Investigation of the Relationships Between Sleep Behaviors and Risk of Health Lifespan Termination: A Prospective Cohort Study Based on 323,373 UK-Biobank Participants

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Abstract

Objectives: To examine the associations between insomnia, napping, daytime sleepiness, and getting up from bed with the risk of health lifespan termination using a prospective cohort design based on the UK-Biobank (UKB) database.

Methods: Our study population consisted of 323,373 UKB participants enrolled in the UKB study from 2006 to 2010 and followed up to 2016. The outcome variable was health lifespan that was characterized by eight events strongly associated with ageing. Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for risk of terminated health lifespan were computed in Cox proportional hazards models. Furthermore, we collapsed each of the four sleep behavior factors into binary categories (high vs. low-risk groups) to explore the Population Attributable Risk percentages (PAR%).

Results: Participants in the high-risk subgroups of the four sleep behaviors had a significantly higher risk of terminated health lifespan; that is, 'usually insomnia' (HR=1.05, 95% CI: 1.03-1.07; \( P < 0.001 \)), 'usually napping' (HR=1.22, 95% CI: 1.18-1.26; \( P < 0.01 \)), 'excessive daytime sleepiness' (HR=1.25, 95% CI: 1.19-1.32; \( P < 0.001 \)), and 'difficult getting up from bed' (HR=1.08, 95% CI: 1.05-1.10; \( P < 0.001 \)). The corresponding PAR% indicated that about 7% of the terminated health lifespan events in this cohort would have been eliminated if all people were in the low-risk sleep groups.

Conclusion: We observed that frequent insomnia, napping, daytime sleepiness, and 'difficult getting up from bed' are associated with increased risk of terminated health lifespan. Therefore adherence to healthy sleep behavior is significant for healthy lifespan.

Introduction

Health lifespan has recently become a significant public health concern with much interest over lifestyle factors influencing observed variations in the human population [1]. Although global life expectancy has increased, matching improvement in healthy life expectancy still lagged far behind [2–5]. Evidence has shown that, on average, we live up to 20% of our lives unhealthy, thus attracting much attention to the associated factors of health lifespan [6]. However, genetic variants only account for about 25–30% of health lifespan [7], which corroborates that lifestyle factors, including sleep behavior, are crucial markers of terminated health lifespan. Genetic variants associated with a healthy lifespan are also related to sleep and circadian phenotypes [8]. Moreover, sleep mediates numerous body functions, including metabolic, nervous, and hormonal physiology [9–12]. Thus, sleep disturbance could alter these functions, resulting in atherosclerosis, inflammatory responses, cardiovascular diseases (CVD), and oxidative stress [10, 13, 14]. Additionally, good sleep behavior was associated with lower CVD risks, chronic heart diseases (CHD), and stroke among participants with low, intermediate, or high genetic risk [15]. Furthermore, daytime sleepiness often resulting from either inadequate night sleep, insomnia, or sleep-wake control disorder was associated with harmful events such as stroke, myocardial infarction (MI), vascular death [16, 17], CVD, quality of life, and workplace accident [8, 16]. Similarly, insomnia was related to CVD [18], acute
myocardial infarction (AMI), and stroke [19, 20]. Although napping is associated with late chronotype, total sleep time (TST), and hypertension [21], it can serve to replenish the loss of sleep and fatigue [22], psychomotor vigilance and performance, especially for shift workers, which yet again highlights the crucial role of sleep in the attainment of health and wellbeing [23, 24].

However, poor sleep behavior is becoming common in the population. The Institute of Medicine Committee on Sleep estimated that 50 to 70 million Americans chronically suffer from sleeplessness and sleep disorders [25] which, however, could be attributable to millennial habits such as the use of electronic devices before going to sleep, coupled with changing work schedule/shift work, and unfavorable sleep atmosphere [26, 27]. Hence, large-scale studies of sleep behavior are necessitated to explore the associated effects of sleep behavioral factors on health lifespan. Although some studies have examined the association between sleep behavior and morbidity and mortality, the evidence is still insufficient and inconsistent either due to the modest sample sizes, including patients with certain diseases at baseline, short follow-up, or insufficient control for potential confounders [28]. Therefore, we aimed to examine the associations between daytime sleepiness, napping, insomnia, getting up from sleeping bed, and the risk of health lifespan termination using a prospective cohort design based on UK Biobank. To our knowledge, this is the first study that assessed the association between these four sleep behaviors and healthy lifespan, consisting of eight health events, in a large prospective cohort.

Methods

Study population

The data used in this study comprised of 323,373 participants of the UK Biobank. Briefly, the UKB is a large-scale prospective study with over 500,000 participants aged 37 to 73 years, enrolled from 2006 to 2010 and followed up to 2016. These participants attended one of 22 assessment centers in England, Wales, and Scotland, where they completed baseline questionnaires, underwent various anthropometric measurements, and reported medical conditions. The North West Multicenter Research Ethical Committee approved the study, and all participants signed written informed consent. A detailed description of the study design of the UKB was detailed elsewhere [29, 30]. We applied for the related data according to the rules of the UKB data sharing policy under the approved 64689. All sleep behaviors were self-reported, and details of assessment were available online.

We excluded 72,457 participants whose health lifespan had terminated before, according to in-patient hospital admissions data (UKB data category 2000). Then, we excluded 28,816 participants whose health lifespan had terminated prior, according to self-reported diagnoses obtained via verbal interview (UKB data category 100074) as a compliment. Additionally, 77861 participants who had missing data on sleep-related variables were also excluded. Finally, the study population comprises 323,373 participants of the UK Biobank (Figure S1).

Definition of health lifespan
Based on the incidence of chronic diseases, a study based on the UKB database reported a cluster of the top-eight morbidities strongly associated with ageing, which we used to define health lifespan [31]. These top-eight morbidities included congestive heart failure (CHF), myocardial infarction (MI), chronic obstructive pulmonary disease (COPD), stroke, dementia, diabetes, cancer, and death. A participant diagnosed with any of these conditions first during the study period was considered to have terminated health lifespan. For each selected condition, except for cancer and death, we compiled a list of hospital data codes (ICD-10) and self-reported data codes (UKB data coding 6) that define these conditions in our study. We used National cancer registries linkage to UKB (UKB data category 100092) to define cancer and National death registries linkage to UKB (UKB data category 100093) to define death event. However, the National cancer registry linkage to UKB was updated only to 14th December 2016, earlier than the other two databases (in-patient hospital admissions data: 31st March 2017; National death registries linkage to UKB: 14th February 2018). To ensure consistency between the three database update dates used to build a healthy lifespan, we had to set 14th December 2016 as the end of follow-up.

**Statistical analysis**

Personal follow-up time was calculated from the baseline assessment date until the date health lifespan was terminated or end of followed up. We applied descriptive statistics (mean and percentages) and multivariate adjusted Cox proportional hazards regression models to examine the association between sleep behaviors and risk of health lifespan termination. Model 1 was adjusted for age, sex, ethnicity, Townsend index, and education; Model 2 was further adjusted for Townsend index, BMI, smoking status, alcohol consumption, physical exercise, diet, family history of diseases, and taking sleep-related drugs. The proportional hazards assumptions were tested using Schoenfeld residual method [32].

Furthermore, we collapsed each of the sleep behavior factors into two categories (High vs. Low risk). For instance, 'usually napping' was considered as high risk, whiles 'never/rarely' and 'sometimes napping' as low risk ('Rarely'); 'Usually insomnia/sleeplessness' vs. 'Rarely insomnia' ('sometimes' and 'Never/rarely' insomnia); 'Usually/Excessive daytime sleepiness' ('often' and 'always' daytime sleepiness) vs. 'Rarely daytime sleepiness' ('never/rarely' and 'sometimes' daytime sleepiness); and, 'Difficult getting-up' ('not at all easy' and 'not very easy' getting up/waking out of bed) vs. 'Easy getting-up' ('fairly easy' and 'very easy' as low risk). These binary factors were analyzed in a multivariate-adjusted model to examine the hazard risk associated with health lifespan termination (Table 3). Using these binary categories, we performed stratification analysis according to age, gender, BMI, smoking status, physical activity, and healthy diet (Figure 1). In addition, we calculated the PAR % for the high risk sleep behaviors using the epi2by2 function of the "epiR" package in R language (Table 3). All statistical analyses were performed using R, version 4.1.0, and statistical significance was defined as P-values <0.01.

**Results**

The participants' demographic and sleep behavior characteristics were summarized and tabulated in Table 1, according to 'daytime sleepiness'. In brief, out of 323, 373 participants, 84.91% of participants
did not have a terminated health lifespan, of whom the majority never/rarely had daytime sleepiness. The female population was slightly larger (55.8%), and the Caucasian race forms the majority (94.82%). The proportion of "never smokers" was slightly higher (56.51%) than current and previous smokers. Townsend-Deprivation index mean was lowest for 'never/rarely DS' (-1.58), which means that participants with never/rarely DS reside in less deprived areas [33], and have healthy diet intake (78.03%). However, BMI mean was higher in 'frequent DS' (28.30). Participants with 'usually insomnia' mostly had frequent DS (45.98%), and most participants in the 'Never/rarely DS' category could more easily wake up from bed (82.29%). We also observed that most participants who sometimes (56.17%) and usually napped (30.15%) were in the frequent DS category. And the majority of the study population had no history of taking sleep-related drugs.
| Characteristic (%)                  | Daytime sleepiness |
|-----------------------------------|--------------------|
|                                   | Never/Rarely       | Sometimes | Frequently |
| Terminated health lifespan         | 14.23              | 17.83     | 20.20      |
| Median Age                        | 56.00              | 59.00     | 58.00      |
| Female                            | 56.79              | 52.34     | 51.99      |
| Caucasian race                    | 95.69              | 92.03     | 89.62      |
| Mean Townsend Index               | -1.58              | -1.21     | -0.79      |
| Moderate physical activity        | 34.19              | 33.68     | 3075       |
| High physical activity            | 34.96              | 32.71     | 33.33      |
| College education                 | 35.07              | 31.75     | 29.73      |
| Mean BMI (kg/m²)                  | 27.00              | 27.60     | 28.30      |
| Current smokers                   | 10.05              | 9.61      | 12.12      |
| Previous smoker                   | 32.94              | 34.38     | 32.84      |
| Alcohol drinking (≥ 3 times/week) | 46.42              | 41.55     | 37.13      |
| Alcohol drinking (≤ 2 times/week) | 26.46              | 26.01     | 24.14      |
| Family history of CVD             | 55.48              | 55.44     | 61.02      |
| Healthy diet                      | 75.03              | 71.97     | 67.53      |
| Take sleep-related pills          | 0.62               | 0.75      | 1.47       |

**Napping (%)**

|                | Never/Rarely | Sometimes | Frequently |
|----------------|--------------|-----------|------------|
| Sometimes      | 29.65        | 61.98     | 56.17      |
| Usually        | 3.13         | 6.63      | 30.15      |

**Insomnia (%)**

|                | Never/rarely | Sometimes | Frequently |
|----------------|--------------|-----------|------------|
| Never/rarely   | 26.47        | 20.93     | 20.06      |
| Sometimes      | 48.46        | 49.43     | 33.96      |
| Usually        | 25.07        | 29.63     | 45.98      |

**Getting-up (%)**

|                | Never/Rarely | Sometimes | Frequently |
|----------------|--------------|-----------|------------|
| Difficult      | 16.67        | 20.02     | 30.35      |
| Characteristic (%) | Daytime sleepiness |
|--------------------|-------------------|
|                    | Never/Rarely      | Sometimes | Frequently |
| Easy               | 83.29             | 79.88     | 69.49      |

The Chi-squared test used to calculate the \( P \) values across the sleep categories (daytime sleepiness, napping, sleeplessness, getting up) and all the variables had a \( P \) value < 0.001.

Furthermore, in Table 2, we observed a decrease risk of health lifespan termination for 'never/rarely' insomnia [HR = 0.96, 95% CI: 0.94–0.99; \( P < 0.001 \)] and 'sometimes insomnia' [HR = 0.95, 95% CI: 0.93–0.97; \( P < 0.001 \)]; 'never/rarely' napping [HR = 0.78, 95% CI: 0.75–0.81; \( P < 0.001 \)] and 'sometimes napping' [HR = 0.87, 95% CI: 0.83–0.89; \( P < 0.001 \)], considering 'usually insomnia' and 'usually napping' as reference respectively. Participants in 'usually daytime sleepiness' had 26% higher risk of terminated health lifespan (HR = 1.26, 95% CI: 0.19–1.33; \( P < 0.001 \)). In addition, we observed a 16% decreased risk of terminated health lifespan for 'easy getting up' ('fairly easy' (HR = 0.84, 95% CI: 0.79–0.88; \( P < 0.001 \)) and 'very easy' (HR = 0.85, 95% CI: 0.81–0.88; \( P < 0.001 \)). Significant association at \( P \) value < 0.001 was observed for all the four sleep behaviors.
Table 2
Multivariate adjusted HRs (95%CIs) for health lifespan event by four sleep factors

| Risk factors          | N     | Event | Model 1 HR (95%CI) | Model 2 HR (95%CI) | Trend HR |
|-----------------------|-------|-------|---------------------|---------------------|----------|
|                       |       |       | HR (95%CI)          | HR (95%CI)          |          |
| **Daytime sleepiness**|       |       |                     |                     |          |
| Never/rarely          | 251402| 35776 | Ref.                | Ref.                | 1.09     |
| Sometimes             | 64429 | 11489 | 1.08 (1.06–1.10)*** | 1.07 (1.05–1.09)*** |          |
| Often                 | 7524  | 1516  | 1.27 (1.21–1.34)*** | 1.26 (1.19–1.33)*** |          |
| **Nap**               |       |       |                     |                     |          |
| Never/rarely          | 190050| 25200 | 0.78 (0.75–0.81)*** | 0.78 (0.75–0.81)*** | 1.12     |
| Sometimes             | 118710| 20392 | 0.86 (0.83–0.89)*** | 0.87 (0.83–0.89)*** |          |
| Usually               | 14427 | 3170  | Ref.                | Ref.                |          |
| **Sleeplessness (insomnia)** | | | | | |
| Never/rarely          | 81548 | 11237 | 0.96 (0.93–0.98)*** | 0.96 (0.94–0.99)*** | 1.02     |
| Sometimes             | 156229| 23291 | 0.95 (0.93–0.97)*** | 0.95 (0.93–0.97)*** |          |
| Usually               | 85596 | 14261 | Ref.                | Ref.                |          |
| **Getting up**        |       |       |                     |                     |          |
| Not at all easy       | 11561 | 1764  | Ref.                | Ref.                | 0.97     |
| Not very easy         | 45530 | 5989  | 0.87 (0.82–0.92)*** | 0.87 (0.83–0.92)*** |          |
| Fairly easy           | 162596| 23314 | 0.83 (0.79–0.87)*** | 0.84 (0.79–0.88)*** |          |
| Very easy             | 103512| 17692 | 0.84 (0.79–0.88)*** | 0.85 (0.81–0.88)*** |          |

Sleep factors: daytime sleepiness, sleeplessness, Napping, Getting up

Hazard ratio, HR; CI, confidence interval; p-value(***, < 0.001; **,<0.01; *, < 0.05)

**Model 1**: Adjusted for age, sex, ethnicity, Townsend index, education level, BMI, smoking status, alcohol frequency, physical activity and diet; **Model 2**: Further adjusted for family history of cancer, family history of diabetes, family history of diseases and taking sleep related and CVD drugs.

Considering the sleep factors as continuous variables in a fully adjusted model, we found that the hazard risk of terminated health lifespan increased by 9% (HR = 1.09, 95% CI: 1.07–1.11; P < 0.001) and 12% (HR = 1.12, 95% CI: 1.09–1.13; P < 0.001) for every additional level of DS and napping respectively (Table 2; Table S1). Similarly, hazard risk increased for insomnia (HR = 1.08, 95% CI: 1.06–1.09; P < 0.01) and decreased for easy getting-up from bed (HR = 0.94, 95% CI: 0.93–0.95; P < 0.001) (Table S1).
We then categorized each of the sleep behavior factors into two groups, low-risk and high-risk groups, and our findings show an excess hazard risk of health lifespan termination in the high-risk groups: 'Usually insomnia' (HR = 1.05, 95% CI: 1.03–1.07; P < 0.001); 'Usually napping' (HR = 1.22, 95% CI: 1.18–1.26; P < 0.01); 'excessive daytime sleepiness' (HR = 1.25, 95% CI: 1.19–1.32; P < 0.001), and 'Difficult getting up from bed' (HR = 1.08, 95% CI:1.05–1.10; P < 0.001) (Table 3). This finding is validated by the stratified analysis presented in the forest plot, with observed risk differences between subgroups (Fig. 1). The corresponding PAR % were 3.75% (95% CI: 3.25–4.26) for insomnia; 2.12% (95% CI: 1.93–2.34) for napping, 0.81 % (95% CI: 0.67–0.95) for excessive daytime sleepiness (EDS), and −2.14% (95% CI:-2.51,-1.78) for 'Difficult getting up from bed'. The combined PAR% for sleeplessness, napping, and EDS suggests that about 7% of the terminated health lifespan events in the population would be avoided if all people were in the low-risk sleep groups (Table 3).

**Table 3: Multivariate adjusted HRs (95%CIs) for terminated health lifespan and PAR% by insomnia, napping, daytime sleepiness and getting up**

| High risk group                  | % of participants | Terminated health lifespan |  |
|---------------------------------|-------------------|----------------------------|---|
|                                 |                   | HR (95% CI)<sup>a</sup>  | PAR% (95% CI)<sup>b</sup>|  |
| Usually insomnia                | 26.47             | 1.05 (1.03-1.07)<sup>***</sup> | 3.75 (3.25,4.26) |  |
| Usually napping                 | 4.46              | 1.22 (1.18-1.26)<sup>**</sup>  | 2.13 (1.93,2.34)  |  |
| Excessive/usually Daytime sleepiness | 26.47       | 1.25 (1.19-1.32)<sup>***</sup> | 0.81 (0.67,0.95) |  |
| Difficult getting Up from bed   | 17.65             | 1.08(1.05-1.10)<sup>***</sup>  | -2.14 (-2.51,-1.78) |  |

Binary sleep factors: Usually sleeplessness, usually napping, Excessive daytime sleepiness, Not at all Getting up from bed.

Hazard ratio, HR; CI, confidence interval; population attributable risk percent, PAR%; p-value (***, <0.001; **, <0.01; *, <0.05).<sup>a</sup>Compared with the opposite category participants.

The model was adjusted for age, sex, ethnicity, Townsend index, education level, BMI, smoking status, alcohol frequency, physical activity, diet, family history of diseases and taking sleep related drugs and CVD drugs. <sup>b</sup>Compared with the opposite category participants.<sup>(a)</sup>

**Discussion**

We examined the associations between four sleep factors and the risk of terminated health lifespan based on 323,373 UKB participants in cox-proportional hazard regression models. The baseline results indicated that 20.20% of terminated health lifespan events in the study population had frequent daytime sleepiness. And the majority of the study population had a healthy diet intake, had at least a college education, and resided in less deprived areas, which could explain why there were fewer terminated health
lifespan events (15.14%). However, we observed an association between frequent DS, napping, insomnia, difficulty getting up from the bed, and an increased risk of terminated health lifespan.

**Napping and insomnia**

Our results also revealed a decreased hazard risk for participants with "never/rarely" or "sometimes" insomnia and napping, respectively, compared to those who "usually" had insomnia and napping (Table 2). Similarly, after categorizing the sleep behavior factors into low-risk vs. high-risk groups, we also observed an increased hazard risk of terminated health lifespan among high-risk groups (Table 3). Consistent with our results, insomnia was previously shown to be associated (independently and jointly) with increased risk of acute myocardial infarction (AMI) by 68% [19, 20], hypertension (HTN), chronic heart disease (CHD) [14, 34], short sleep duration, circadian misalignment [35], melatonin reduction and indirectly with cancer through circadian rhythm disruption [36]. A comparative study also reported a significant association between daytime napping and hypertension [21]; our study further showed that about 4% and 2.13% of terminated health lifespan events would have been eliminated if all the participants were in the low-risk group for insomnia and napping, respectively. In support of our results, a related study from a 13-year follow-up study of a British population reported a 32% increase in the risk of all-cause mortality, particularly respiratory diseases, for every 1-hour increase in napping [37]. However, other studies showed that nurses who napped at work reported having less drowsiness while driving home, and napping in night shift workers could reduce fatigue-related workplace accidents and sleepiness [38]. This implies that napping may support sleep imbalance and improve 24 hour total sleeping time (TST), especially for shift workers [22]. Another population-based cohort study showed that participants who napped had 10% higher serum C reactive protein (CRP) than those not napping [39]. Hence, restriction of frequent napping in the day may boost sleep quality in the night and eventually enhance healthy lifespan, especially for patients with sleep-onset insomnia and delayed sleep phase syndrome [27]. Additionally, poor sleep at night was previously associated with poor attention, impaired cognitive performance during the day, occupational fatigue, and daytime sleepiness [40, 41].

**Excessive daytime sleepiness**

Our study also highlights that excessive daytime sleepiness is harmful to health (HR = 1.25) and may well reflect other abnormal health conditions. A related study among healthy community-dwelling elderly population also agreed with our findings that DS was associated with vascular events and stroke [16]. In contrast, another study among a cohort of women from the 'Nurses' Health Study 2' did not find an independent association between DS and CVD [42]. Similarly, 0.81% of terminated health lifespan events would have been eliminated if all the participants 'rarely' had daytime sleepiness. Thus, excessive daytime sleepiness might be a valuable marker for underlying health risk among adults.

**Getting-up from bed**

Additionally, this study showed a decrease hazard risk of terminated health lifespan by at least 3% (HR = 0.97) as getting-up from bed gets easy (Table 2; Table S1). Similarly, in Table 3, we observed an 8% (HR =
1.08) increased risk among participants with difficulty getting up from bed, compared to the low-risk group (easy getting up from bed). Epidemiological evidence shows that early morning waking from the bed was associated with restless leg syndrome, insomnia, circadian disruption, and stress [43], demonstrating that sleep behaviors are intertwined and affect each other.

Moreover, our stratified analysis showed slight subgroups risk differences such as BMI, smoking status, and healthy diet intake, suggesting a possible association between these other lifestyle factors and sleep behavior, although we had robust confounder control in the analysis. In line with our finding, previous studies also reported that sleep is an independent risk factor for a wide range of other risk behaviors, including tobacco smoking, alcohol consumption, physical inactivity, self-regulation, and dietary intake [44–46]. Hence correcting sleep behaviors could have a beneficial effect on other disease risk behaviors as well.

Pieces of evidence from our study and related findings underscore sleep behavior as a significant health determinant that warrants greater attention [47]. Thus, sustainable sleep health programs and policy interventions are needed to augment sleep behaviors in the population, particularly at workplaces, to extend health lifespan [48]. Similarly, enhancing general fitness could alleviate sleep-related complains associated with reduced absenteeism, and better overall life quality [47]. At the workplace, adequate staffing, correct shift scheduling, work environment design, employee fatigue training, sleep disorder screening and management, and sleepiness and fatigue monitoring can mitigate fatigue and the risk of daytime sleepiness [41].

**Strengths and limitations**

This is the first time a study assessed the association between these four sleep behaviors and risk of health lifespan termination in a large prospective cohort study design, giving our study great power, in addition to adequate confounders control in the analysis. However, the study participants were mostly Caucasian race, and the because sleep behaviors were self-reported, we may not be able to establish causality or generalize our results to other populations.

**Conclusion**

We observed that frequent insomnia, napping, daytime sleepiness, and 'difficult getting up from bed' are associated with increased risk of terminated health lifespan. Therefore adherence to healthy sleep behavior is significant for healthy lifespan.

**Declarations**

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Authors’ contributions

MLS and XZ conducted the statistical analysis and wrote the first draft. TH, AS and TBB helped apply for permission to use data and offered technical support during the study. GJ, ELH, and MN critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

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Figures
Figure 1

Stratified multivariate adjusted HRs (95%CIs) of terminated health lifespan according to daytime sleepiness, napping, insomnia and getting-up. Event N, number of terminated health lifespan; HR, Hazard Ratio; 95%CI, 95% Confidence Interval; the models were fully adjusted.

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