Original Article

J Prev Med Public Health 2023;56:458-466 • https://doi.org/10.3961/jpmph.23.311

pISSN 1975-8375 eISSN 2233-4521

Journal of Preventive Medicine & Public Health

Sleep Duration, Comorbidities, and Mortality in Korean Health Examinees: A Prospective Cohort Study

Sukhong Min[1], Woo-Kyoung Shin[1,2], Katherine De la Torre[1,3], Dan Huang[1,2], Hyung-Suk Yoon[4,5], Aesun Shin[1,2,6], Ji-Yeob Choi[1,3], Daehee Kang[1,2]

[1]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea; [2]Integrated Major in Innovative Medical Science, Seoul National University Graduate School, Seoul, Korea; [3]Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Korea; [4]Department of Surgery, University of Florida College of Medicine, Gainesville, FL, USA; [5]University of Florida Health Cancer Center, Gainesville, FL, USA; [6]Cancer Research Institute, Seoul National University, Seoul, Korea

Objectives: The association between long sleep duration and mortality is frequently attributed to the confounding influence of comorbidities. Nevertheless, past efforts to account for comorbidities have yielded inconsistent outcomes. The objective of this study was to evaluate this relationship using a large prospective cohort in Korea.

Methods: The study included 114 205 participants from the Health Examinees Study, who were followed for a median of 9.1 years. A composite comorbidity score was developed to summarize the effects of 21 diseases. Using Cox proportional hazards regression, hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, cancer, and cardiovascular mortality associated with sleep duration were estimated. These estimates were adjusted for socio-demographic factors, lifestyle factors, body mass index, and comorbidity score. Additionally, a stratified analysis by subgroups with and without comorbidities was conducted.

Results: Throughout the follow-up period, 2675 deaths were recorded. After all adjustments, an association was observed between a sleep duration of 8 hours or more and all-cause mortality (HR, 1.10; 95% CI, 1.01 to 1.20). However, no such association was detected in the stratified analysis for the subgroups based on comorbidity status.

Conclusions: Long sleep duration was found to be associated with all-cause mortality among Koreans, even after adjusting for comorbidities. Additional studies are required to explore the mechanism underlying the association between sleep duration and major causes of mortality.

Key words: Sleep duration, Mortality, Comorbidity, Prospective studies

INTRODUCTION

Extreme durations of sleep, both short and long, have been linked to an elevated risk of mortality [1-4]. Previous studies have described the relationship between sleep duration and mortality as a U-shaped curve, indicating an increased risk at the extremes and the lowest relative risk for those who sleep for 7 hours to 8 hours [3].

While both excessively long and short sleep durations have been associated with increased mortality risk, the mechanisms proposed by prior research differ for each extreme. Previous studies have demonstrated that short sleep can lead to increased energy intake, decreased energy expenditure, insulin resistance, glucose intolerance, compromised immunity, and inflammation, all of which elevate mortality risk [5,6]. However, other studies have indicated that comorbidities may serve

Received: July 7, 2023 Accepted: September 8, 2023

Corresponding author: Daehee Kang
Department of Preventive Medicine, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Korea
E-mail: dhkang@snu.ac.kr

as a confounding factor in the association between long sleep duration and mortality. As such, poor health would be the cause of both extended sleep and higher mortality rates [4,7,8].

Efforts to adjust for the confounding effect of comorbidity and isolate the impact of prolonged sleep duration on mortality have been limited and have yielded inconsistent results. Magee et al. [9] noted in a prospective cohort study involving approximately 228 000 Australians that extended sleep was only a mortality risk factor in individuals with 1 or more comorbidities, as measured by the Charlson comorbidity index (CCI). This was not the case for those without any comorbidities. In contrast, Cai et al. [10] monitored around 113 000 Chinese adults, using the CCI to assess their degree of comorbidities, and found that prolonged sleep increased the risk of mortality, irrespective of comorbidities. Similarly, Kwon et al. [11] determined from a prospective cohort of roughly 34 000 Korean adults that extended sleep heightened the risk of mortality when adjusted for self-rated health.

Recent studies have associated extreme sleep length with detrimental effects on cognitive, metabolic, mental, cardiovascular, and cerebrovascular health [12-15]. However, the mechanism connecting sleep duration to mortality remains poorly defined. Specifically, it is unclear whether the increased mortality among those with long sleep durations is due to confounding effects related to comorbidities, or whether long sleep duration itself poses a risk of mortality. Given that sleep durations and their associations with mortality are closely associated with social and cultural factors [16,17], research is needed to clarify the relationship between long sleep duration and mortality in the Korean population, with a rigorous adjustment for comorbidity.

In this study, we evaluated the association between sleep duration and mortality among Koreans, utilizing data from the Korean Genome and Epidemiology Study-Health Examinees (KoGES HEXA) cohort. We adjusted for comorbidity by using a composite score derived from a statistical model that estimates the impact of individual comorbidity on mortality risk. Additionally, we examined the relationship between sleep duration and mortality among subgroups with and without comorbidity.

METHODS

Study Population

The KoGES HEXA study is a large-scale, community-based, prospective cohort study that was conducted in Korea between 2004 and 2013 to gather baseline data. The study's participants were recruited from health examination centers and training hospitals throughout the country. The rationale, design, and baseline characteristics of the study have been previously described [18]. The baseline surveys were conducted in 2 phases: the first from 2004 to 2008 (n=89 169) and the second from 2009 to 2013 (n=84 033), for a total of 173 202 participants recruited. The present study used the Health Examinees-Gem (HEXA-G) participant sample (n=139 267). This sample is a subset of the HEXA study, excluding participants who were under 40 years or over 69 years of age, as well as those recruited from sites that only participated in the pilot phase, participated for less than 2 years, or did not meet the biospecimen quality control criteria. Further details have been provided previously [19].

Among the participants in the HEXA-G study, individuals with missing mortality data (n=23 211) or with follow-up periods of less than 2 years (n=307) were excluded to account for disease latency. Participants missing sleep duration data (n=910) or who reported sleep durations that were outliers, defined as the highest and lowest 1%, were also excluded (n=634). In total, the study included and followed 114 205 participants for a median duration of 9.1 years.

Exposure Assessment

The sleep duration was self-reported through in-person interviews. In the first phase, participants were asked "In the past year, on average, how many hours of sleep (including daytime naps) did you get per day?" The potential answers were provided in multiple-choice format: less than 6 hours, 6 hours to less than 8 hours, 8 hours to less than 10 hours, and 10 hours or more. In the second phase, participants were asked the same question, but they were required to provide their responses in numerical form, specifying hours and minutes. The responses were then classified according to the categories established in the first phase. Due to a low number of participants (n=1574), the category of 10 hours or more was combined with that of 8 hours to less than 10 hours.

Outcome Ascertainment

The date and cause of death for each participant were determined using the death registry data supplied by the National Statistical Office of Korea. These data were then linked to the HEXA study using the unique national identification number of each participant. The cause of death is recorded in

the registry in accordance with the International Classification of Diseases, 10th revision. The outcomes evaluated in this study included all-cause mortality, cancer mortality (coded as C00-C97), and cardiovascular disease (CVD) mortality (coded as I00-I99).

Covariates

Socio-demographic factors, including age (treated as a continuous variable), sex, marital status, education, and body mass index (BMI), were incorporated as covariates. Sex was divided into 2 categories: male and female. Marital status was classified as single (which includes those who had never married, were separated, were divorced, or were widowed) and married or cohabiting. Education was divided into 3 categories: middle school or below, high school graduate, and bachelor's degree or above. BMI was determined by dividing body weight by the square of height (kg/m^2) and then categorized according to the Asia-Pacific classification recommended by the World Health Organization [20]. The categories were as follows: underweight (<18.5 kg/m^2), normal weight (≥18.5 and <23.0 kg/m^2), overweight (≥23.0 and <25.0 kg/m^2), obese class I (≥25.0 and <30.0 kg/m^2), and obese class II (≥30.0 kg/m^2).

This study also incorporated lifestyle factors, including smoking, drinking, and physical activity. The smoking status of participants was classified into 3 categories: never smokers, former smokers, and current smokers. Similarly, drinking status was categorized as never drinkers, former drinkers, and current drinkers. Information regarding physical activity was gathered through a self-reported question that required a yes-or-no response. Participants were asked, "Do you engage in regular exercise intense enough to induce sweating?" Based on their responses, they were then categorized into either the regular exercise group or the non-regular exercise group.

All covariates were determined through interview-based questionnaires, except for BMI, which was computed using anthropometric measurements.

Comorbidity Score

A composite score for comorbidities was formulated and incorporated as a covariate in this study. The comorbidities considered included hypertension, diabetes, hyperlipidemia, stroke, myocardial infarction, gastrointestinal polyp, acute liver disease, fatty liver disease, chronic liver disease, cholelithiasis/cholecystitis, thyroid disease, arthritis, osteoporosis, depression, tuberculosis, asthma, cataract, chronic gastritis, gastric ulcer, duodenal ulcer, and cancer. Participants were queried about whether they had received a diagnosis for each of these diseases, to which they could respond "yes" or "no." A missing response for a given comorbidity was assigned as "no" through mode imputation.

The comorbidity score was calculated for each participant in accordance with the methods outlined by Sullivan et al. [21]. In summary, a multivariate Cox regression analysis was conducted using all previously mentioned covariates to determine the regression coefficient for each comorbidity. This coefficient was then divided by the coefficient for age to compute the risk point associated with each comorbidity. The risk points were subsequently summed to yield the comorbidity score. This procedure was replicated for all-cause, cancer, and CVD mortality. Supplemental Material 1 illustrates the comorbidity score calculation process using a hypothetical participant as an example.

Comorbidity was also assessed using the CCI. The CCI was determined based on the assessment of specific diseases through the HEXA questionnaire. These diseases included diabetes, stroke, myocardial infarction, chronic liver disease, gastric ulcer, and cancer. The allocation and summation of points based on comorbidity and age aligned with the method outlined by Charlson et al. [22].

Statistical Analysis

The baseline characteristics of the study population were presented as percentages for categorical variables and as means with standard deviations for continuous variables. The chi-square test was employed to compare these baseline characteristics across different categories of sleep duration for categorical variables. For continuous variables, however, analysis of variance was utilized.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression, using the category of 6 hours to less than 8 hours of sleep as the reference. The survival time for each participant was determined by subtracting the recruitment date from either the date of death or the end of the follow-up period (December 2019), depending on which came first. Four models were constructed in total, with all-cause, cancer, and CVD mortality as outcomes. Model 1 was adjusted for age and sex; model 2 was additionally adjusted for marital status, education, obesity, smoking, drinking, and physical activity; and model 3A and B were further adjusted for comorbidity score and CCI, respectively.

To examine the change in sleep duration assessment between the 2 baseline phases, we conducted a sensitivity analysis using model 3A. This model was used to determine all-cause, cancer, and CVD mortality as outcomes for each baseline phase. Subsequently, we assessed the results for heterogeneity using the Cochran Q test.

To further investigate the impact of potential confounding variables, the study population was divided based on comorbidity score (comorbidity score=0 and ≠0). Within each stratum, model 3A was constructed, using all-cause mortality, cancer mortality, and CVD mortality as outcomes.

Evaluation of model prediction performance

To assess the validity of the comorbidity index, we evaluated the predictive performance of models that utilized different comorbidity measures. This was accomplished by comparing

Table 1. Characteristics of the study population

Characteristics	All sample (n)	Sleep duration (hr)			*p*-value[1]
		<6	6-7	≥8	
No. of individuals	114 205	10 625 (9.3)	74 852 (65.5)	28 728 (25.2)	
Person-years (y)	1 052 384	100 839	686 403	265 142	
Years of follow-up, median (y)	9.1	9.6	9.1	9.1	
Sex					<0.001
Male	39 087	3285 (8.4)	26 546 (67.9)	9256 (23.7)	
Female	75 118	7340 (9.8)	48 306 (64.3)	19 472 (25.9)	
Age, mean±SD (y)	52.8±8.0	54.3±8.0	52.4±7.9	53.3±8.1	<0.001
Education					<0.001
Less than middle school	34 698	3963 (11.4)	20 782 (59.9)	9953 (28.7)	
High school	49 467	4259 (8.6)	32 776 (66.3)	12 432 (25.1)	
More than college degree	30 040	2403 (8.0)	21 294 (70.9)	6343 (21.1)	
Marital status					<0.001
Single	11 787	1537 (13.0)	7255 (61.6)	2995 (25.4)	
Married/cohabitating	102 418	9088 (8.9)	67 597 (66.0)	25 733 (25.1)	
Smoking					<0.001
Never	83 193	7988 (9.6)	54 170 (65.1)	21 035 (25.3)	
Former	17 077	1349 (7.9)	11 485 (67.3)	4243 (24.8)	
Current	13 935	1288 (9.2)	9197 (66.0)	3450 (24.8)	
Alcohol					<0.001
Never	58 335	5734 (9.8)	37 463 (64.2)	15 138 (26.0)	
Former	4202	437 (10.4)	2586 (61.5)	1179 (28.1)	
Current	51 668	4454 (8.6)	34 803 (67.4)	12 411 (24.0)	
BMI, mean±SD (kg/m^2)[2]	23.9±2.9	24.2±3.1	23.9±2.9	23.8±2.9	<0.001
Underweight	2053	207 (10.1)	1307 (63.7)	539 (26.3)	
Normal	43 685	3610 (8.3)	28 838 (66.0)	11 237 (25.7)	
Overweight	31 660	2909 (9.2)	20 748 (65.5)	8003 (25.3)	
Obese class I	33 630	3468 (10.3)	21 928 (65.2)	8234 (24.5)	
Obese class II	3177	431 (13.6)	2031 (63.9)	715 (22.5)	
Physical activity					<0.001
Regularly exercise	61 196	5209 (8.5)	40 936 (66.9)	15 051 (24.6)	
Do not regularly exercise	53 009	5416 (10.2)	33 916 (64.0)	13 677 (25.8)	

Values are presented as number (%).
BMI, body mass index.
[1]Significance tests for the categories of sleep duration were based on analysis of variance for continuous variables and the chi-square test for categorical variables.
[2]The categories were defined as underweight (<18.5 kg/m^2), normal (≥18.5 and <23.0 kg/m^2), overweight (≥23.0 and <25.0 kg/m^2), obese class I (≥25.0 and <30.0 kg/m^2), and obese class II (≥30.0 kg/m^2).

the Harrell C statistics for models 3A and B.

For all analyses, *p*-values were 2-sided and considered to indicate statistical significance if less than 0.05. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics Statement

Participants who provided written informed consent contributed information through questionnaires, physical examinations, and laboratory tests. The study protocol received approval from the Institutional Review Board of Seoul National University Hospital (IRB No. E-2009-117-1159) and the Korea National Institute of Health (IRB No. 2014-08-02-3C-A).

RESULTS

Table 1 presents a summary of the baseline characteristics of the participants, categorized by sleep duration. Over a median follow-up period of 9.1 years, 2675 deaths were identified. The participants were predominantly females, comprising 65.8% of the group, and the average age was 52.8 years. Most of the participants had graduated from high school (43.3%), were married (89.7%), had never smoked (72.8%), and had never drank alcohol (50.9%). The mean BMI was 23.9 kg/m^2. A slightly higher percentage of participants engaged in regular exercise (53.6%) compared to those who did not (46.4%). All baseline characteristics exhibited significant differences across sleep duration categories ($p<0.001$).

Association Between Sleep Duration and Mortality

Table 2 presents the associations between sleep duration and all-cause, cancer, and CVD mortality. In model 1, both the group sleeping less than 6 hours and the group sleeping 8 hours or more demonstrated an elevated risk of all-cause mortality (for <6 hours: HR, 1.19; 95% CI, 1.05 to 1.34; for ≥8 hours: HR, 1.18; 95% CI, 1.09 to 1.29). After further adjustments, only the group sleeping 8 hours or more retained an increased risk of all-cause mortality (for model 2: HR, 1.12; 95% CI, 1.03 to 1.23; for model 3A: HR, 1.10; 95% CI, 1.01 to 1.20; for model 3B: HR, 1.11; 95% CI, 1.02 to 1.21). The group sleeping less than 6 hours showed a marginally significant association in the final model (for model 3A: HR, 1.10; 95% CI, 0.97 to 1.24; for model 3B: HR, 1.11; 95% CI, 0.98 to 1.25).

For cancer mortality, increased risk was observed among those who slept for less than 6 hours or for at least 8 hours (for <6 hours: HR, 1.21; 95% CI, 1.02 to 1.43; for ≥8 hours: HR, 1.15; 95% CI, 1.02 to 1.30) according to model 1. However, after further adjustments, a marginally significant increase in cancer mortality risk was noted for both those who slept for less than 6 hours (for model 3A: HR, 1.16; 95% CI, 0.98 to 1.36; for model 3B: HR, 1.16; 95% CI, 0.98 to 1.37) and those who slept at least 8 hours (for model 3A: HR, 1.09; 95% CI, 0.97 to 1.24; for model 3B: HR, 1.10; 95% CI, 0.97 to 1.24). No significant associations were identified between CVD mortality risk and either shorter or longer sleep duration categories in models 1, 2, 3A, or B.

Supplemental Material 2 presents the results of model 3A for each baseline phase, along with the heterogeneity between the results concerning all-cause mortality. Across all mortality outcomes and categories of sleep duration, no significant heterogeneity was detected.

Table 2. Association between sleep duration and mortality[1]

Cause of death	Sleep duration (hr)		
	<6	6 to <8	≥8
Person-years (y)	100 839	686 403	265 142
Total (n)	10 625	74 852	28 728
All-cause[2]			
No. of deaths	321	1582	772
Model 1	1.19 (1.05, 1.34)	1.00 (reference)	1.18 (1.09, 1.29)
Model 2	1.11 (0.99, 1.26)	1.00 (reference)	1.12 (1.03, 1.23)
Model 3A	1.10 (0.97, 1.24)	1.00 (reference)	1.10 (1.01, 1.20)
Model 3B	1.11 (0.98, 1.25)	1.00 (reference)	1.11 (1.02, 1.21)
Cancer[3]			
No. of deaths	169	810	384
Model 1	1.21 (1.02, 1.43)	1.00 (reference)	1.15 (1.02, 1.30)
Model 2	1.16 (0.98, 1.37)	1.00 (reference)	1.11 (0.98, 1.25)
Model 3A	1.16 (0.98, 1.36)	1.00 (reference)	1.09 (0.97, 1.24)
Model 3B	1.16 (0.98, 1.37)	1.00 (reference)	1.10 (0.97, 1.24)
CVD[4]			
No. of deaths	47	254	113
Model 1	1.04 (0.76, 1.43)	1.00 (reference)	1.07 (0.86, 1.33)
Model 2	0.96 (0.71, 1.32)	1.00 (reference)	1.00 (0.80, 1.25)
Model 3A	0.96 (0.70, 1.32)	1.00 (reference)	0.99 (0.80, 1.24)
Model 3B	0.96 (0.70, 1.32)	1.00 (reference)	0.99 (0.79, 1.23)

Values are presented as hazard ratio (95% confidence interval).
CVD, cardiovascular disease; BMI, body mass index; ICD-10, the 10th revision of the International Classification of Disease.
[1]Model 1: Cox proportional hazards analysis, adjusted by age and sex; Model 2: Model 1+marital status, education level, BMI, smoking, drinking, and physical activity; Model 3A: Model 2+comorbidity score; Model 3B: Model 2+Charlson comorbidity index.
[2]Cause of death identified by ICD-10 codes A00-Z99.
[3]Cause of death identified by ICD-10 codes C00-C97.
[4]Cause of death identified by ICD-10 codes I00-I99.

Table 3. Association between sleep duration and mortality, with stratification

Sleep duration (hr)	Person-years (y)	n	All-cause death[1]		Cancer death[2]		CVD death[3]	
			No. of deaths	HR (95% CI)[4]	No. of deaths	HR (95% CI)[4]	No. of deaths	HR (95% CI)[4]
Individuals without comorbidity[5]								
<6	41 175	4338	86	1.16 (0.92, 1.46)	47	1.15 (0.84, 1.57)	10	0.84 (0.43, 1.63)
6 to <8	317 148	34 408	474	1.00 (reference)	261	1.00 (reference)	74	1.00 (reference)
≥8	115 433	12 379	209	1.10 (0.94, 1.30)	113	1.08 (0.87, 1.35)	27	0.89 (0.57, 1.38)
Individuals with comorbidity[6]								
<6	59 664	6287	235	1.04 (0.88, 1.24)	122	1.00 (0.76, 1.31)	37	1.03 (0.64, 1.66)
6 to <8	369 255	40 444	1108	1.00 (reference)	549	1.00 (reference)	180	1.00 (reference)
≥8	149 709	16 349	563	1.07 (0.95, 1.21)	271	1.16 (0.97, 1.40)	86	1.04 (0.74, 1.46)

CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ICD-10, the 10th revision of the International Classification of Disease.
[1]Cause of death identified by ICD-10 codes A00-Z99.
[2]Cause of death identified by ICD-10 codes C00-C97.
[3]Cause of death identified by ICD-10 codes I00-I99.
[4]HRs and 95% CIs were obtained using Cox proportional hazards analysis, adjusted by age, sex, marital status, education level, BMI, smoking, drinking, physical activity, and comorbidity score.
[5]Comorbidity score=0.
[6]Comorbidity score≠0.

Stratified Analysis

The results of the stratified analysis, which was conducted based on the presence of comorbidity and controlled for all covariates in model 3A except for the comorbidity score, are displayed in Table 3. In both subgroups, those with comorbidity and those without, no significant associations were found between sleep duration and any cause of death.

Evaluation of Model Prediction Performance

Supplemental Material 3 presents the C-index of models 3A and B. The C-index for all-cause mortality was 0.77 (95% CI, 0.76 to 0.78) for model 3A and 0.76 (95% CI, 0.75 to 0.77) for model 3B. Regarding cancer mortality, the C-index was 0.76 (95% CI, 0.74 to 0.77) for model 3A and 0.75 (95% CI, 0.73 to 0.76) for model 3B. For CVD mortality, the C-index for 3A was 0.80 (95% CI, 0.77 to 0.82), while for model 3B, it was 0.80 (95% CI, 0.78 to 0.82).

DISCUSSION

Association Between Sleep Duration and Mortality

In this study, we explored the association between sleep duration and all-cause, cancer, and CVD mortality. The risk of all-cause mortality was found to be significantly elevated in participants who slept for 8 hours or more. However, after making all necessary adjustments, we found no significant association between sleep duration and mortality from either cancer or CVD. Furthermore, we observed comparable HRs for models 3A and B across all mortality types and categories of sleep duration.

The finding that long sleep duration was associated with all-cause mortality, even after adjusting for comorbidities, aligns with previous research [10,11]. Cai et al. [10] adjusted for comorbidities using the CCI and found significantly elevated risks associated with sleep duration of 8 hours or more. These risks escalated further with increased sleep duration, resulting in a J-curve. Kwon et al. [11], who incorporated self-rated health and considered the presence of metabolic syndrome as a comorbidity, found that only sleep durations of 9 hours or longer were significantly associated with all-cause mortality. The slight but significant increase in all-cause and cancer mortality risk for short sleep durations also concurs with the findings of Cai et al. [10]. Specifically, they found that a sleep duration of 4-5 hours per day was associated with an HR of 1.11 (95% CI, 1.00 to 1.23) and an HR of 1.06 (95% CI, 0.91 to 1.24) for all-cause and cancer mortality, respectively [10].

However, the absence of an association between long sleep duration and mortality due to cancer or CVD is inconsistent with other studies that have identified associations with cancer [4,23-26] or CVD mortality [2,27-29]. This difference could be attributed to the method of adjusting for comorbidities. Earlier studies accounted for the history of diabetes, hypertension, cancer, or a combination of these, incorporating these comorbidities as binary absent/present categorical covariates

in regression models.

Additionally, our results may have diverged from those of prior studies due to differences in how comorbidities were defined. Many studies incorporating a measure of comorbidities have utilized the CCI, which encompasses 16 diseases and more severe conditions such as acquired immune deficiency syndrome, hematologic cancers, and hemiplegia [9,10,30]. In contrast, our definition of comorbidity was based on a questionnaire surveying 21 diseases, including less severe conditions like hyperlipidemia, arthritis, and cataracts for model 3A, or on the 6 diseases assessed by the questionnaire in alignment with the CCI criteria for model 3B. This variation in the diseases included in the analyses may have facilitated the divergence of our results from those of earlier studies.

The HEXA study utilized slightly different sleep duration questionnaires during its first and second baseline phases. We evaluated the effect of this modification on sleep duration assessment through a sensitivity analysis. The results from model 3A, which was constructed independently for each phase, revealed no significant heterogeneity. This suggests that the modification had a minimal impact on our analysis. We therefore concluded that the data from both phases were sufficiently homogeneous to be combined.

Stratified Analysis

Our research uncovered no significant associations between sleep duration and mortality in subgroups with and without comorbidity. Our findings align with those of Magee et al. [9] for the subgroup without comorbidity, but they differ from previous results for the subgroup with comorbidity [9,10]. This disagreement may also stem from the difference in the definition of comorbidities. Whereas we quantified comorbidities as a continuous score, Magee et al. [9] and Cai et al. [10] employed the CCI, which measured it as positive integers. In the subsequent stratification by those with and without comorbidity, more information may have been lost in our study compared to those of Magee et al. [9] and Cai et al. [10].

Evaluation of Model Prediction Performance

Models incorporating either the comorbidity score or the CCI as covariates displayed comparable C-indices. This indicates that the selection of the comorbidity index did not influence the performance of the models. However, for all-cause and cancer mortality, model 3A, which utilized the comorbidity score, demonstrated the best performance. The fact that our comorbidity score either matched or exceeded the predictive performance of the CCI for each cause-specific mortality rate implies that our score is a valid measure of the impact of comorbidities on mortality.

Possible Mechanism

Several mechanisms have been proposed to explain the connection between extended sleep duration and increased mortality. One potential explanation is that the reported extended sleep duration is indicative of sleep fragmentation, in which sleep is interspersed with wakefulness. A similar hypothesis suggests that individuals with poor sleep quality may report longer sleep durations due to decreased sleep efficiency, which could contribute to increased mortality [31,32]. Other theories propose that, similar to short sleep, extended sleep durations can lead to alterations in cytokine levels, potentially increasing the risk of mortality [33]. Further investigation is necessary to clarify the biophysiological mechanism linking sleep duration to mortality.

Strengths and Limitations

This study did present some limitations. The sleep duration was self-reported, which may have led to misclassification. However, it is generally accepted that self-reported sleep duration correlates well with actigraphic measurements, making them a viable alternative [34]. The study also operated under the assumption that the sleep duration data collected at baseline remained constant throughout the follow-up period. Notably, this study did not incorporate sleep quality or sleep apnea, both of which are recognized confounders to reported sleep duration and associated comorbidities. Consequently, future research should employ repeated measures or longitudinal data to accurately measure and validate habitual sleep durations, while also adjusting for factors such as sleep quality and sleep apnea.

Despite these limitations, our study benefitted from a substantial sample size and an extended follow-up period. These aspects were essential to capture the long-term effects of habitual sleep duration and to permit sufficient disease latency. Furthermore, our comorbidity scoring system not only facilitated the adjustment of comorbidity in our analyses, but also expanded the scope of included comorbidities beyond those covered by the CCI.

In conclusion, the present findings indicate long sleep durations increase risk of all-cause mortality even after adjusting

for comorbidities, challenging the hypothesis that such an association is solely due to comorbidities. Further research is necessary to explore the mechanism linking extended sleep durations with major-cause mortalities.

SUPPLEMENTAL MATERIALS

Supplemental materials are available at https://doi.org/10.3961/jpmph.23.311.

CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

FUNDING

This work was supported by the Research Program funded by the Korea Centers for Disease Control and Prevention (grant No. 2004-E71004-00; 2005-E71011-00; 2005-E71009-00; 2006-E71001-00; 2006-E71004-00; 2006-E71010-00; 2006-E71003-00; 2007-E71004-00; 2007-E71006-00; 2008-E7100600; 2008-E71008-00; 2009-E71009-00; 2010-E71006-00; 2011-E71006-00; 2012-E71001-00; 2013-E71009-00). Additionally, this work received support from a grant provided by the National Research Foundation of Korea (NRF), which is funded by the Korean government (MSIT) (2022R1A2C1004608).

ACKNOWLEDGEMENTS

This study was supported by the National Genome Research Institute, the Korea Centers for Disease Control and Prevention, and a grant from the Seoul National University Hospital. We would like to thank the study participants and all members of the KoGES HEXA study group.

The funding source played a role in the design of the study and the collection of data.

AUTHOR CONTRIBUTIONS

Conceptualization: Min S, Kang D. Formal analysis: Min S. Funding acquisition: Shin A, Choi JY, Kang D. Methodology: Min S, Shin WK, De La Torre K, Huang D, Yoon HS. Project administration: Shin A, Choi JY, Kang D. Visualization: Min S. Writing – original draft: Min S. Writing – review & editing: Min S, Shin WK, De La Torre K, Huang D, Yoon HS, Shin A, Choi JY, Kang D.

ORCID

Sukhong Min	*https://orcid.org/0000-0002-1018-1920*
Woo-Kyoung Shin	*https://orcid.org/0000-0003-2725-4652*
Katherine De La Torre	*https://orcid.org/0000-0003-2654-0171*
Dan Huang	*https://orcid.org/0000-0002-0956-780X*
Hyung-Suk Yoon	*https://orcid.org/0000-0001-6368-2684*
Aesun Shin	*https://orcid.org/0000-0002-6426-1969*
Ji-Yeob Choi	*https://orcid.org/0000-0001-5365-8189*
Daehee Kang	*https://orcid.org/0000-0003-4031-5878*

REFERENCES

1. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep 2010;33(5):585-592.
2. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. J Am Heart Assoc 2017;6(9):e005947.
3. Åkerstedt T, Narusyte J, Alexanderson K, Svedberg P. Sleep duration, mortality, and heredity-a prospective twin study. Sleep 2017;40(10):zsx135.
4. Svensson T, Saito E, Svensson AK, Melander O, Orho-Melander M, Mimura M, et al. Association of sleep duration with all- and major-cause mortality among adults in Japan, China, Singapore, and Korea. JAMA Netw Open 2021;4(9):e2122837.
5. Grandner MA, Hale L, Moore M, Patel NP. Mortality associated with short sleep duration: the evidence, the possible mechanisms, and the future. Sleep Med Rev 2010;14(3):191-203.
6. Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. Sleep Med 2017;32:246-256.
7. Jike M, Itani O, Watanabe N, Buysse DJ, Kaneita Y. Long sleep duration and health outcomes: a systematic review, meta-analysis and meta-regression. Sleep Med Rev 2018;39:25-36.
8. Svensson T, Inoue M, Saito E, Sawada N, Iso H, Mizoue T, et al. The association between habitual sleep duration and mortality according to sex and age: the Japan Public Health Center-based Prospective Study. J Epidemiol 2021;31(2):109-118.
9. Magee CA, Holliday EG, Attia J, Kritharides L, Banks E. Investi-

gation of the relationship between sleep duration, all-cause mortality, and preexisting disease. Sleep Med 2013;14(7):591-596.
10. Cai H, Shu XO, Xiang YB, Yang G, Li H, Ji BT, et al. Sleep duration and mortality: a prospective study of 113 138 middle-aged and elderly Chinese men and women. Sleep 2015;38(4):529-536.
11. Kwon S, Lee H, Lee JT, Shin MJ, Choi S, Oh H. Sleep duration and mortality in Korean adults: a population-based prospective cohort study. BMC Public Health 2020;20(1):1623.
12. Ramar K, Malhotra RK, Carden KA, Martin JL, Abbasi-Feinberg F, Aurora RN, et al. Sleep is essential to health: an American Academy of Sleep Medicine position statement. J Clin Sleep Med 2021;17(10):2115-2119.
13. Alvarez GG, Ayas NT. The impact of daily sleep duration on health: a review of the literature. Prog Cardiovasc Nurs 2004;19(2):56-59.
14. Matsubayashi H, Nagai M, Dote K, Turana Y, Siddique S, Chia YC, et al. Long sleep duration and cardiovascular disease: associations with arterial stiffness and blood pressure variability. J Clin Hypertens (Greenwich) 2021;23(3):496-503.
15. Zhou L, Yu K, Yang L, Wang H, Xiao Y, Qiu G, et al. Sleep duration, midday napping, and sleep quality and incident stroke: the Dongfeng-Tongji cohort. Neurology 2020;94(4):e345-e356.
16. Wang C, Bangdiwala SI, Rangarajan S, Lear SA, AlHabib KF, Mohan V, et al. Association of estimated sleep duration and naps with mortality and cardiovascular events: a study of 116 632 people from 21 countries. Eur Heart J 2019;40(20):1620-1629.
17. Yeo Y, Ma SH, Park SK, Chang SH, Shin HR, Kang D, et al. A prospective cohort study on the relationship of sleep duration with all-cause and disease-specific mortality in the Korean Multi-center Cancer Cohort study. J Prev Med Public Health 2013;46(5):271-281.
18. Health Examinees Study Group. The Health Examinees (HEXA) study: rationale, study design and baseline characteristics. Asian Pac J Cancer Prev 2015;16(4):1591-1597.
19. Shin S, Lee HW, Kim CE, Lim J, Lee JK, Lee SA, et al. Egg consumption and risk of metabolic syndrome in Korean adults: results from the Health Examinees Study. Nutrients 2017;9(7):687.
20. Zheng W, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K, et al. Association between body-mass index and risk of death in more than 1 million Asians. N Engl J Med 2011;364(8):719-729.
21. Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. Stat Med 2004;23(10):1631-1660.
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-383.
23. Wilunda C, Abe SK, Svensson T, Sawada N, Tsugane S, Wada K, et al. Sleep duration and risk of cancer incidence and mortality: a pooled analysis of six population-based cohorts in Japan. Int J Cancer 2022;151(7):1068-1080.
24. Li Y, Cai S, Ling Y, Mi S, Fan C, Zhong Y, et al. Association between total sleep time and all cancer mortality: non-linear dose-response meta-analysis of cohort studies. Sleep Med 2019;60:211-218.
25. Ma QQ, Yao Q, Lin L, Chen GC, Yu JB. Sleep duration and total cancer mortality: a meta-analysis of prospective studies. Sleep Med 2016;27-28:39-44.
26. Tao F, Cao Z, Jiang Y, Fan N, Xu F, Yang H, et al. Associations of sleep duration and quality with incident cardiovascular disease, cancer, and mortality: a prospective cohort study of 407,500 UK biobank participants. Sleep Med 2021;81:401-409.
27. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J 2011;32(12):1484-1492.
28. da Silva AA, de Mello RG, Schaan CW, Fuchs FD, Redline S, Fuchs SC. Sleep duration and mortality in the elderly: a systematic review with meta-analysis. BMJ Open 2016;6(2):e008119.
29. Jin Q, Yang N, Dai J, Zhao Y, Zhang X, Yin J, et al. Association of sleep duration with all-cause and cardiovascular mortality: a prospective cohort study. Front Public Health 2022;10:880276.
30. Åkerstedt T, Trolle-Lagerros Y, Widman L, Ye W, Adami HO, Bellocco R. Sleep duration and mortality, influence of age, retirement, and occupational group. J Sleep Res 2022;31(3):e13512.
31. Youngstedt SD, Kripke DF. Long sleep and mortality: rationale for sleep restriction. Sleep Med Rev 2004;8(3):159-174.
32. Bliwise DL, King AC, Harris RB. Habitual sleep durations and health in a 50-65 year old population. J Clin Epidemiol 1994;47(1):35-41.
33. Born J, Lange T, Hansen K, Mölle M, Fehm HL. Effects of sleep and circadian rhythm on human circulating immune cells. J Immunol 1997;158(9):4454-4464.
34. Lockley SW, Skene DJ, Arendt J. Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. J Sleep Res 1999;8(3):175-183.