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Association of healthy sleep patterns with incident sepsis: a large population-based prospective cohort study

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Abstract

Background The role that sleep patterns play in sepsis risk remains poorly understood.

Objectives The objective was to evaluate the association between various sleep behaviours and the incidence of sepsis.

Methods In this prospective cohort study, we analysed data from the UK Biobank (UKB). A total of 409,570 participants who were free of sepsis at baseline were included. We used a composite sleep score that considered the following five sleep behaviours: sleep chronotype, sleep duration, insomnia, snoring, and daytime sleepiness. Cox proportional hazards regression analysis was used to estimate the associations between healthy sleep scores and incident sepsis.

Results During a mean follow-up of 13.54 years, 13,357 (3.26%) incident sepsis cases were recorded. Among the 409,570 participants with a mean age of 56.47 years, 184,124 (44.96%) were male; 9942 (2.43%) reported 0 to 1 of the five healthy sleep behaviours; 46,270 (11.30%) reported 2 behaviours; 115,272 (28.14%) reported 3 behaviours; 150,522 (36.75%) reported 4 behaviours; and 87,564 (21.38%) reported 5 behaviours at baseline. Each one-point increase in the sleep score was associated with a 5% lower risk of developing sepsis (hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.93–0.97). Compared with a healthy sleep score of 0–1, for a sleep score of 5, the multivariate-adjusted HR (95% CI) for sepsis was 0.76 (0.69–0.83). In addition, we found that the negative correlation was stronger in participants who were aged < 60 years than in their older counterparts (p for interaction < 0.001). However, healthy sleep pattern was not associated with sepsis-related death and critical care admission.

Conclusions Findings from this cohort study suggest that a healthy sleep pattern may reduce the risk of developing sepsis, particularly among younger individuals.

Keywords Sleep pattern, Sepsis, Cohort study, UK Biobank

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Introduction

Numerous studies focusing on sleep disorders, such as insomnia and sleep insufficiency, have suggested that these conditions are risk factors for adverse Outcomes [1–5]. Specifically, sleep disorders are correlated with altered immune function and elevated markers of systemic inflammation [6–8]. Moreover, evidence suggests that poor sleep quality may impact inflammatory activation, particularly in women [9]. Patients with compromised immune systems are more likely to develop infections, which may lead to sepsis, accompanied by high mortality [10]. Studies have shown that the pathophysiology of sepsis involves an imbalance in the immune response to infection. Depending on variations in the host, pathogen, and stage of sepsis, the response may manifest as either a dominant hyperinflammatory or immunosuppressive phenotype, both of which are associated with a poor prognosis [10]. Therefore, identifying efficient measures to reduce the incidence of sepsis is important [11].

It has been previously reported that insomnia is potentially causally related to the risk of sepsis [12]. Individuals with insomnia are at a doubled risk of developing sepsis [12]. Approximately one-third of the correlation between insomnia and the risk of sepsis is mediated by cardiometabolic risk factors for sepsis [12]. The link between insomnia and sepsis is more pronounced in women than in men [12]. Notably, various sleep behaviours are intricately linked to each other. It is therefore vital to assess overall sleep patterns in combination with these sleep behaviours. Indeed, as indicated in previous studies, sleep behaviours such as sleep chronotype, sleep duration, insomnia, snoring, and daytime sleepiness, are usually related and may have a joint impact on health and quality of life and can reliably reflect an individual's actual sleep status [13]. Previous studies have demonstrated that a healthy sleep pattern is related to a lower risk of diabetes, chronic kidney disease, and cardiovascular disease (CVD) [14–16]. On the basis of these findings, we hypothesized that greater adherence to a healthy sleep pattern is associated with a lower incidence of sepsis.

This study aimed to prospectively analyse the associations between healthy sleep patterns and the incidence of sepsis utilizing data from the UK Biobank (UKB), a large prospective cohort study with 409,570 participants.

Methods

Study population

More than 500,000 British residents aged 40–70 years were recruited from the general population for the UKB study between 2006 and 2010. All participants completed a touchscreen-based questionnaire followed by a verbal interview with a nurse on demographics, life-course exposures, and medical history as baseline assessments. The participants also underwent full physical exams and provided biological samples. The participants were then followed up to update the information mentioned above. A detailed description of the UKB study can be found elsewhere [17, 18].

The UKB study was approved by the National Information Governance Board for Health and Social Care in England and Wales, the Community Health Index Advisory Group in Scotland, and the North West Multicenter Research Ethics Committee. Written informed consent was obtained from all participants. In this study, we excluded participants with missing data on the components of the healthy sleep score (n = 91,912) and those with sepsis at baseline (n = 1048); a total of 409,570 participants were included in the final analysis (Supplemental Fig. 1).

Ascertainment of exposure

Information on sleep behaviours, including sleep duration, sleep chronotype, insomnia, snoring, and excessive daytime sleeping, was obtained at baseline through a touchscreen questionnaire. Sleep duration was assessed by asking the participants "About how many hours of sleep do you get every 24 h? (including naps)", with responses listed in hourly increments. Chronotype was assessed by asking "Do you consider yourself to be?", with the following answers: "definitely a 'morning' person", "more a 'morning' than an 'evening' person", "more an 'evening' than a 'morning' person", "definitely an 'evening' person", "do not know" or "prefer not to answer". Insomnia symptoms were assessed by asking "Do you have trouble falling asleep at night or do you wake up in the middle of the night?", with the following answer options: "never/rarely", "sometimes", "usually" or "prefer not to answer". Information on snoring was collected by asking "Does your partner or a close relative or friend complain about your snoring?", with the following response options: "no", "yes", "do not know" or "prefer not to answer". Finally, daytime sleeping was assessed on the basis of the question "How likely are you to doze off or fall asleep during the daytime when you don't mean to?", with the following response options: "never/rarely", "sometimes", "often", "all of the time", "do not know" or "prefer not to answer".

Healthy sleep patterns were assessed according to the following five sleep behaviours: sleep chronotype, sleep duration, insomnia, snoring, and excessive daytime sleepiness [15, 19]. To construct a healthy sleep score, these behaviours were dichotomized as healthy or unhealthy. Healthy sleep behaviours were defined as follows: an early chronotype ("morning" person or "morning" person rather than an "evening"

person); a sleep duration of 7–8 h per day; no frequent insomnia symptoms ("sometimes" or "never/rarely"); no self-reported snoring; and no frequent daytime sleepiness ("sometimes" or "never/rarely"). For each healthy sleep behaviour, the participants received a score of 1 if they met the criterion or 0 otherwise. The overall healthy sleep score was the sum of the individual scores of all five sleep behaviours, ranging from 0 to 5, with a higher score indicating a healthier sleep pattern.

Ascertainment of outcome

The primary outcome was the incidence of sepsis, which was defined via the International Classification of Diseases, Tenth Revision (ICD-10). All-cause mortality was extracted from relevant national mortality data [20]. Relevant critical care data were available for participants in England [20]. Individuals with sepsis were identified by using the ICD-10 codes A02, A39, A40, and A41, in line with previous literature [21]. Death due to sepsis were defined as any death within 28 days of admission for sepsis [20]. Critical care admission was considered as any admission to a critical care unit (receiving level 2 or 3 care) during the initial admission for sepsis [20]. The follow-up time for each participant was calculated from the enrolment date to the earliest date of the following events: sepsis diagnosis, death, loss to follow-up, or end of follow-up.

Ascertainment of covariates

The following covariates were included in our analysis: age, sex (male or female), ethnicity (white or other), education level (university or college degree or other), Townsend Deprivation Index (TDI) (quintiles), household income, body mass index (BMI), smoking status (never, previous, or current), frequency of alcohol consumption, physical activity level, healthy diet score (0–5), baseline cholesterol level, medication use (cholesterol-lowering medication, antihypertensive medication, antihyperglycemic medications, or exogenous hormones), lung disease status (yes or no), kidney disease status (yes or no), Human Immunodeficiency Virus (HIV) infection status (yes or no), cancer status (yes or no), diabetes status (yes or no), CVD status (yes or no), history of surgery (yes or no), history of injuries (yes or no), catheter use (yes or no), and breathing tube use (yes or no). A healthy diet score was calculated based on the following factors: fruit intake of at least 3 pieces per day, vegetable intake of at least 4 tablespoons per day, unprocessed red meat intake of no more than twice per week, processed meat intake of no more than twice per week, and fish intake at least twice per week. One point was assigned for each healthy dietary factor, and the final score ranged from 0 to 5 [22]. In cases of missing covariate information, we imputed the median values for continuous variables and used a missing indicator for categorical variables.

Statistical analyses

The baseline characteristics of the participants were summarized across the categories of healthy sleep scores. We present continuous variables as the means ± standard deviations (SDs) and compared them among groups via t tests or variance tests. Categorical variables are expressed as numbers (percentages) and were compared among groups via either Fisher's exact test or the $\chi 2$ test. Owing to the limited number of participants, those who received healthy sleep scores of 0 and 1 were combined into one category. A Cox proportional hazards regression model was used to estimate the risk of incident sepsis associated with a healthy sleep score. We checked the proportional hazards assumption via the Schoenfeld residuals method after fitting a Cox proportional hazards model, and no iolation was found. The P for trend was based on a Wald test for linear contrast of the healthy sleep score in the model. Additionally, the healthy sleep score was also modelled as a continuous variable for every one-point increment. For categories and each one-point increment of healthy sleep score, models were fitted in three adjusted models in addition to an unadjusted model, as follows: Model 1 was adjusted for age, sex, ethnicity, education level, household income, and TDI; Model 2 was additionally adjusted for BMI, smoking status, frequency of alcohol consumption, diet score, and physical activity level; and Model 3 was further adjusted for cholesterol level, blood pressure, medication use, lung disease status, kidney disease status, HIV infection status, cancer status, diabetes status, cardiovascular disease status, history of surgery, history of injuries, catheter use, and breathing tube use.

Subgroup analyses by age ($<60, \geq 60$ years), sex (male, female), BMI ($<30, \geq 30$ kg/m^2), smoking status (never, previous/current), frequency of alcohol consumption (daily, nondaily), and preexisting diabetes at baseline (yes, no) were conducted to identify potential modifying effects. The interaction effect of the stratified factors on the risk of sepsis and the healthy sleep score was tested via the likelihood ratio test, which compared models both with and without a cross-product term. Individual healthy sleep behaviours and healthy sleep scores were evaluated to calculate the proportion of the population that could be attributable to unhealthy sleep patterns (population-attributable risk percent [PAR%]). We estimated the PAR% with the formula $p^* (HR-1)/(1+p^*[HR-1])$, where HR is the associated fully adjusted hazard ratio of participants and p is the proportion of participants not in the healthy group.

We also performed several sensitivity analyses to test the robustness of our study.

First, participants who developed sepsis within 1 and 2 years of follow-up were excluded to avoid reverse causation. Second, Model 3 was additionally adjusted for depression at baseline. Third, participants with preexisting diabetes, cancer, or CVD at baseline were excluded. Fourth, participants who were taking cholesterol-lowering medication, antihypertension medication, antihyperglycemic medications, and exogenous hormones were excluded. Fifth, participants with missing data on covariates were excluded. Sixth, given the COVID-19 pandemic, we divided the follow-up into three non-overlapping periods. Finally, we constructed a weighted healthy sleep score on the basis of the five sleep behaviours, where the weights were the adjusted hazard ratios (HRs) from the Cox proportional hazard models.

All analyses were performed with Stata statistical software version 18.0 (StataCorp). A two-sided $p < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics

The mean (standard deviation [SD]) age was 56.47 (8.09) years, and 55.04% of all 409,570 participants were female. As shown in Table 1, a total of 9942 (2.43%) participants had a healthy sleep score of 0–1, 46,270 (11.30%) had a score of 2, 115,272 (28.14%) had a score of 3, 150,522 (36.75%) had a score of 4, and 87,5 64 (21.38%) had a score of 5. Participants with higher healthy sleep scores were more likely to be female, white, normal or underweight, more educated, high household income, follow a healthy diet, and physically active. They also tended to be less likely to be current or previous smokers, socially deprived, higher levels of blood pressure, and overweight or obese, use medications, and a lower proportion of these participants had preexisting surgery, injuries, lung disease, HIV infection, diabetes, cancer, CVD, and catheter use.

Healthy sleep score and the risk of incident sepsis, sepsis-related death, and critical care admission

During a mean follow-up of 13.54 years, 13,357 (3.26%) incident sepsis cases were recorded. In the crude model, a healthy sleep score was negatively associated with the risk of sepsis in a dose–response pattern (P trend < 0.001). After additional adjustments for the three models, although the estimates gradually decreased, they followed the same pattern of a decreasing risk with an increasing healthy sleep score (P trend < 0.001). In fully adjusted Model 3, a healthy sleep score of 5 was associated with a significantly lower risk of sepsis (HR, 0.76; 0.69–0.83; P-trend < 0.001) than a sleep score of 0–1. Moreover, each one-point increase in the healthy sleep score was associated with a 5% lower risk of sepsis (HR, 0.95; 95% CI 0.93–0.97) (P for trend < 0.001) (Table 2). However, healthy sleep pattern was not associated with sepsis-related mortality and critical care admission (Supplementary Tables 2,3).

When individual sleep behaviours were considered binary classifications (high risk vs. low risk), having an early chronotype, having a sleep duration of 7–8 h per day, never/rarely experiencing insomnia, and having no frequent daytime sleepiness were associated with 7%, 9%, 7% and 17% lower risks of sepsis, respectively. The participants with an overall healthy sleep score of 5 had a PAR% of 7.52% (95% CI 4.00, 10.92) for sepsis, suggesting that approximately one-tenth of sepsis events in this population would not have occurred if all participants had been included in the healthy sleep behaviour group for all five behaviours (Fig. 1). Supplementary Table 1 shows the associations between individual sleep behaviours and sepsis risk. After adjusting for age, sex, ethnicity, education level, household income, the TDI, lifestyle factors, having an evening chronotype, a short (< 7 h) or long sleep duration (> 9 h), sometimes or usually experiencing insomnia, snoring, and having excessive daytime sleepiness were associated with an increased risk of sepsis. The association remained significant after adjusting for cholesterol level, blood pressure, medication use, lung disease status, kidney disease status, HIV infection status, cancer status, diabetes status, cardiovascular disease status, history of surgery, history of injuries, catheter use, and breathing tube use (fully adjusted models), but not snoring.

Subgroup analyses

We conducted subgroup analyses on the basis of sex, age, BMI, smoking status, frequency of alcohol consumption, and diabetes status to identify potential effect modifiers, but no significant interactions were observed, except for age. The negative correlation between a healthy sleep score and the risk of sepsis was stronger in individuals aged < 60 years than in their older counterparts (P-interaction < 0.001, Table 3). A comparison of a healthy sleep score of 5 with a sleep score of 0–1 revealed that the HRs (95% CI) for sepsis were 0.66 (0.57–0.77) among individuals aged < 60 years and 0.84 (0.74–0.96) for those aged ≥ 60 years (Table 3).

The association between higher healthy sleep scores and a lower risk of developing sepsis was generally preserved when analysed in sex, age, BMI, smoking status, and diabetes status subgroups (Supplementary Tables 4–9). In addition, a dose–response relationship was observed for all subgroups in terms of sex, age, BMI,

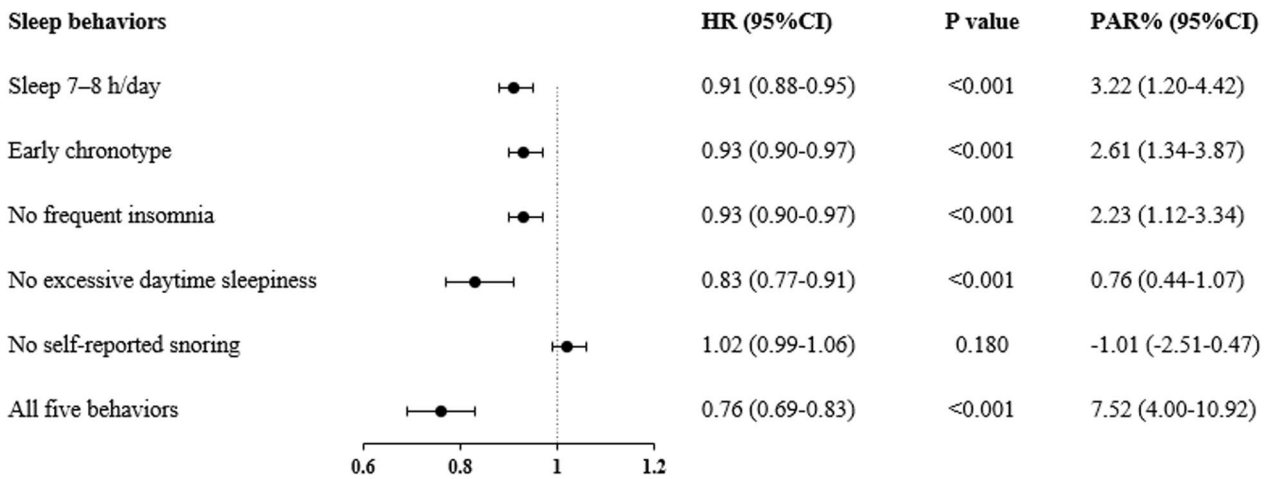

Fig. 1 Associations of each healthy sleep behaviours with the risk of sepsis. Hazard ratios were adjusted for age, sex, ethnicity, household income, educational level, Townsend deprivation index, body mass index, smoking status, alcohol frequency, diet score, physical activity level, cholesterol, blood pressure, medication use, lung disease, kidney disease, HIV infection, cancer, diabetes, cardiovascular disease, history of surgery, history of injuries, catheter use, and breathing tube use. PAR, population attributable fraction; HR, hazard ratio; CI, confidence interval

and smoking status, with all *P* values < 0.05. Similarly, when a one-point increase in the healthy sleep score was considered, consistent results were observed in subgroup analyses across sex, age, BMI, and smoking status, with all P values < 0.05 (Fig. 2, Supplementary Tables 4–9).

Sensitivity analysis

The associations between healthy sleep scores and sepsis risk in the sensitivity analyses remained robust. Similar associations were observed when (1) participants who developed sepsis within 1 and 2 years of the follow-up period were excluded; (2) depression at baseline was adjusted for; (3) participants with preexisting diabetes, cancer, and CVD at baseline were excluded; (4) participants who were taking cholesterol-lowering medication, antihypertension medication, antihyperglycemic medications, and exogenous hormones were excluded; and (5) participants with missing data on covariates were excluded; (6) we divided the follow-up into three non-overlapping periods, given the COVID-19 pandemic. Furthermore, the results did not markedly change after we constructed a weighted healthy sleep score on the basis of the five sleep behaviours (Supplementary Table 10).

Discussion

This cohort study used data from the large UKB study to examine the associations between healthy sleep patterns and the risk of sepsis. Our findings indicated that adopting a combination of healthy sleep patterns, including having an early chronotype, having a sleep duration of 7–8 h per day, never or rarely experiencing insomnia, having no snoring, and having no excessive daytime sleepiness, was significantly associated with a lower risk of subsequent incident sepsis even after adjustment for potential confounders. Furthermore, this association was more apparent in individuals younger than 60 years. These findings may offer new evidence and insights into the associations between healthy sleep patterns and the prevention of sepsis.

Previous studies have linked individual sleep behaviours to the risk of developing sepsis. Consistent with our findings, insomnia was reported to be associated with an increased risk of sepsis in a previous study [12]. Similar associations with insomnia were also observed with the risk of an altered immune response [23] and bloodstream infection [24]. Poor sleep quality was associated with elevated white blood cell counts, particularly among females [9]. Other studies reported that experimental sleep deprivation increased the blood leukocyte count in healthy male subjects, specifically increasing the number of monocytes and natural killer (NK) cells [25]. In addition, nocturnal awakening increased the number of circulating CD4 + and CD8 + T cells in humans [25–27]. Lange et al. reported that sleep promoted T-cell lymph node homing by reducing cortisol and adrenaline levels. These changes in leukocyte homing may disrupt the circadian regulation of leukocyte trafficking, which initiates adaptive immune responses at night [7]. Some reports have indicated that sleep and circadian rhythms impact baseline cytokine levels in participants [7, 8], with potential effects on sepsis risk. In male participants with regular

Table 1 Baseline characteristics according to healthy sleep score in the cohort

Characteristics	Overall (n = 409570)	Healthy sleep score					*P* value
		0–1	2	3	4	5	
		(n = 9,942)	(n = 46,270)	(n = 115,272)	(n = 150,522)	(n = 87,564)	
Age, years	56.47 ± 8.09	56.58 ± 7.73	56.72 ± 7.83	56.71 ± 7.97	56.39 ± 8.15	56.16 ± 8.31	< 0.001
Male	184,124 (44.96)	4,859 (48.87)	21,942 (47.42)	55,687 (48.31)	69,235 (46.00)	32,401 (37.00)	< 0.001
White	388,110 (94.76)	9212 (92.66)	43,619 (94.27)	109,151 (94.69)	142,799 (94.87)	83,329 (95.16)	< 0.001
Townsend deprivation index	−1.41 ± 3.03	−0.59 ± 3.38	−1.05 ± 3.20	−1.32 ± 3.07	−1.51 ± 2.96	−1.62 ± 2.91	< 0.001
University or college degree	134,060 (32.73)	2414 (24.28)	12,627 (27.29)	35,418 (30.73)	51,621 (34.29)	31,980 (36.52)	< 0.001
Household income > £52,000	75,705 (18.48)	1334 (13.42)	7319 (15.82)	20,411 (17.71)	29,254 (19.44)	17,387 (19.86)	< 0.001
BMI							< 0.001
< 18.5 kg/m^2	2,090 (0.51)	25 (0.25)	177 (0.38)	508 (0.44)	787 (0.52)	593 (0.68)	
18.5–24.9 kg/m^2	133,317 (32.55)	1,762 (17.72)	10,913 (23.59)	32,572 (28.26)	51,137 (33.97)	36,933 (42.18)	
25.0–29.9 kg/m^2	175,562 (42.86)	3,871 (38.94)	19,478 (42.10)	50,785 (44.06)	65,640 (43.61)	35,788 (40.87)	
≥ 30 kg/m^2	98,601 (24.07)	4,284 (43.09)	15,702 (33.94)	31,407 (27.25)	32,958 (21.90)	14,250 (16.27)	
Smoking status							< 0.001
Never	222,719 (54.38)	4,248 (42.73)	21,547 (46.57)	58,857 (51.06)	83,716 (55.62)	54,351 (62.07)	
Previous	143,120 (34.94)	3,878 (39.01)	17,736 (38.33)	42,195 (36.60)	52,174 (34.66)	27,137 (30.99)	
Current	42,527 (10.38)	1,786 (17.96)	6,838 (14.78)	13,839 (12.01)	14,200 (9.43)	5,864 (6.70)	
Alcohol intake							< 0.001
Never	31,316 (7.65)	1,011 (10.17)	3,791 (8.19)	8,597 (7.46)	10,908 (7.25)	7,009 (8.00)	
Special occasions only	45,478 (11.10)	1,439 (14.47)	5,765 (12.46)	12,647 (10.97)	15,762 (10.47)	9,865 (11.27)	
1–3 times / month	45,094 (11.01)	1,182 (11.89)	5,177 (11.19)	12,526 (10.87)	16,123 (10.71)	10,086 (11.52)	
1–2 times / week	106,485 (26.00)	2,374 (23.88)	11,523 (24.90)	29,260 (25.38)	39,563 (26.28)	23,765 (27.14)	
3–4 times / week	96,193 (23.49)	1,891 (19.02)	9,883 (21.36)	26,964 (23.39)	36,503 (24.25)	20,952 (23.93)	
Daily or almost daily	84,798 (20.70)	2,040 (20.52)	10,099 (21.83)	25,208 (21.87)	31,601 (20.99)	15,850 (18.10)	
SBP, mmHg	137.64 ± 18.15	138.30 ± 17.72	138.42 ± 17.76	138.28 ± 18.08	137.61 ± 18.21	136.37 ± 18.35	< 0.001
DBP, mmHg	82.15 ± 9.85	83.37 ± 10.04	82.98 ± 9.91	82.61 ± 9.86	82.07 ± 9.83	81.10 ± 9.71	< 0.001
Characteristics	**Overall**	**Healthy sleep score**					***P* value**
		0–1	**2**	**3**	**4**	**5**	
Healthy diet score	2.87 ± 1.28	2.59 ± 1.30	2.70 ± 1.30	2.79 ± 1.29	2.89 ± 1.27	3.07 ± 1.25	< 0.001
Cholesterol, mmol/L	5.70 ± 1.11	5.64 ± 1.16	5.69 ± 1.15	5.71 ± 1.12	5.70 ± 1.10	5.71 ± 1.08	< 0.001
Physical activity, MET-h/w	44.32 ± 41.04	40.04 ± 41.89	41.50 ± 40.69	43.36 ± 41.08	44.72 ± 40.84	46.88 ± 41.22	< 0.001
Medical history	130,707 (31.91)	4356 (43.81)	17,420 (37.65)	39,015 (33.85)	45,874 (30.48)	24,042 (27.46)	< 0.001
Surgery history	264,606 (64.61)	7126 (71.68)	31,889 (68.92)	75,784 (65.74)	95,587 (63.50)	54,220 (61.92)	< 0.001
Injuries history	19,699 (4.81)	662 (6.66)	2590 (5.60)	5867 (5.09)	6,901 (4.58)	3679 (4.20)	< 0.001
Diabetes	21,563 (5.26)	1139 (11.46)	3576 (7.73)	6747 (5.85)	6,982 (4.64)	3119 (3.56)	< 0.001
Cancer	44,433 (10.85)	1178 (11.85)	5390 (11.65)	12,556 (10.89)	16,027 (10.65)	9282 (10.60)	< 0.001
Cardiovascular disease	33,511 (8.18)	1453 (14.61)	5,145 (11.12)	10,401 (9.02)	11,160 (7.41)	5352 (6.11)	< 0.001
Lung disease	14,614 (3.57)	756 (7.60)	2475 (5.35)	4576 (3.97)	4,561 (3.03)	2246 (2.56)	< 0.001
HIV infection	139 (0.03)	9 (0.09)	23 (0.05)	43 (0.04)	46 (0.03)	18 (0.02)	0.001
Catheter use	1131 (0.28)	60 (0.60)	172 (0.37)	334 (0.29)	375 (0.25)	190 (0.22)	< 0.001
Breathing tube use	73 (0.02)	3 (0.03)	17 (0.04)	13 (0.01)	24 (0.02)	16 (0.02)	0.010
Low-risk sleep factors							
Sleep 7–8 h/day	279,106 (68.15)	431 (4.34)	9,472 (20.47)	58,378 (50.64)	12,326 (81.89)	–	< 0.001
Early chronotype	256,968 (62.74)	902 (9.07)	13,236 (28.61)	54,620 (47.38)	100,646 (66.86)	–	< 0.001
No frequent insomnia	295,724 (72.20)	483 (4.86)	12,754 (27.56)	66,424 (57.62)	128,499 (85.37)	–	< 0.001
No self-reported snoring	257,342 (62.83)	657 (6.61)	14,608 (31.57)	54,291 (47.10)	100,222 (66.58)	–	< 0.001
No frequent daytime sleepiness	398,368 (97.26)	6771 (68.11)	42,470 (91.79)	112,103 (97.25)	149,460 (99.29)	–	< 0.001

The values for continuous variables are given as mean ± SD and values for categorical variables are given as numbers (percentage). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MET, metabolic equivalent

Table 2 Risk of incident sepsis associated with healthy sleep score

	Healthy sleep score					Per 1-point increment	P for trend
	0–1	2	3	4	5		
Participants, n	9942	46,270	115,272	150,522	87,564	–	–
Incident sepsis, n	530	1887	3993	4680	2267	–	–
Follow-up period, person-years	133,455	624,282	1,559,763	2,039,301	1,188,425	–	–
Follow-up period, y							
Means ± SD	13.4 ± 1.7	13.5 ± 1.5	13.5 ± 1.4	13.5 ± 1.4	13.6 ± 1.3	–	–
Median (IQR)	13.7 (13.0–14.3)	13.7 (13.0–14.3)	13.7 (13.0–14.3)	13.7 (13.0–14.3)	13.7 (13.0–14.3)	–	–
Hazard ratio for incident sepsis (95% CI)							
Crude model	Reference	0.76 (0.69–0.84)	0.64 (0.59–0.70)	0.58 (0.53–0.63)	0.48 (0.44–0.53)	0.85 (0.84–0.87)	< 0.001
Adjusted model 1	Reference	0.77 (0.70–0.85)	0.66 (0.60–0.72)	0.61 (0.56–0.67)	0.54 (0.49–0.59)	0.88 (0.87–0.90)	< 0.001
Adjusted model 2	Reference	0.84 (0.76–0.93)	0.76 (0.70–0.83)	0.74 (0.68–0.81)	0.68 (0.62–0.75)	0.93 (0.92–0.95)	< 0.001
Adjusted model 3	Reference	0.88 (0.80–0.97)	0.82 (0.75–0.90)	0.81 (0.74–0.89)	0.76 (0.69–0.83)	0.95 (0.93–0.97)	< 0.001

A Cox proportional hazard model was conducted. Adjusted model 1, age, sex, ethnicity, household income, educational level, and Townsend deprivation index were adjusted for in this model; adjusted model 2, body mass index, smoking status, alcohol frequency, diet score, and physical activity level additionally were adjusted for in this model; and adjusted model 3, cholesterol, blood pressure, medication use, lung disease, kidney disease, HIV infection, cancer, diabetes, cardiovascular disease, history of surgery, history of injuries, catheter use, and breathing tube use additionally were adjusted for in this model IQR, interquartile range; CI, confidence interval

Table 3 Associations between healthy sleep score and the risk of incident sepsis stratified by subgroups

Subgroups	Adjusted hazard ratio* (95%CI)						
	Healthy sleep score					P for trend	P for interaction#
	0–1	2	3	4	5		
Sex							0.105
Male (n = 184,124)	1 (reference)	0.88 (0.77–1.00)	0.82 (0.73–0.92)	0.82 (0.72–0.92)	0.77 (0.68–0.88)	< 0.001	
Female (n = 225,446)	1 (reference)	0.89 (0.76–1.03)	0.83 (0.72–0.95)	0.80 (0.70–0.92)	0.75 (0.64–0.86)	< 0.001	
Age							< 0.001
< 60 years (n = 233,391)	1 (reference)	0.82 (0.71–0.96)	0.74 (0.64–0.85)	0.73 (0.63–0.84)	0.66 (0.57–0.77)	< 0.001	
≥ 60 years (n = 176,179)	1 (reference)	0.94 (0.83–1.07)	0.91 (0.80–1.02)	0.89 (0.79–1.01)	0.84 (0.74–0.96)	0.001	
BMI							0.861
< 30 kg/m^2 (n = 310,969)	1 (reference)	0.90 (0.78–1.03)	0.83 (0.73–0.95)	0.83 (0.73–0.95)	0.76 (0.66–0.87)	< 0.001	
≥ 30 kg/m^2 (n = 98,601)	1 (reference)	0.87 (0.76–0.99)	0.81 (0.71–0.92)	0.79 (0.70–0.90)	0.77 (0.67–0.89)	< 0.001	
Smoking							0.254
Never (n = 222,719)	1 (reference)	0.78 (0.67–0.92)	0.71 (0.61–0.82)	0.69 (0.60–0.80)	0.68 (0.59–0.79)	< 0.001	
Previous/current (n = 185,647)	1 (reference)	0.95 (0.84–1.07)	0.90 (0.80–1.01)	0.90 (0.80–1.01)	0.81 (0.71–0.92)	< 0.001	
Alcohol drinking							0.543
Daily (n = 84,798)	1 (reference)	0.95 (0.76–1.19)	0.94 (0.76–1.17)	0.92 (0.74–1.14)	0.86 (0.68–1.08)	0.081	
Non-daily (n = 324,566)	1 (reference)	0.87 (0.78–0.96)	0.79 (0.72–0.88)	0.79 (0.71–0.87)	0.74 (0.66–0.82)	< 0.001	
Diabetes							0.283
Yes (n = 21,563)	1 (reference)	0.85 (0.69–1.04)	0.81 (0.67–0.98)	0.81 (0.67–0.98)	0.79 (0.64–0.99)	0.078	
No (n = 388,007)	1 (reference)	0.89 (0.80–0.99)	0.83 (0.74–0.92)	0.81 (0.73–0.90)	0.76 (0.68–0.85)	< 0.001	

* Hazard ratios were adjusted for age, sex, ethnicity, household income, educational level, Townsend deprivation index, body mass index, smoking status, alcohol frequency, diet score, physical activity level, cholesterol, blood pressure, medication use, lung disease, kidney disease, HIV infection, cancer, diabetes, cardiovascular disease, history of surgery, history of injuries, catheter use, and breathing tube use

BMI, body mass index; CI, confidence interval

P for interaction < 0.008 was considered statistically significant after corrected by multiple testing

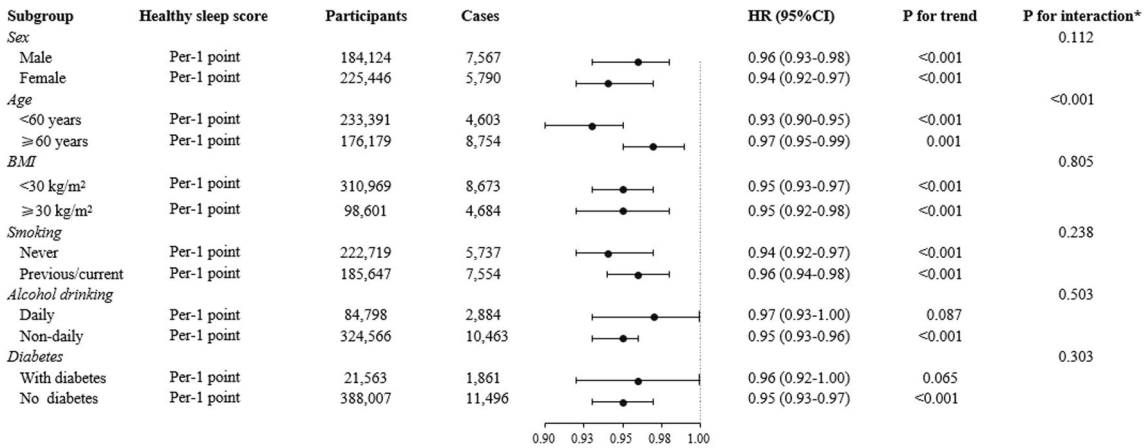

Fig. 2 Subgroup analysis for the association between per-1 point increment of healthy sleep score and incident sepsis. A Cox proportional hazard model was conducted. All hazard ratios (HRs) were calculated by adjusting the following: age, sex, ethnicity, household income, educational level, Townsend deprivation index, body mass index, smoking status, alcohol frequency, diet score, physical activity level, cholesterol, blood pressure, medication use, lung disease, kidney disease, HIV infection, cancer, diabetes, cardiovascular disease, history of surgery, history of injuries, catheter use, and breathing tube use. BMI, body mass index; HR, hazard ratio; CI, confidence interval. *P for interaction < 0.008 was considered statistically significant after corrected by multiple testing

sleep patterns, serum interleukin-6 (IL-6) was shown to have a biphasic circadian rhythm. However, a single night of experimentally induced sleep deprivation disrupted this rhythm, resulting in an elevated daytime peak in IL-6 [7]. Sleep deprivation was shown to increase the level of tumour necrosis factor α (TNF-α) in healthy men [28]. Both severe and partial sleep deprivation could increase serum C-reactive protein (CRP) levels in healthy individuals [29]. Additionally, primary insomnia was linked to increased levels of nocturnal serum IL-6 [30]. It has also been reported that sleep deprivation not only increases serum cytokine levels but also induces gut microbiome dysbiosis in both humans and mice [31]. Notably, germ-free mice exhibit a weakened serum cytokine response to sleep deprivation, indicating that the gut microbiome regulates the inflammatory response induced by sleep deprivation [31]. These reports suggest a close interaction between sleep and baseline inflammatory states. In terms of the association between comprehensive sleep behaviours and sepsis, there are no relevant reports to date. The present study was the first to investigate the association between adherence to a healthy sleep pattern and sepsis in a prospective cohort. Our findings indicate that overall healthy sleep patterns are associated with a reduced risk of sepsis and emphasize the importance of considering comprehensive sleep behaviours in the prevention of sepsis.

Redwine L et al. reported that sleep disorders were associated with increased serum CRP and IL-6 levels. Compared with a normal sleep duration, a short sleep duration was linked to higher serum CRP levels, whereas a long sleep duration was associated with higher serum CRP and IL-6 levels [32]. Interestingly, the impact of sleep on IL-6 levels was more pronounced in studies with a greater proportion of women [32]. These results highlight that the effect of sleep on inflammation differs between women and men. Previous research has suggested a potential relationship between sex hormones and sleep regulation in both males and females [33]. In males, low testosterone levels are associated with poor sleep quality [33]. In females, pregnancy and the postpartum period are linked to sleep disturbances, whereas the transition to menopause is also associated with poor sleep quality [33]. Furthermore, ageing is associated with variations in sleep quality, an increased incidence of sepsis, and worse sepsis outcomes in humans [34]. Variations in sleep quality may play a role in "inflammation" and poor sepsis outcomes in older adults [34]. However, the negative correlation between healthy sleep scores and the risk of sepsis was stronger in individuals younger than 60 years in our study. In other words, younger people might derive greater benefits from adhering to a healthy sleep pattern. We hypothesize that one of the reasons for this finding may be the decline in sleep quality with age [35]. Declining sleep quality is a prevalent complaint among individuals undergoing the aging process [35]. Aging is associated with alterations in sleep architecture, most notably the increase in sleep fragmentation, which hinders restorative sleep [35]. Another reason may be that aging increases the risk of chronic diseases, as well as the overall decline in the body's immune function [34]. Consequently, the benefits of healthy sleep patterns may be less pronounced in older populations than in younger ones.

However, little is known about how sleep influences the risk of sepsis. There are several reports that sleep has an effect on toll-like receptor (TLR) expression and function, with potential effects on sepsis [36]. In individuals with untreated sleep apnoea, elevated expression levels of TLR2, TLR4, and TLR6 in blood leukocytes were observed [37, 38]. Furthermore, these patients demonstrated increased production of IL-8, IL-6, and TNF-α by peripheral blood mononuclear cells (PBMCs) in response to lipopolysaccharide (LPS; a bacterial cell wall component that activates TLR4) [39, 40]. Compared with mice with normal sleep patterns, mice subjected to sleep deprivation showed increased production of inflammatory cytokines and reduced levels of IL-10 following LPS stimulation, leading to more severe damage to the lungs, liver, and kidneys; additionally, the study revealed that gut dysbiosis and vagal nerve signalling serve as mechanistic contributors to this process [41]. Sleep deprivation was also shown to exacerbate LPS-induced anxiety-like behaviours and decrease dopamine turnover [42].

Our findings have important implications for public health. Our data suggest that sleep behaviours are multifactorial and interrelated. The concept of sleep patterns, which integrates various sleep behaviours, including sleep chronotype, sleep duration, insomnia, snoring, and daytime sleepiness, offers a comprehensive and easily measurable framework. According to our results, if individuals can improve their sleep hygiene, sepsis can be prevented or substantially delayed. Notably, sepsis can also adversely affect sleep, both acutely and chronically, creating a vicious cycle [43–45]. Therefore, considering unhealthy sleep patterns as a fundamental target for sepsis prevention may be crucial in alleviating the current clinical burden of sepsis.

In light of the observed absence of correlation between healthy sleep patterns and sepsis-related mortality as well as critical care admission, it is imperative to consider several potential explanations. Primordially, the limited sample size may compromise the precision of the findings. Moreover, the prognosis of sepsis is contingent upon a multitude of variables, such as age, comorbid conditions, the anatomical location of the infection, and the overall disease severity, among others [46]. Furthermore, interventions employed in the management of sepsis, including antibiotic treatments, fluid resuscitation, support with vasoactive medications, and mechanical ventilation, significantly influence patient outcomes [47]. In summation, these contributing factors may partially obfuscate the influence of sleep patterns on the severity and ultimate prognosis of sepsis.

Our study elucidates the long-term risk of incident sepsis associated with healthy sleep patterns on the basis of a large prospective cohort. Moreover, various sensitivity analyses yielded robust findings. This study also has limitations. First, owing to the limitations of the observational study design, a causal relationship between healthy sleep patterns and sepsis development could not be determined. Second, the use of self-reported data on sleep behaviours among participants constitutes a limitation. Recall bias and misclassifications are inevitable. However, misclassifications arising from self-reporting methods often result in regression dilution bias, thereby underestimating the observed associations. Moreover, the incorporation of accelerometer measurements into sleep studies may provide more robust data compared to self-reported information [48]. Third, we only used data on sleep behaviours at baseline without considering changes in these behaviours during the long-term follow-up in our study. Fourth, residual or unknown confounding factors cannot be completely ruled out due to the observational study design, although comprehensive adjustments were made to account for confounders. Fifth, there may be an issue of reverse causality between healthy sleep patterns and risk of incident sepsis due to the observational nature of our study. Finally, the UKB study comprises predominantly white participants, and the generalizability of our study results to other populations is unknown.

Conclusions

In this cohort study, adherence to a healthy sleep pattern was associated with a lower risk of incident sepsis, particularly among younger individuals. However, healthy sleep pattern was not associated with sepsis-related mortality and critical care admission. These results indicate that promoting healthy sleep practices should be considered a key primary prevention strategy for sepsis. Future studies with repeated measurements of sleep behaviours are needed to confirm our findings.

Abbreviations

BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MET	Metabolic equivalent
ICD	International classification of diseases
UKB	UK Biobank
IQR	Interquartile range
CI	Confidence interval
HR	Hazard ratio
PAR	Population attributable fraction
CVD	Cardiovascular disease
HIV	Human immunodeficiency virus

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05287-w.

Additional file1 (DOCX 100 KB)

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Author contributions
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Availability of data and materials
This research has been conducted using the UK Biobank Resource under Application Number 44430. The UK Biobank data are available on application to the UK Biobank (www.ukbiobank.ac.uk/). No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This research utilized the UK Biobank Resource under Application Number 44430. Approval for data collection and use was granted by the North West Multi-Centre Research Ethics Committee. All participants provided written informed consent before their involvement in the study.

Competing interests
The authors declare that they have no competing interests.

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