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Adherence to a healthy sleep pattern is associated with lower risks of all-cause, cardiovascular and cancer-specific mortality

Tao Zhou^{1,2}, Yu Yuan³, Qiaochu Xue², Xiang Li², Mengying Wang^{2,4}, Hao Ma², Yoriko Heianza², Lu Qi^{2,5,*}

¹School of Public Health (Shenzhen), Sun Yat-sen University, Guangzhou, Guangdong 510006, China

²Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA

³Department of Occupational and Environmental Health, Key Laboratory of Environment and Health, Ministry of Education and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

⁴Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, China

⁵Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA

Abstract

Background: Individual unhealthy sleep behaviors have been associated with increased risks of all-cause mortality and deaths due to cardiovascular disease (CVD) or cancer. The evidence regarding the association of sleep patterns with these risks is limited.

Objective: To examine the associations of sleep patterns with all-cause, CVD, and cancer mortality in a large prospective cohort.

Methods: This prospective cohort study included 283443 adults from UK Biobank without CVD and cancer at baseline. We created a healthy sleep score and sleep patterns combining five individual sleep behaviors.

Results: During a mean (SD) of 8.9 (1.1) years (2.5 million person-years) of follow up, a total of 7936 all-cause deaths, 762 CVD-caused deaths, and 4540 cancer-caused deaths occurred during follow up. One point increase of the healthy sleep score was associated with a 4-11%

*Corresponding author and person to whom reprint requests should be addressed: Dr. Lu Qi, Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA 70112; Telephone: 504-988-3549; Fax: 504-988-1568; lqi1@tulane.edu.

Authors' Contributions

Lu Qi: Conceptualization (Equal); Data curation (Equal); Funding acquisition (Equal); Resources (Equal); Supervision (Equal); Writing-review & editing (Equal). Tao Zhou: Conceptualization (Equal); Methodology (Equal); Writing-original draft (Lead); Writing-review & editing (Equal). Yu Yuan: Data curation (Equal); Methodology (Equal); Writing-review & editing (Equal). Xiang Li: Writing-review & editing (Equal). Mengying Wang: Writing-review & editing (Equal). Hao Ma: Writing-review & editing (Equal). Yoriko Heianza: Writing-review & editing (Equal). Qiaochu Xue: Writing-review & editing (Equal).

Conflicts of interest

The authors declare no conflicts of interest.

lower risk of all-cause mortality (HR, 0.94; 95% CI, 0.92-0.96), CVD mortality (HR, 0.89; 95% CI, 0.83-0.95), and cancer mortality (HR, 0.96; 95% CI, 0.93-0.99), with adjustment for age, sex, assessment centers, smoking status, alcohol intake status, socioeconomic status, and physical activity. Compared with participants with an unfavorable sleep pattern, those with a favorable sleep pattern had 24%-42% lower risks of all-cause and CVD mortality. The association with all-cause mortality tended to be stronger among underweight participants and those with insufficient physical activity.

Conclusions: A healthy sleep pattern was associated with lower risks of all-cause mortality and mortality from CVD and cancer. Our findings highlight the importance of improving overall sleep behaviors in lowering mortality.

Keywords

Sleep; Sleep pattern; CVD; Cancer; Mortality

Introduction

Sleep is a vital indicator of overall health and well-being in humans. Increasing evidence suggests that healthy sleep behaviors are related to decreased risks of various life-threatening diseases such as cardiovascular disease (CVD) [1, 2] and cancer [3, 4]. In epidemiological studies, a variety of unhealthy sleep behaviors, including abnormal sleep duration, excessive daytime sleepiness, evening chronotype, insomnia, have been associated with higher risks of all-cause mortality [5-9] and deaths due to CVD [6] or cancer[3].

Most of the previous studies, however, investigated the associations between individual sleep behaviors and mortality risk. Notably, sleep behaviors are usually correlated and interact with each other, and the compensatory changes in one sleep behavior may occur when another sleep behavior has been changed [2]. We recently developed a healthy sleep score to define habitual sleep patterns by incorporating five sleep behaviors: chronotype, sleep duration, insomnia, snoring, and daytime sleepiness. The score been validated by our previous studies both in the UK Biobank study and China Kadoorie Biobank study [2, 10]. No study has examined the association between the newly developed sleep patterns and mortality risk in the prospective cohorts.

In the current study, we prospectively analyzed the relationship of the sleep patterns with the risks of all-cause mortality and mortality from CVD and cancer among 283443 adults from the UK Biobank.

Methods

Study design

Participants included in the current analysis were from the UK Biobank, the design of which has been described in detail elsewhere [11]. Briefly, UK Biobank is a prospective cohort of 0.5 million people aged between 40 and 69 at recruitment from the UK. Participants with available information on sleep behaviors were included in the analysis. Participants were

excluded if they have cancer and CVD disease at baseline, or have missing information on covariates such as age, sex, ethnic, and physical activity (Supplementary figure 1).

UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820). This study was approved by the Biomedical Committee of the Tulane University (New Orleans, Louisiana) Institutional Review Board. All participants gave written informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

Assessment of sleep behaviors

All sleep behaviors were obtained from the touchscreen questionnaire (<http://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100057>). Sleep duration was obtained by asking 'About how many hours sleep do you get in every 24 h? (include naps)'. Chronotype preference by asking the following question, 'Do you consider yourself to be 1) definitely a "morning" person, 2) more a "morning" than "evening" person, 3) "more an "evening" than "morning" person', or 4) definitely an "evening" person'. Insomnia symptoms were obtained by asking 'Do you have trouble falling asleep at night or do you wake up in the middle of the night?' with responses of 1) never/rarely, 2) sometimes, or 3) usually. Information on snoring was collected by asking 'Does your partner or a close relative or friend complain about your snoring?' with responses of 1) yes or 2) no. Subjective daytime sleepiness was coded according to the question 'How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g. when working, reading, or driving)' with responses of 1) never/rarely, 2) sometimes, 3) often, or 4) all of the time. Those who responded "Do not know" or "prefer not to answer" were excluded from the analysis. The detail of the calculation of the sleep pattern score has been described previously [7]. Briefly, we treated adequate sleep duration (7-8 hours), early chronotype, free of insomnia, no snoring, and no frequent daytime sleepiness as low-risk sleep factor and then created dichotomous variables (low risk, coded as 1 and high risk coded as 0) for each of the 5 sleep components. Then we summed the score of all the five components to obtain a healthy sleep score. The score ranged from 0 to 5, with a higher healthy sleep score indicating a healthier sleep pattern. The score was then categorized into favorable (4), intermediate (2-3), and unfavorable (1) subgroups.

Assessment of outcome

The outcomes were all-cause mortality and mortality from CVD and cancer. The date and cause of death were obtained by linking to death registries of the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register Scotland from Scotland. We censored follow-up on 14 February 2018 or at the date of death, whichever occurred first. We classified the causes of deaths according to the International Classification of Diseases edition 10 (ICD-10). Primary outcomes for our study were mortality from cancer (C00-C97), CVD (I21-I23, I24.1, I25.2, I60, I61, I63, and I64), and all cause.

Assessment of covariates

Baseline information including age and sex was obtained from the touchscreen questionnaire. Height and weight were also measured in the assessment centers, and BMI was calculated as weight in kilograms divided by the square of height in meters. MET-minutes per week of physical activity were calculated based on time spent in walking, moderate, or vigorous physical activity weighted by the energy expended for these types of activity [12]. Smoking status and drinking status were recorded as “Never”, “Previous”, and “Current” and those who reported “Prefer not to answer” were excluded from the analysis.

Statistical analysis

We presented continuous data as means and standard deviations (SDs) and categorical data as numbers and percentages. We used the Cox regression model to estimate hazard ratios (HRs) for incident mortality with the adjustment for age, sex, assessment centers, smoking status, alcohol intake status, socioeconomic status, and physical activity. The proportional hazards assumption was determined by testing the interaction term between exposure and time using the Wald test. *P* for interaction <0.05 was regarded as a violation of the assumption. We performed stratified analysis according to age (<56 and ≥56), sex (male and female), BMI (<18.5, 18.5-25, and ≥25), smoking status (never, previous and current), drinking status (never, previous, and current) and physical activity (low, moderate and high). Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). All statistical tests were two-tailed, and *P* < 0.05 was considered significant.

Results

Baseline characteristics of the study participants according to the unfavorable, intermediate, and favorable healthy sleep patterns are shown in Table 1. Of the 283443 participants, the mean (SD) age was 55.6 (8.1) years and 53.1% were female. Overall, 59.6% (168878) of the participants reported a healthy sleep pattern (healthy sleep score 4-5), 38.3% (108439) reported an intermediate sleep pattern (healthy sleep score 2-3), and 2.2% (6126) reported an unfavorable sleep pattern, which is relatively few (Table 1).

During a mean (SD) of 8.9 (1.1) years (2.5 million person-years) of follow up, we documented 7936 death events. Of these death events, 762 were caused by CVD, and 4540 were caused by cancer. Deaths due to cancer were much more common than CVD deaths. One point increase of the healthy sleep score was associated with 4-11% lower risks of all-cause mortality (HR, 0.94; 95% CI, 0.92-0.96), CVD mortality (HR, 0.89; 95% CI, 0.83-0.95), and cancer mortality (HR, 0.96; 95% CI, 0.93-0.99), with adjustment for age, sex, assessment centers, smoking status, alcohol intake status, socioeconomic status, and physical activity (Table 2). We further analyzed the sleep patterns defined by the healthy sleep score categories. Compared with those with an unfavorable sleep pattern, participants with a favorable sleep pattern was associated with 24% and 42% lower risks of all-cause mortality (HR, 0.76; 95% CI, 0.67-0.86) and CVD mortality, respectively, while no such association was found for cancer mortality (Figure 1).

We further performed stratified analyses by the potential confounders. We found that the associations between the healthy sleep score and all-cause mortality were stronger among the subgroup with insufficient BMI than the subgroups with normal and higher body weight ($P_{interaction}=4.70E-05$). In addition, we found that the associations were stronger among participants with low physical activity compared with those with moderate and high physical activity ($P_{interaction}=2.20E-02$). No significant difference was observed for the associations in subgroups by age, sex, smoking, status, and alcohol status (Figure 2). As for CVD mortality and cancer mortality, the associations per 1 higher score were consistent across all the subgroups (Supplementary figure 2-3).

In a sensitivity analysis, we created a new healthy sleep score with four sleep factors by removing snoring from the original score, given its potential protective association with cancer mortality and all-cause mortality. The results appeared to be similar. We also proposed a weighted sleep score through summing each sleep behavior weighted by the regression coefficients with mortality from the single-sleep behavior models. The results showed that one-point increase of weighted sleep score was associated with 9% lower risk of mortality (HR, 0.91; 95% CI, 0.90-0.92), which was similar to the results using the un-weighted sleep score (HR, 0.94; 95% CI, 0.92-0.96). The association of five individual binary categories sleep behaviors (low risk and high risk), early chronotype, adequate sleep duration, free of insomnia, no frequent daytime sleepiness, and no insomnia with cancer, CVD, and all cause mortality were shown in supplementary Table 1. To evaluate the affection of reversed causality, we excluding endpoint data from the first 3 years of follow-up. The results were comparable with the results of the population with full follow-up.

Discussion

In the current study of 283443 participants from UK Biobank, a higher healthy sleep score was significantly associated with lower risks of all-cause mortality and mortality from CVD and cancer. People with a healthy sleep pattern was associated with 24% to 42% lower risks of all-cause mortality and CVD mortality than those with an unhealthy sleep pattern. In addition, the protective association between the healthy sleep score and all-cause mortality was stronger in participants with insufficient body weight or low physical activity. Our data offer valuable information to tailor healthy sleep recommendations against the long-term mortality risk.

Previous epidemiological studies have associated various unhealthy sleep behaviors with elevated risks of all-cause and disease-specific mortality [6, 13-15]. For example, a meta-analysis of 40 prospective cohort studies showed that insufficient or prolonged sleep was related to an increased risk of all-cause mortality [16]. Similar associations were also observed with cancer mortality [3]. Other sleep behaviors including excessive daytime sleepiness [7, 17], evening chronotype [8, 18], and insomnia [9] have also been associated with increased risks of all-cause mortality, CVD mortality, or cancer mortality.

For the first time, we found that adherence to a healthy sleep pattern, which combined early chronotype, adequate sleep duration, free of insomnia, no snoring, and no excessive daytime sleepiness, was associated with a lower risk of all-cause mortality. Our findings

suggest that various sleep behaviors may affect mortality in an additive manner. Previous evidence has shown that the effect of single sleep behavior on mortality may depend on the presence of other sleep factors. For example, long sleep without daytime sleepiness or difficulties falling asleep was not associated with all-cause mortality [9]. Sleep behaviors are multifaceted and typically correlated. Modifications in one sleep behavior usually lead to compensatory changes in other sleep behaviors. The highly interrelated nature of various sleep behaviors makes it essential to treat these factors in an integral approach. In the current study, instead of considering the individual sleep behaviors in isolation, our newly defined healthy sleep score provides comprehensive measures of sleep factors and therefore represents a comprehensive assessment of sleep behaviors. Also, to analyze the overall sleep patterns would make it easier to interpret the findings and facilitate the application in clinical and public health practice.

CVD and cancer are among the leading causes of death. We also found significant associations of a healthy sleep pattern with lower risks of CVD mortality and cancer mortality. These findings indicate that the protective association of the healthy sleep pattern with all-cause mortality could be partly attributed to its beneficial association with CVD and cancer-specific mortality. Several mechanisms may explain the benefit of healthy sleep behaviors on lowering the risks of mortality. Unhealthy sleep may be related to circadian, endocrine, and metabolic disruption [19-23]. Poor sleep is positively associated with serum inflammatory marker levels [6, 24, 25]. Evening chronotype had poorer glycemic control [26] and increased risk of type 2 diabetes [27]. In addition, hypnotic use caused by insomnia has been associated with mortality, which might be another explanation [28]. Taken together, the healthy sleep pattern may lower the risks of CVD and cancer mortality through various mechanisms, which contributes to a lower risk of all-cause mortality.

Interestingly, we found that the protective association of the sleep patterns with all-cause mortality was more marked among participants with insufficient BMI and low physical activity. Underweight [29] and low physical activity [30] are well-established risk factors of all-cause mortality. Evidence has suggested that underweight was associated with increased mortality risk, especially among those with mental and behavioral, and neurological causes [31]. And healthy sleep may offset the adverse effect through its beneficial effect on mental health [32] and neurological disease [33]. As a life-threatening factor, lower physical activity is likely to be associated with poor sleep quality [34]. Thus, a relatively healthy sleep pattern may overwhelm the potential adverse effect of poor sleep caused by lower physical activity.

Strengths and limitations

Our study has several major strengths. First, the large sample size of the cohort provided adequate statistical power to examine the association of a healthy sleep pattern with outcome events. Second, detailed information on covariates such as socioeconomic status and lifestyle factors was available to minimize the influence of confounders and to perform sensitivity analyses in subgroups of the risk factors. Finally, we for the first time applied a novel tool to assess the overall healthy sleep pattern in a large prospective study. Our study also has several potential limitations. First, imprecise measurements or unknown factors might lead to residual confoundings. Second, the observational study design makes it is

unreasonable to interpret the association as causal. Third, the data were self-reported, which might raise the concern of misclassification. Notably, misclassification is more likely to attenuate our findings toward the null, which means the observed associations would be underestimated. Fourth, five sleep factors were dichotomized to generate a healthy sleep score and might lead to the loss of sleep information.

In summary, our study indicates that the newly developed healthy sleep score was associated with lower risks of all-cause mortality and mortality from CVD and cancer. Our findings have important public health implications and highlight that improving overall sleep behaviors rather than only modifying single sleep habits may reduce the risk of premature deaths.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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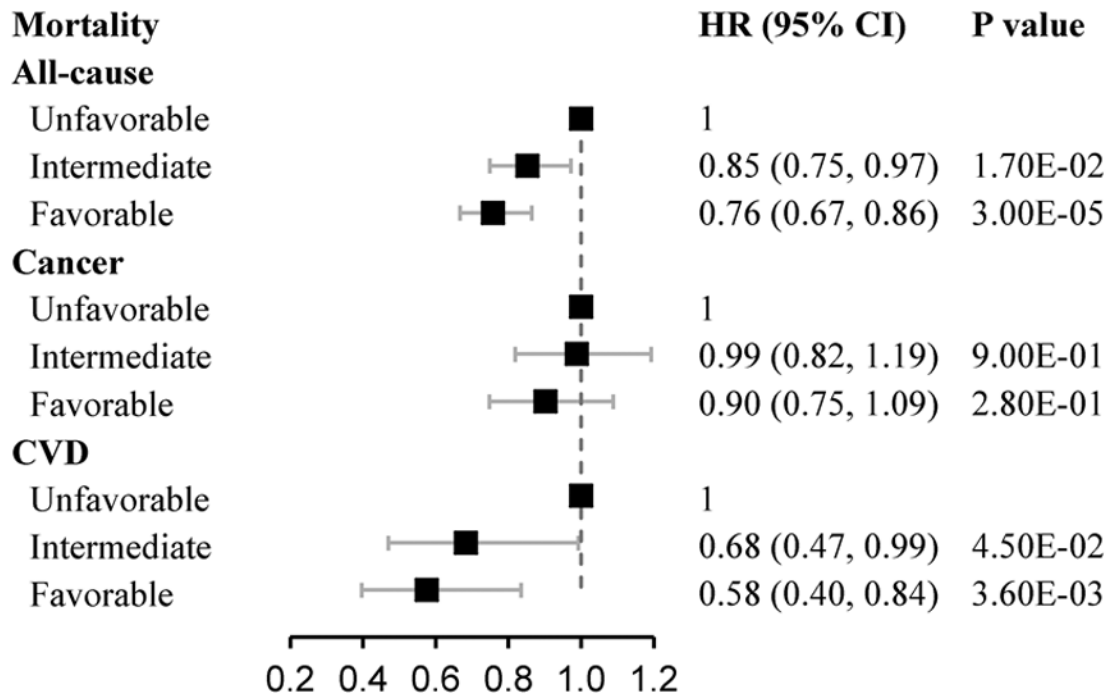


Fig. 1. The association of healthy sleep score with all-cause mortality, cancer-specific mortality, and CVD-specific mortality. Data were adjusted for age, sex, assessment centers, smoking status, alcohol intake status, socioeconomic status, and physical activity.

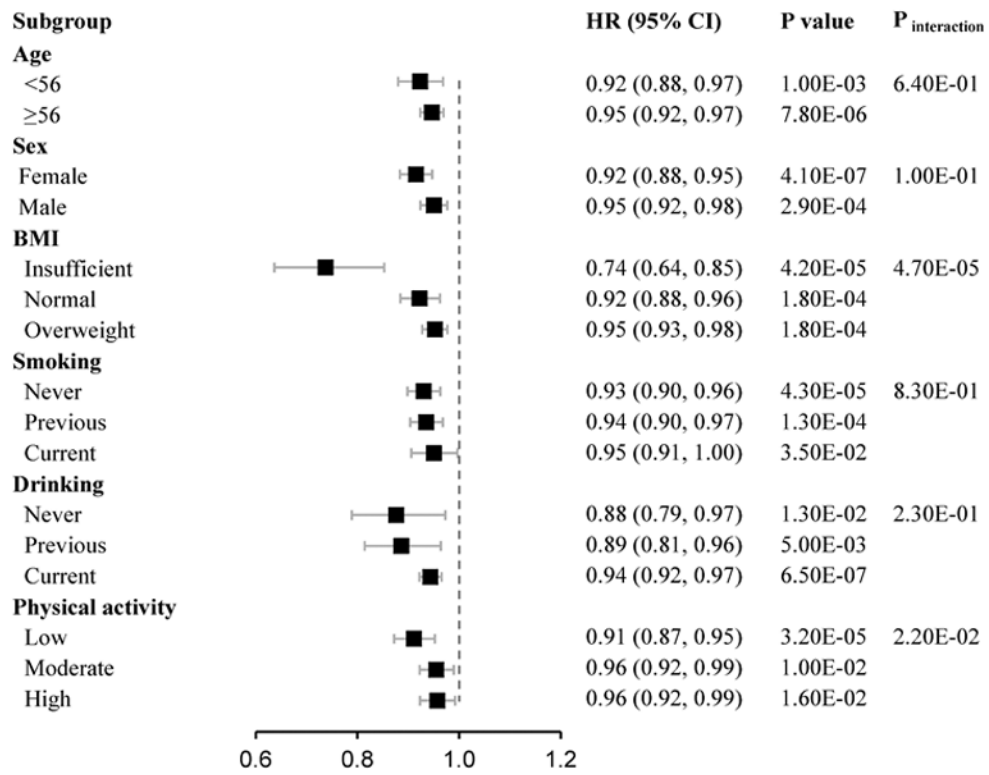


Fig 2. The stratified associations of healthy sleep score with all-cause mortality in the subgroups. Data was adjusted for age, sex, assessment centers, smoking status, alcohol intake status, socioeconomic status, and physical activity.

Table 1.

Baseline characteristics of UK Biobank participants according to healthy sleep score

	Favorable	Intermediate	Unfavorable
N	168878	108439	6126
Age, year	55 ± 8	56 ± 8	56 ± 8
Female (%)	93884 (55.6)	53549 (49.4)	2979 (48.6)
White (%)	160624 (95.1)	102427 (94.5)	5669 (92.5)
BMI, kg/m ²	27 ± 4	28 ± 5	30 ± 6
Smoking status (%)			
Never	100344 (59.4)	55840 (51.5)	2746 (44.8)
Previous	54817 (32.5)	39051 (36.0)	2331 (38.1)
Current	13717 (8.1)	13548 (12.5)	1049 (17.1)
Drinking status (%)			
Never	6651 (3.9)	3927 (3.6)	253 (4.1)
Previous	4959 (2.9)	3538 (3.3)	299 (4.9)
Current	157268 (93.1)	100974 (93.1)	5574 (91.0)
Townsend deprivation index	-1.6 ± 2.9	-1.3 ± 3.1	-0.8 ± 3.4
METs hours/wk	2749 ± 2692	2572 ± 2733	2398 ± 2862
Death (%)	4265 (2.5)	3428 (3.2)	243 (4.0)
CVD death (%)	395 (0.2)	337 (0.3)	30 (0.5)
Cancer death (%)	2497 (1.5)	1928 (1.8)	115 (1.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent of tasks.

Adjusted hazard ratios (HR) and 95% confidence interval for the associations of sleep score with the risk of cancer, CVD, and all-cause mortality.

Table 2.

Healthy sleep score	N (%)	Cancer	CVD	All-cause
Model 1	62892 (22.2)	0.91 (0.89, 0.94)	0.83 (0.78, 0.89)	0.88 (0.86, 0.90)
Model 2	62892 (22.2)	0.96 (0.93, 0.99)	0.89 (0.83, 0.95)	0.94 (0.92, 0.96)

Model 1 was unadjusted. Model 2 was adjusted for age, sex, assessment centers, smoking status, alcohol intake status, socioeconomic status, and physical activity.