Sleep Duration and Its Associations with Mortality and Quality of Life in Chronic Obstructive Pulmonary Disease: Results from the 2007–2015 KNAHNES

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Keywords
Sleep duration · Mortality · Quality of life · Chronic obstructive pulmonary disease

Abstract
Background: While extreme sleep duration negatively affects mortality and health-related quality of life (HRQOL) in general populations, the relationship remains uncertain in patients with chronic obstructive pulmonary disease (COPD).
Objectives: To evaluate the association between sleep duration and mortality and HRQOL in patients with COPD.
Methods: We analyzed 3,349 participants with COPD enrolled in the 2007–2015 Korea National Health and Nutrition Examination Survey (KNHANES). Participants aged 40 years or older with a smoking history and prebronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) <0.7 were eligible. The participants were categorized as short sleepers (<6 h), 6–8 h, and long sleepers (>8) according to self-reported sleep duration. The outcome variables were all-cause mortality and HRQOL. HRQOL was measured using the European Quality of Life-5 Dimensions (EQ-5D) index.
Results: During a median of 6.5 years, 386 (11.5%) participants died. In unadjusted Cox regression analysis, short sleepers with COPD had an increased risk of death (hazard ratio, 1.35; 95% confidence interval [CI]: 1.07–1.71). However, this association was not significant after adjusting for sociodemographic factors, BMI, FEV1, and comorbidities. In unadjusted and adjusted multiple linear regression, short sleepers had significantly worse HRQOL. The adjusted means of the EQ-5D index were 0.88 (95% CI: 0.87–0.89) for short sleepers, 0.90 (95% CI: 0.90–0.91) for 6- to 8-h sleepers, and 0.89 (95% CI: 0.87–0.91) for long sleepers (p = 0.01).
Conclusions: In patients with COPD, sleep duration was not associated with all-cause mortality. However, short sleep duration was significantly associated with worse HRQOL.

Introduction
Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation due to airway or alveolar abnormalities [1]. COPD affects approximately 10% of adult populations worldwide and in Korea [2, 3]. Individuals with COPD frequently have hypertension, type 2 diabetes, and
cardiovascular disease [1]. Thus, COPD is a leading cause of poor health-related quality of life (HRQOL) and mortality worldwide and imposes considerable economic and social burdens [1, 4].

Adequate amounts of sleep are essential for optimal health [5]. In recent decades, accumulating evidence has suggested associations between sleep duration and adverse health outcomes in the general population [6, 7]. Studies have shown associations between inadequate sleep duration and increased risk of chronic diseases such as hypertension, type 2 diabetes, and cardiovascular disease, resulting in worse HRQOL and all-cause mortality [8–10].

Most patients with COPD experience poor sleep quality, which is associated with adverse COPD outcomes [11–15]. Previous studies reported that poor sleep quality in patients with COPD was associated with COPD exacerbation [13, 15], emergency health care utilization, and mortality [13]. In addition, poor sleep quality is a major determinant of HRQOL in patients with COPD [11, 14]. However, few studies have investigated the effects of sleep duration on HRQOL and mortality in patients with COPD. Therefore, we conducted this study using data from the Korea National Health and Nutrition Examination Survey (KNHANES) IV–VI to examine the relationships between sleep duration and adverse health outcomes, especially HRQOL and mortality, in individuals with COPD.

Materials and Methods

Study Design and Participants

This study was based on the KNHANES linked Cause of Death data (ver. 1.1). The methodology of KNHANES has been described in detail elsewhere [16]. All participants provided written informed consent. The study protocol for the survey was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention (KCDC). The current study was granted an exemption from the requirement for ethical approval by the Institutional Review Board of the Korea Centers for Disease Control and Prevention.

Variables and Their Definitions

The self-reported sleep duration was classified into <6 h (short sleepers), 6–8 h, and >8 h (long sleepers) [17–19]. Smokers, including former and current smokers, were defined as individuals who had smoked ≥100 cigarettes during their entire lifetime. Heavy drinkers were defined as participants who consumed ≥7 drinks on a single occasion for men and ≥5 drinks for women at least twice per week [20, 21]. Education level was divided into middle school or lower and high school or higher. Graduation was classified by the current academic background, and completion/dropout/enrollment/leave from school was classified by previous education. Income level was based on quartiles of raw income data. Living situation was classified as “spouse, yes” for participants who were married and living with their spouse and as “spouse, no” for those who were unmarried, widowed, divorced, or separated.

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). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, the COPD severity was divided into 4 stages: stage 1 (mild; FEV1 ≥80%), stage 2 (moderate; FEV1 50–80%), stage 3 (severe; FEV1 30–50%), and stage 4 (very severe; FEV1 <30%) [1].

Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication [20, 22]. Diabetes was defined as a self-reported physician diagnosis of diabetes, glycated hemoglobin (HbA1c) ≥6.5%, fasting plasma glucose ≥126 mg/dL, or current diabetes treatment [20, 23]. The participants were considered to have cardiovascular disease if they had a previous physician diagnosis of angina, myocardial infarction, or stroke [24] and were considered to have cancer if they had a previous physician diagnosis of malignancy in 6 major organs (stomach, liver, colon, breast, cervical, or lung) [25].

Outcome Variables

The outcome variables were all-cause mortality and HRQOL. The dates and causes of death were collected from the Statistics of Korea. The follow-up duration was calculated from the month and year of the survey to the month and year of death or December 2018, whichever was sooner.

HRQOL was measured using the European Quality of Life-5 Dimensions (EQ-5D) in the KNHANES. The EQ-5D is a questionnaire comprising 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with 3 possible answers for each item (no problems, some problems, and extreme problems) [26]. This descriptive profile score can be converted into the EQ-5D index using Korean population-based preference weights [27, 28]. 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 χ2 or Fisher’s exact tests. The amount of missing data ranged from 0% (age and sex), 2% (sleep duration and the EQ-5D index), and 7% (diabetes). All missing values were imputed using multiple imputations. Kaplan-Meier curves and Cox proportional hazards models were used to compare survival among short, 6–8 h, and long sleepers. Multiple linear regression models were used to assess the association between...
sleep duration and the EQ-5D index. For the above multivariable analyses, 3 models were constructed: model 1 was adjusted for age (40–49, 50–59, 60–69, or ≥70 years), sex, BMI, FEV₁ (% predicted), and history of tobacco smoking (former or current smoker, or not); model 2 was adjusted for all covariates in model 1 plus alcohol drinking (heavy drinker or not), education (high school or above, or not), income (lowest quartile or not), living with a spouse (yes or no), occupation (yes or no), and regular exercise (yes or no); and model 3 was adjusted for all covariates in model 2 plus the presence of hypertension, diabetes, cardiovascular disease, and cancer. Statistical significance was set at \( p < 0.05 \). Statistical analyses were performed using R 4.0.1 (http://www.r-project.org) and Stata 13.1 (StataCorp, College Station, TX, USA) software.

**Results**

Among 38,650 participants aged 40 years or older, 3,349 (8.7%) with COPD were analyzed. Most participants with COPD were men, aged ≥60 years, and former or current smokers (Table 1). The median FEV₁ was 78.8% predicted (interquartile range [IQR], 69.1–87.9% predicted). About half of the participants had hypertension and one-quarter had diabetes. The median sleep duration was 7 h (IQR, 6–8 h), 693 (20.7%) were short sleepers (<6 h), and 266 (7.9%) were long sleepers (>8 h).

The characteristics of the 3,349 participants with COPD according to sleep duration are presented in Table 1. The proportions of men and former or current smokers were lower in short sleepers than in 6- to 8-h sleepers and long sleepers. Short and long sleepers were less likely to have high school education or above and to have an occupation and more likely to have income in the lowest quartile than the 6- to 8-h sleepers. Hypertension was more prevalent in short sleepers, whereas diabetes was more prevalent in long sleepers. However, the FEV₁ % predicted and GOLD stages did not differ with sleep duration.

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shown in Figure 1. In the unadjusted model, short sleepers with COPD had an increased risk of death (hazard ratio [HR]: 1.35; 95% confidence interval [CI]: 1.07–1.71) (Table 2 and online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000516381). However, this association was not significant after adjusting for age, sex, BMI, FEV$_1$ (% predicted), and history of tobacco smoking (former or current smoker, or never smoker). Model 2: adjusted for all covariates in model 1 plus alcohol drinking (heavy drinker or not), education (high school or above, 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 3: adjusted for all covariates in model 2 plus the presence of hypertension, diabetes, cardiovascular disease, and cancer.

### Table 2. Multivariable analysis of all-cause mortality by sleep duration

<table>
<thead>
<tr>
<th>Sleep duration, h/day</th>
<th>Unadjusted</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>1.35 (1.07, 1.71)</td>
<td>1.13 (0.89, 1.43)</td>
<td>1.07 (0.85, 1.36)</td>
<td>1.06 (0.84, 1.35)</td>
</tr>
<tr>
<td>6–8</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>1.21 (0.85, 1.73)</td>
<td>0.98 (0.69, 1.41)</td>
<td>0.93 (0.65, 1.34)</td>
<td>0.94 (0.65, 1.35)</td>
</tr>
</tbody>
</table>

Data were analyzed with Cox proportional hazard models and are presented as adjusted hazard ratios (95% confidence intervals). Model 1: adjusted for age (40–49, 50–59, 60–69, and ≥70 years), sex, BMI, FEV$_1$ (% predicted), and history of tobacco smoking (former or current smoker, or never smoker). Model 2: adjusted for all covariates in model 1 plus alcohol drinking (heavy drinker or not), education (high school or above, 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 3: adjusted for all covariates in model 2 plus the presence of hypertension, diabetes, cardiovascular disease, and cancer.

### Discussion

In the current study using data from a nationally representative Korean survey linked with death certificates, sleep duration was not associated with all-cause mortality in individuals with COPD. However, short sleep duration was significantly associated with worse HRQOL in those with COPD.

Poor sleep quality is common among patients with COPD and is associated with adverse health outcomes in this population [11–15]. In a cross-sectional study of a cohort of patients with COPD participating in the Sub-
populations and Intermediate Outcome Measures in COPD Study (SPIROMICS), sleep quality was a significant predictor of HRQOL [14]. Other longitudinal studies reported that sleep quality was predictive of COPD exacerbation [13, 15] and mortality [13]. Thus, poor sleep quality has been suggested as a modifiable risk factor for poor HRQOL in patients with COPD [14].

Besides sleep quality, adequate sleep duration is also important for health [5]. In the general population, sleep duration showed a U-shaped association with increased mortality, with a nadir at 7 h of sleep [7]. Short sleep duration was associated with obesity, hypertension, type 2 diabetes, coronary heart disease, and stroke [10]. However, the effects of sleep duration on health outcomes in individuals with COPD are poorly understood. A recent cross-sectional study reported that the longer total sleep time in African Americans with GOLD stages 0–2 who smoked ≥10 cigarettes smoked per day was associated with better functional exercise capacity [29]. The study participants’ mean total sleep time was 5 h; thus, for example, in a smoker who smoked 20 cigarettes smoked per day, an additional 20 min of total sleep time was associated with an additional 4.40 m in the 6-min walk test [29].

The results from our study are consistent with these prior findings. In the present study, short sleep duration was significantly associated with poor HRQOL in participants with COPD, although sleep duration was not predictive of all-cause mortality. Our results suggest that sleep duration might be a modifiable risk factor for HRQOL in patients with COPD. Further studies are required to investigate whether interventions to promote adequate sleep duration can improve HRQOL in this population.

There are several potential explanations for the association between short sleep duration and poor HRQOL. Sleep restriction not only leads to daytime sleepiness and fatigue but may also gradually change certain brain and neuroendocrine systems in a manner similar to that seen in stress-related disorders [30, 31]. Sleep deprivation results in sympathetic activation and inflammation, which could lead to an increased risk of cardiovascular disease [32, 33]. In previous studies, sleep deprivation increased the levels of pro- and anti-inflammatory markers such as C-reactive protein and cytokines [34, 35]. Chronic sleep loss has a detrimental effect on glucose metabolism and increases insulin resistance [36]. It is also associated with behavioral changes and reductions in cognitive function and memory [36].

To appropriately appreciate the results of our study, its limitations must be recognized. First, we used self-reported sleep duration rather than objective measures such as actigraphy or polysomnography. Previous studies reported a correlation between self-reported and objective measures of sleep duration of 0.43, which is generally considered a moderate correlation [37]. Although self-reports of

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</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>−0.04 (−0.06, −0.03)</td>
<td>−0.03 (−0.04, −0.01)</td>
<td>−0.02 (−0.04, −0.01)</td>
<td>−0.02 (−0.04, −0.01)</td>
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<tr>
<td>6–8 (reference)</td>
<td>(reference)</td>
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<td>(reference)</td>
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</tr>
<tr>
<td>&gt;8</td>
<td>−0.02 (−0.04, 0.003)</td>
<td>−0.01 (−0.03, 0.01)</td>
<td>−0.01 (−0.03, 0.01)</td>
<td>−0.01 (−0.03, 0.01)</td>
</tr>
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Data were analyzed with linear regression and are presented as linear regression coefficients (95% confidence interval). Model 1: adjusted for age (40–49, 50–59, 60–69, or ≥70 years), sex, BMI, FEV₁ (% predicted), and history of tobacco smoking (former or current smoker, or not). Model 2: adjusted for all covariates in model 1 plus alcohol drinking (heavy drinker or not), education (high school or above, 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 3: adjusted for all covariates in model 2 plus the presence of hypertension, diabetes, cardiovascular disease, and cancer.
sleep duration could lead to nondifferential misclassification bias, nondifferential misclassification of sleep duration would result in underestimation of the real effects [38]. Second, there was a lack of information on sleep quality and sleep disorders, including insomnia and obstructive sleep apnea, as these data were not collected in the KNHANES. Third, as the diagnosis of COPD was based on prebronchodilator spirometry, there might have been an overestimation of COPD. Fourth, since most participants were GOLD stages 1–2, it is difficult to generalize our findings to those with severe disease. Lastly, our study is limited by the relatively short follow-up duration, which might result in an attenuated association between sleep duration and mortality after multivariable adjustment.

In conclusion, we found that sleep duration was not associated with all-cause mortality in individuals with COPD. However, short sleep duration was significantly associated with worse HRQOL in those with COPD. Further large-scale 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 COPD population.

**Acknowledgement**

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**References**


**Statement of Ethics**

All participants of the Korea National Health and Nutrition Examination Survey provided written informed consent. The study protocol for the survey was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention. The current study was granted an exemption from the requirement for 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.

**Conflict of Interest Statement**

There are no conflicts of interest.

**Funding Sources**

The authors did not receive any funding.

**Author Contributions**

J.C. had full access to all the data used in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.J.K. and J.C. contributed to the study concept and design, data analysis and interpretation, and manuscript writing and revision. N.K., S.M.C, J.J.L, Y.S.P., C.H.L., S.M.L., and C.G.Y. contributed to the data interpretation and manuscript review. All authors have read and approved the final manuscript.
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