (<i>n</i> = 1,123)	>8 (<i>n</i> = 212)	
Age, years					
19–59	183 (10)	30 (7)	139 (12)	14 (7)	<0.0001
60–69	458 (26)	92 (21)	320 (29)	46 (22)	
70–79	840 (47)	237 (53)	500 (45)	103 (49)	
≥80	302 (17)	89 (20)	164 (15)	49 (23)	
Women	899 (50)	278 (62)	521 (46)	100 (47)	<0.0001
BMI, kg/m ²	24.4 (22.2–26.5)	24.4 (22.1–26.7)	24.4 (22.3–26.5)	24.1 (22.0–26.3)	0.532
eGFR, mL/min per 1.73 m ²	53 (46–57)	53 (46–56)	54 (47–57)	52 (44–56)	0.011
CKD stage					
Stage 3	1,677 (94)	429 (96)	1,055 (94)	193 (91)	0.055
Stage 4–5	106 (6)	19 (4)	68 (6)	19 (9)	
Former or current smoker	852 (48)	197 (44)	554 (49)	101 (48)	0.158
Education (high school or higher)	502 (28)	74 (17)	377 (34)	51 (24)	<0.0001
Income (lowest quartile)	452 (25)	126 (28)	274 (24)	52 (25)	0.296
Living with a spouse	1,164 (65)	240 (54)	786 (70)	138 (65)	<0.0001
Occupation	477 (27)	102 (23)	332 (30)	43 (20)	0.002
Regular exercise	314 (18)	64 (14)	221 (20)	29 (14)	0.011
Anemia	519 (29)	135 (30)	306 (27)	78 (37)	0.017
Hypertension	1,303 (73)	324 (72)	812 (72)	167 (79)	0.138
Diabetes	785 (44)	192 (43)	483 (43)	110 (52)	0.049
Cardiovascular disease	367 (21)	100 (22)	215 (19)	52 (25)	0.118
Cancer	117 (7)	30 (7)	70 (6)	17 (8)	0.623
Depression	106 (6)	33 (7)	63 (6)	10 (5)	0.299

Data are presented as median (interquartile range) or *n* (%). eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

score can be assigned a summary index score using Korean population-based preference weights [26, 27]. The EQ-5D index ranges from –0.171 to 1, with higher values indicating better health status.

Statistical Analysis

Clinical characteristics were compared between groups using Kruskal-Wallis tests for continuous variables. Categorical variables were compared using either the χ^2 test or Fisher's exact test. The amount of missing data ranged from 0% (age and sex) to 6% (sleep duration, EQ-5D index, education, and exercise). All missing values were handled using multiple imputations.

Kaplan-Meier survival curves were used to estimate survival and compared using the log-rank test. Cox proportional hazard regression models were constructed to calculate adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for all-cause mortality among short sleepers, 6- to 8-h sleepers, and long sleepers. Four models were constructed. Model 1 included age, sex, and BMI as covariates. Model 2 included CKD stage (stage 3 or stage 4–5) and all covariates in model 1. Model 3 added socioeconomic characteristics such as history of tobacco smoking, education, income, living with a spouse, occupation, and regular exercise to all covariates in model 2. The final model (model 4) included the presence of comorbidities such as anemia, hypertension, diabetes, cardiovascular disease, cancer, and depression and all covariates included in model 3. Multiple linear regression models were used to assess the association of sleep duration with the EQ-5D index ad-

justed for the same covariates in each model, and the results are presented as linear regression coefficients and 95% CIs.

Statistical significance was set at *p* < 0.05. Statistical analyses were performed using R 4.0.1 software (<http://www.r-project.org>) and Stata 13.1 software (StataCorp., College Station, TX, USA).

Results

Of the 1,783 eligible adults with CKD, about half were women. Most participants had stage 3 CKD, and the median eGFR was 53 mL/min per 1.73 m². Approximately three-quarters of the participants had hypertension, half had diabetes, and one-fifth had cardiovascular disease. The median sleep duration was 7 h, and short (<6 h) and long (>8 h) sleepers accounted for 25 and 12% of the participants, respectively.

The baseline characteristics of the study participants according to sleep duration are listed in Table 1. The proportion of women was higher among short sleepers than among 6- to 8-h sleepers or long sleepers. Participants who had short or long sleep durations were less likely to

Fig. 1. Distribution of the participants according to stage of CKD. CKD, chronic kidney disease.

have an education of high school or higher, to live with a spouse, to have an occupation, and to exercise regularly than those with a sleep duration of 6–8 h. Anemia and diabetes had the highest prevalence among long sleepers. Participants with stage 4–5 CKD accounted for 4, 6, and 9% of short, 6–8 h, and long sleepers, respectively (Fig. 1).

During a median follow-up period of 6.4 years (interquartile range [IQR], 4.1–9.0 years), 481 (27%) deaths occurred. Cardiovascular disease (29%) was the most common cause of death, followed by cancer (24%). Figure 2 shows the unadjusted Kaplan-Meier survival curves of all-cause mortality according to sleep duration. In an unadjusted model, long sleepers with CKD had an increased risk of death (HR, 1.62; 95% CI: 1.26–2.09; Table 2; see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000516096). This significant association remained in model 1 adjusting for age, sex, and BMI (HR, 1.36; 95% CI: 1.05–1.75); however, it was lost after adjusting for CKD stage, social and lifestyle factors, and presence of comorbidities (models 2–4; Table 2). In model 4, the HR for long sleep duration was 1.15 (95% CI: 0.89–1.49; Table 2). Short sleep duration was not associated with all-cause mortality in the unadjusted and adjusted models (Table 2; online suppl. Table 1). We found no interactions indicating effect modification by age, sex, or presence of comorbidities (online suppl. Table 2).

The median EQ-5D index of the 1,783 participants with CKD was 0.85 (IQR, 0.72–1.00). Compared with

participants with CKD with a 6- to 8-h sleep duration, those with a sleep duration of >8 h had significantly worse HRQOL in unadjusted and adjusted models ($\beta = -0.05$; 95% CI: -0.08 to -0.02 in model 4; Table 3; online suppl. Table 3). However, short sleep duration was not associated with worse HRQOL in adjusted models ($\beta = -0.01$; 95% CI: -0.04 to 0.01 in model 4; Table 3). The adjusted means of the EQ-5D index in model 4 were 0.80 (95% CI: 0.77–0.82) for short sleepers, 0.81 (95% CI: 0.80–0.82) for 6- to 8-h sleepers, and 0.76 (95% CI: 0.73–0.79) for long sleepers (Fig. 3). We found no interactions indicating effect modification by age, sex, or presence of comorbidities except cancer (online suppl. Table 4).

Discussion

In the present study, we found that the significant association between long sleep duration and all-cause mortality was attenuated after controlling for renal function, social and lifestyle factors, and comorbidities in Korean adults with CKD. However, long sleep duration was consistently associated with lower HRQOL, even after multivariable adjustment. Short sleep duration was not associated with all-cause mortality or HRQOL in individuals with CKD.

Many studies have shown a J-shaped association between sleep duration and mortality in the general population: both short and long sleep durations are associated with an increased risk of all-cause mortality [8, 10]. However, studies examining the association between sleep duration and adverse health outcomes, including mortality in the CKD population, are limited, and most of them have focused on short sleep duration. Previous studies reported that short sleep duration was associated with increased risks of inadequate hydration [28] and CKD development [15–18, 29]. Other studies reported that short sleep duration in individuals with CKD was associated with progression to ESRD [19, 20], low HRQOL [30], and death [31].

Our study suggests the adverse effects of long sleep duration on health in adults with CKD, which is also consistent with previous research findings. Previous meta-analyses have shown that the association between long sleep duration and all-cause mortality is stronger in older than in younger people and in East Asian countries than in Western countries [32–34]. In addition, results from different large prospective cohorts in South Korea consistently indicated the clinical impacts of long sleep duration: long sleep duration rather than short sleep duration

Fig. 2. Unadjusted Kaplan-Meier curve for all-cause mortality according to sleep duration.

Table 2. Multivariable analysis of all-cause mortality according to sleep duration

Sleep duration, h/day	Unadjusted		Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
<6	1.12 (0.91–1.39)	0.273	1.02 (0.83–1.26)	0.821	1.01 (0.82–1.25)	0.897	0.98 (0.79–1.21)	0.849	0.97 (0.79–1.20)	0.797
6–8	1.00 (reference)	Reference	1.00 (reference)	Reference	1.00 (reference)	Reference	1.00 (reference)	Reference	1.00 (reference)	Reference
>8	1.62 (1.26–2.09)	<0.0001	1.36 (1.05–1.75)	0.019	1.26 (0.98–1.63)	0.077	1.23 (0.95–1.59)	0.116	1.15 (0.89–1.49)	0.278

Data were analyzed with Cox proportional hazard models and are presented as adjusted HR (95% CI). Model 1: adjusted for age (19–59, 60–69, 70–79, and ≥80 years), sex, and BMI. Model 2: adjusted for all covariates in model 1 plus stage of CKD (stage 3 or stage 4–5). Model 3: adjusted for all covariates in model 2 plus history of tobacco smoking (former or current smoker or never smoker), education (high school or higher or not), income (lowest quartile or not), living with a spouse (yes or no), occupation (yes or no), and regular exercise (yes or no). Model 4: adjusted for all covariates in model 3 plus presence of anemia, hypertension, diabetes, cardiovascular disease, cancer, and depression. CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval.

was associated with higher urinary albumin excretion in the KNHANES [35] and higher prevalence of CKD in the Korean Genome and Epidemiology Study-Kangwha study [36]. In KNHANES participants, long sleep duration was reported to be associated with sarcopenia [37], which is highly prevalent in patients with advanced CKD [38].

Long sleep duration may have several possible causes. First, impaired quality of nocturnal sleep could result in prolonged sleep duration. Fragmented sleep might not sufficiently reduce sleep pressure and could therefore cause a long sleep duration [39]. Second, comorbid OSA may have an effect on sleep duration. In an epidemiologic study, long sleepers had a greater risk of being diagnosed with OSA [40]. Third, long sleep duration may be a result rather than a cause of comorbidities. Several comorbidities, such as hypertension, diabetes, obesity, and

depression, are associated with long sleep duration [41]. Moreover, in patients with CKD, the association between long sleep duration and metabolic comorbidities seems to be modified by comorbid OSA [42, 43]. In other words, long sleepers may need prolonged sleep because of their comorbid metabolic or mental conditions [39].

Plausible biological mechanisms explaining the association between long sleep duration and adverse health outcomes in the general population have been proposed, including sleep fragmentation, fatigue, change in immune function, photoperiodic abnormalities, lack of physiological challenge, depression, or underlying disease [32, 44]. In particular, activation of the renin-angiotensin-aldosterone system caused by immune dysfunction can lead to progressive kidney dysfunction [3, 45]. Moreover, long sleep duration combined with habitual late sleep onset is often associated with disturbances in

Fig. 3. Adjusted means of the European Quality of Life-5 Dimensions (EQ-5D) index. *Data were analyzed with linear regression with adjustment for the covariates in model 4.

the circadian rhythm [39], which may lead to chronobiological alterations of the renin-angiotensin-aldosterone system [14]. The association of long sleep duration with poor outcomes in individuals with CKD could be explained by potential confounding factors and comorbidities such as sarcopenia, hypertension, and diabetes [11, 41]. This could be the reason for the attenuated association between long sleep duration and all-cause mortality after adjusting for various confounding factors and comorbidities in our study.

Our study had several limitations. First, we relied on self-reported sleep duration, although actigraphy and polysomnography can provide more objective measures. Second, long sleepers accounted for only 12% of the participants. Third, information on sleep quality and sleep disorders, including OSA and restless legs syndrome, was lacking, as these data were not collected in the KNHANES. OSA may be particularly prevalent in patients with CKD because of nocturnal rostral fluid shift [46]. Fourth, as serum creatinine was measured once in the KNHANES participants, the chronicity of CKD (>3 months) was not examined. Fifth, because most participants had stage 3 CKD, it is difficult to generalize our findings to those with advanced diseases such as ESRD. Sixth, although our study did not find a significant association between short sleep duration and adverse health outcomes in the CKD population, sleep deprivation may remain a considerable problem in this population.

In conclusion, we found that long sleep duration is associated with poor HRQOL in Korean adults with CKD. Although the weak association between long sleep duration and mortality was attenuated after multivariable ad-

Table 3. Association between sleep duration and the European Quality of Life-5 Dimensions index

Sleep duration, h/day	Unadjusted	Model 1		Model 2		Model 3		Model 4	
	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value	
<6	-0.05 (-0.08 to -0.02)	0.001	-0.02 (-0.05 to 0.003)	0.086	-0.02 (-0.05 to 0.01)	0.075	-0.02 (-0.05 to 0.01)	0.133	
6-8	0.00 (reference)	Reference	0.00 (reference)	Reference	0.00 (reference)	Reference	0.00 (reference)	Reference	
>8	-0.08 (-0.12 to -0.04)	<0.0001	-0.07 (-0.10 to -0.03)	<0.0001	-0.06 (-0.10 to -0.02)	0.001	-0.06 (-0.10 to -0.02)	0.001	

Data were analyzed with linear regression and are presented as the linear regression coefficient (95% CI). Model 1: adjusted for age (19-59, 60-69, 70-79, and ≥80 years), sex, and BMI. Model 2: adjusted for all covariates in model 1 plus stage of CKD (stage 3 or stage 4-5). Model 3: adjusted for all covariates in model 2 plus history of tobacco smoking (former or current smoker or never smoker), education (high school or higher or not), income (lowest quartile or not), living with a spouse (yes or no), occupation (yes or no), and regular exercise (yes or no). Model 4: adjusted for all covariates in model 3 plus presence of anemia, hypertension, diabetes, cardiovascular disease, cancer, and depression. CKD, chronic kidney disease; CI, confidence interval.

Data were analyzed with linear regression and are presented as the linear regression coefficient (95% CI). Model 1: adjusted for age (19-59, 60-69, 70-79, and ≥ 80 years), sex, and BMI. Model 2: adjusted for all covariates in model 1 plus stage of CKD (stage 3 or stage 4-5). Model 3: adjusted for all covariates in model 2 plus history of tobacco smoking (former or current smoker or never smoker), education (high school or higher or not), income (lowest quartile or not), living with a spouse (yes or no), occupation (yes or no), and regular exercise (yes or no). Model 4: adjusted for all covariates in model 3 plus presence of anemia, hypertension, diabetes, cardiovascular disease, cancer, and depression. CKD, chronic kidney disease; CI, confidence interval.

justment in this study, we believe that this finding still supports the importance of the role of nephrology health-care providers in encouraging adequate sleep duration in patients with CKD. Further large longitudinal studies using objective measures of sleep duration are needed to expand our findings on the effects of sleep duration on adverse health outcomes in the CKD population.

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Statement of Ethics

The study was approved by the Institutional Review Board (IRB), Seoul National University Hospital.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors (H.J.L., N.K.K., Y.C.K., S.M.C., J.W.L., Y.S.P., C.H.L., S.M.L., C.G.Y., and J.Y.C.) made substantial contributions to the conception or the acquisition, analysis, or interpretation of data for the study. H.J.L. and J.Y.C. drafted the manuscript, and each author provided important intellectual content during revision of the manuscript. All authors approved the final version of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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