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ORIGINAL RESEARCH

Association of Sleep Pattern and Genetic Susceptibility with Obstructive Sleep Apnea: A Prospective Analysis of the UK Biobank

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Purpose: The prevalence of obstructive sleep apnea (OSA) is high worldwide. This study aimed to quantify the relationship between the incidence of OSA and sleep patterns and genetic susceptibility.

Methods: A total of 355,133 white British participants enrolled in the UK Biobank between 2006 and 2010 with follow-up data until September 2021 were recruited. We evaluated sleep patterns using a customized sleep scoring method based on the low-risk sleep phenotype, defined as follows: morning chronotype, 7–8 hours of sleep per day, never/rarely experience insomnia, no snoring, no frequent daytime sleepiness, never/rarely nap, and easily getting up early. The polygenic risk score was calculated to assess genetic susceptibility to OSA. Cox proportional hazard models were used to evaluate the associations between OSA and sleep patterns and genetic susceptibility.

Results: During a mean follow-up of 12.57 years, 4618 participants were diagnosed with OSA (age: 56.83 ± 7.69 years, women: 31.3%). Compared with those with a poor sleep pattern, participants with a normal (HR: 0.42, 95% CI: 0.38–0.46), ideal (HR: 0.21, 95% CI: 0.19–0.24), or optimal (HR: 0.15, 95% CI: 0.12–0.18) sleep pattern were significantly more likely to have OSA. The genetic susceptibility of 173,239 participants was calculated, and the results showed that poor (HR: 3.67, 95% CI: 2.95–4.57) and normal (HR: 1.89, 95% CI: 1.66–2.16) sleep patterns with high genetic susceptibility can increase the risk for OSA.

Conclusion: This large-scale prospective study provides evidence suggesting that sleep patterns across seven low-risk sleep phenotypes may protect against OSA in individuals with varying degrees of genetic susceptibility.

Keywords: obstructive sleep apnea, sleep phenotype, sleep pattern, healthy sleep score, genetic susceptibility, polygenic risk score

Introduction

Obstructive sleep apnea (OSA) is a heterogeneous and complex disease[1] associated with various physiological factors, such as upper airway structural changes,[2] cardiovascular risk factors,[3] and serotonin levels.[4] According to the American Academy of Sleep Medicine 2012 diagnostic criteria, approximately 936 million adults aged 30–69 years worldwide experience mild to severe OSA, and 425 million adults are affected by moderate to severe OSA. OSA affects nearly 1 billion individuals, with prevalence rates exceeding 50% in some countries.[5]

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Sleep phenotypes encompass numerous sleep characteristics, including sleep duration, quality, and pattern.[6] Sleep phenotypes have been associated with borderline personality disorder,[7] cardiometabolic diseases,[6] increased health risks,[8] and OSA.[9] Short sleep duration is a risk factor for OSA,[10] and long sleep periods are associated with OSA-related diseases such as diabetes[11,12] and cognitive impairment.[13] However, our understanding of the associations between sleep patterns and OSA is currently lacking. Nocturnal insomnia[14] and morning and evening chronotypes[15] are associated with OSA. In most previous studies, sleep phenotypes were evaluated separately without considering the complexity and correlation of various phenotypes in individuals. However, these sleep phenotypes are often relevant and may be affected in a coordinated manner; changes in one phenotype often lead to compensatory changes in other sleep phenotypes.[16] In addition, whether other sleep phenotypes are related to OSA is still worthy of exploration.[17] Therefore, assessing sleep patterns according to sleep phenotypes may comprehensively reveal the combined effects of these phenotypes on OSA and promote the development of personalized treatment, prognostic assessment, and patient selection in clinical trials.

Research on genetic susceptibility has revealed genetic associations with OSA.[18,19] A meta-analysis and genome-wide association study (GWAS) of Chinese individuals and Biobank Japan revealed multiple variants associated with OSA.[20,21] The large-cohort FinnGen Study[22] and a Hispanic/Latino American study also showed an association between genetic susceptibility and OSA.[23] However, the underlying biological knowledge gained from GWAS-discovered single nucleotide polymorphisms (SNPs) is limited.[24] Determining genetic susceptibility according to multiple SNPs may accurately reveal the genetic risk of OSA.

In general, both genetic and phenotypic factors contribute to the development of OSA.[20] We aimed to identify comprehensive risk factors for OSA by assessing the association between sleep patterns and the incidence of OSA in a prospective study. Through this approach, we estimated the potential reduction in OSA cases that could be achieved if all participants were to adopt healthy sleep patterns. The main approach involved assessing the quality of sleep patterns by assigning healthy sleep scores to participants according to five sleep phenotypes. Subsequently, the effect of sleep patterns on the occurrence rate of OSA was evaluated, considering genetic risk factors.

This study was designed to provide updated evidence regarding the association between sleep patterns, genetic susceptibility, and OSA. To the best of our knowledge, this study is the first to combine five sleep phenotypes with healthy sleep scoring and genetic risk for OSA. This OSA risk analysis could help predict clinical chronic OSA earlier, more effectively, and more accurately. Additionally, our study provides clinicians with effective prevention recommendations.

Methods

Study Population

The study included participants from the UK Biobank. The UK Biobank is a forward-looking cohort study of the natural population that recruited over 500,000 participants aged 37–73 years from 2006 to 2010; follow-up was conducted to record personal epidemiological and genetic data.[25] Health-related conditions were obtained through regular linkages to national electronic health-related datasets. Inpatient hospital data were updated periodically from the Hospital Episode Statistics database, the Scottish Morbidity Record, and the Patient Episode Database in England, Scotland, and Wales, respectively, which have been available to all UK Biobank participants since 1997.[26] We obtained data usage and analysis permission from the UK Biobank team (Application No. 77803) for this study on the characterization of genetic and phenotypic aspects of OSA.

To minimize potential confounding factors related to racial diversity, we excluded nonwhite British participants from the analysis. This exclusion criterion specifically refers to individuals not identifying as white British participants. Participants who did not answer any questions about the seven sleep phenotypes (details in the next section) in the initial assessment (N = 87,994), participants missing body mass index (BMI) data (N = 7,631), and those missing demographic information on other covariant-related factors (N = 13,362) were excluded. To obtain a true association between sleep phenotypes and OSA, we excluded those who had OSA at the time of inclusion and those who self-reported OSA at the time of admission (Figure 1).

Participants who snore were excluded from the genetic susceptibility analysis to prevent false associations with genes related to snoring.[22]

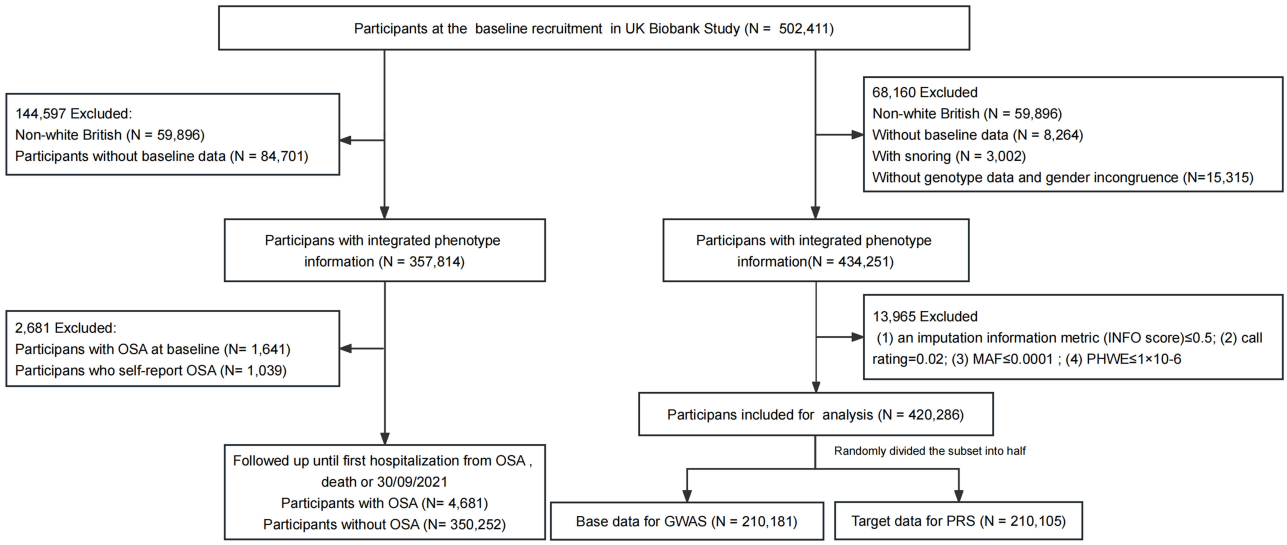

Figure 1 Study design.
Abbreviations: OSA, obstructive sleep apnea; GWAS, genome-wide association study; PRS, polygenic risk score.

Assessment of Low-Risk Sleep Phenotypes

Seven sleep phenotypes obtained through a touchscreen questionnaire and generated by the assessment center environment (ACE) system (UK Biobank Resource 113241) were extracted from the sleep-related category (UK Biobank Category 100057) to define low-risk sleep phenotypes.

1. The "sleep 7–8 hours per day" phenotype was accessed from the answer to the following question: "About how many hours do you sleep every 24 hours?" (Data Field 1160). In the main analysis, the variables were analyzed at three levels: short sleep time (≤6 hours/day), normal sleep time (7–8 hours/day), and long sleep time (≥9 hours/day), consistent with previous studies.[27]
2. The phenotype "easily getting up early" was evaluated by the following question: "Do you think you get up early?" (Data Field 1170); the ACE system provides five answers: (i) not easy at all, (ii) not easy, (iii) easy, (iv) very easy, and (v) unwilling to answer. Answers (iii) and (iv) were recognized as "easily getting up early".
3. The "morning chronotype" phenotype was evaluated by the following question: "You think you're (i) a morning person, (ii) a person whose morning is more than evening, (iii) a person whose evening is more than morning, or (iv) a night person?" (Data Field 1180). Answers (iii) and (iv) were recognized as morning chronotypes.
4. The "never/rarely nap" phenotype was assessed through the following question: "Do you nap during the day?" (Data Field 1190). The ACE answers were (i) never/rarely, (ii) sometimes, and (iii) often. Answers (i) and (ii) were recognized as never/rarely nap.
5. The "never/rarely insomnia" phenotype was obtained by asking, "Do you have difficulty sleeping at night or waking up in the middle of the night?" (Data Field 1200), and the answers were (i) never/rarely, (ii) sometimes, or (iii) normally.
6. The "no snoring" phenotype information was collected by asking, "Do your partner or next of kin or friend complain about your snoring?" (Data Field 1210), and the ACE answer was (i) yes or (ii) no.
7. The "no frequent daytime sleepiness" phenotype was assessed by asking, "How likely are you to undoor fall asleep during the day?" (Data Field 1220). The answers were (i) never/rarely, (ii) sometimes, (iii) often, or (iv) consistently. Answers (i) and (ii) were recognized as no frequent daytime sleepiness.

For all sleep phenotypes, answers "do not know" or "prefer not to answer" were encoded as missing data.

Definition of a Healthy Sleep Score and Pattern

Five low-risk sleep phenotypes were used to evaluate sleep patterns in a prospective study of the effect of sleep pattern on disease risk,[16] including morning chronotype, 7–8 hours of sleep per day, never/rarely experience insomnia, no snoring, no frequent daytime sleepiness, never/rarely nap, and easily getting up early. In our study, two additional sleep phenotypes, never/rarely nap and easily getting up early, were added to the low-risk sleep phenotypes, which were summarized into healthy sleep scores. The participants received a score of 1 if classified as low risk or 0 if they were at high risk for each phenotype. A healthy sleep score ranging from 0 to 7 was summed, and higher scores indicated a healthier sleep pattern. Sleep patterns were defined as "optimal sleep pattern" (healthy sleep score ≥6), "ideal sleep pattern" (≤4 healthy sleep score ≤5), "normal sleep pattern" (≤2 healthy sleep score ≤3), or "poor sleep pattern" (healthy sleep score ≤1).

Outcome

The diagnosis of medical conditions was obtained through hospitalization data from the UK Biobank. Similar to previous studies, we used data from the UK Biobank's hospital inpatient records (Data Field 41270) and death registry (Data Field 40001) to define OSA according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes G473,[22] which pertain to relevant health issues.

Participants who reported having OSA or sleep apnea before the baseline assessments or within 3 months of follow-up were excluded. Using the baseline as the reference point, individuals who had OSA recorded as the primary cause of hospitalization (Data Field 41270) or in the death registry (Data Field 40001) during the follow-up period were classified as incident cases of OSA. The endpoints in the analyses were the date of the first inpatient diagnosis of OSA (Data Field 41280) or the date of death for those who died during the follow-up period without inpatient records relating to OSA (Data Field 40000). The remaining participants were considered controls. The endpoint for those without OSA and who were alive during the follow-up period was December 30, 2021. The total follow-up time for each participant was calculated to obtain the survival time analyzed in this study.

Polygenic Risk Score

We conducted standard quality control of white British participants in the UK Biobank. Briefly, we restricted our analyses to autosomal biallelic SNPs and removed variants with a call rate <98%, genotyping rate <98%, minor allele frequency <0.01%, or deviation from Hardy–Weinberg equilibrium ($p < 10^{-6}$), leaving 420,286 participants for further analysis (Figure 1).

The polygenic risk score (PRS), an objective indicator of the genetic basis of a disorder, was used to establish the presence of a genetic signal and index the underlying genetic burden of a trait.[28] Due to human heterogeneity and the possible limited portability between populations,[29] we conducted GWAS and PRS by randomly splitting participants base and target datasets (Figure 1). We analyzed the case–control ratio imbalance using a scalable and accurate generalized mixed model (SAIGE) with saddle point approximation (SPA) and a model adjusted for covariate sex, age, and the first four principal components (PCs).[30]

The PRS of the target data for OSA was calculated as the weighted sum of the risk alleles according to the summary statistics of the GWAS results mentioned earlier using the standard clumping + thresholding (C+T) approach. The hyperparameters were the cutoff of correlation r^2 (0.05) and p-value threshold (5×10^{-6}), and the window size was 1000 Kb. The participants were classified as having high (<1st tertile), intermediate (1st–2nd tertile), or low (>2nd tertile) genetic susceptibility to OSA.

PLINK (version 1.9) and R software (version 4.0.2) were used for GWAS and PRS calculations.

Statistical Analysis

Baseline characteristics are presented as the mean ± standard deviation (SD) for continuous variables, and the Townsend deprivation index (TDI) are presented as the median with interquartile range and percentages for categorical variables. *T*-tests and chi-square tests were applied to compare the baseline characteristics between the OSA patients and the

controls. The Mann–Whitney *U*-test was used for TDI. The TDI is a region-based alternative to socioeconomic status provided in the Biobank Study in the United Kingdom[31] and is an indicator used to measure the socioeconomic environment of the population. The metabolic equivalent intensity (MET) is the metabolic rate during activity and the standard resting metabolic rate; MET 1 is the resting metabolism rate obtained while sitting quietly, MET 3–6 indicates moderate activity, and MET ≥6 indicates vigorous activity.[32] Those with a BMI ≥30 kg/m^2 were categorized into the obesity subgroup, and those with a BMI > 30 kg/m^2 were categorized as nonobese. Men with a waist circumference ≥ 102 cm and women with a waist circumference ≥ 88 cm composed the nonhealthy subgroup.[33] Missing data were not estimated in the primary analysis.

Three Cox proportional hazards models[31] were performed on the follow-up data to estimate the relationship between sleep phenotypes and OSA: (1) unadjusted; (2) adjusted for age and sex; and (3) adjusted for smoking status, alcohol consumption, waist circumference, TDI, BMI, MET, and history of hypertension and diabetes.

To incorporate follow-up time and accurately measure the frequency of OSA in patients per unit time in this prospective cohort study, we estimated the incidence density of sleep patterns (per 1000 person-years). To estimate the proportion of OSA that theoretically would not have occurred if participants had been in the low-risk sleep phenotype, the population attributable risk percent (PAR%) was calculated to estimate the reduction in cases in the population in the absence of the high-risk phenotype. We also plotted the multiple covariable-adjusted cumulative incidences of OSA according to sleep patterns and genetic risk.

Several sensitivity analyses were performed to validate our study outcomes' robustness. Participants were stratified according to age, sex, BMI, smoking status, drinking status, and other variables, and sleep pattern scores were analyzed as continuous variables in various subgroups. Additionally, we excluded participants with snoring (ICD10: R065) as a comorbid condition and performed a sensitivity analysis as previously described.[22]

A weighted healthy sleep score was created according to seven sleep phenotypes using the following equation: weighted sleep score = (β1*s1 + β2*s2 + … + β7*s7) * (7/(β1+β2+.+β7)).[16] The score ranges from 0 to 7 and considers the adjusted relative risk of each phenotype. We categorized the weighted sleep patterns as follows: "weighted optimal sleep pattern" (weighted healthy sleep score >6), "weighted ideal sleep pattern" (≤4 weighted healthy sleep score ≤6), "weighted normal sleep pattern" (≤2 weighted healthy sleep score <4), and "weighted poor sleep pattern" (weighted healthy sleep score <2). These categories may be useful in assessing sleep quality.

Data preprocessing was conducted using Python (version 3.9.10, Python Software Foundation, https://www.python.org/), and analyses were performed with R software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/). A Bonferroni-corrected *p* value of 0.01 was applied to adjust for multiple testing.

Results

Baseline Characteristics

A total of 355,133 participants from the UK Biobank were included in the analysis (age: 56.61 ± 8.03 years; 187,288 women: 52.7%). During the 12.57-year follow-up, we documented 4,681 incident OSA cases. The other participants were categorized into the non-OSA group. The baseline characteristics of the participants are shown in Table 1.

Association Between Sleep Phenotypes and OSA

After adjusting for multiple covariates (Table 2), seven sleep phenotypes were independently associated with incident OSA. "No frequent daytime sleepiness" and "sleep 7–8 hours a day" were associated with a 65.0% or 6.0% lower risk, respectively. Sleep phenotypes were estimated to explain 1.8% (sleep duration) to 66.0% (excessive daytime sleepiness) of the population's risk of developing OSA when using the low-risk group for comparison.

The degree of each sleep phenotype was classified. The analysis revealed that sleep durations ≥6 hours (HR: 1.27, 95% CI: 1.19–1.36) and ≤9 hours (HR: 1.43, 95% CI: 1.31–1.58) increased the incidence of OSA, and the risk increased with long sleep (Supplementary Figure 1).

Table 1 Basic Characteristics and Sleep Phenotypes of 355,133 UK Biobank Participants

	Non-OSA (n = 350,452)	OSA (n = 4,681)	OR (95% CI)	p (t/U/χ^2)
Sex, n (%)				<0.001
Female	185,823 (53.0)	1,465 (31.3)	REF	
Male	164,629 (47.0)	3,216 (68.7)	2.48 (2.33–2.64)	
Age, years	56.60 (8.04)	56.83 (7.69)	1.00 (1.00–1.01)	0.041
TDI	−2.28 [−3.76,0.03]	−1.59 [−3.34,1.37]		<0.001
BMI, kg/m^2	27.20 (4.56)	32.56 (6.59)	1.17 (1.17–1.18)	<0.001
BMI status, n (%)				<0.001
Nonobese	270,198 (77.1)	1,856 (39.6)	REF	
Obese	80,254 (22.9)	2,825 (60.4)	5.12 (4.83–5.44)	
Waist circumference, n (%)				<0.001
Healthy	204,998 (58.5)	1,405 (30.0)	REF	
Unhealthy	145,454 (41.5)	3,276 (70.0)	3.29 (3.09–3.50)	
Smoke, n (%)				<0.001
No	139,269 (39.7)	1,433 (30.6)	REF	
Yes	211,183 (60.3)	3,248 (69.4)	1.49 (1.40–1.59)	
Drink, n (%)				<0.001
Previous	11,153 (3.2)	275 (5.9)	REF	
Current	328,912 (93.9)	4,258 (91.0)	0.52 (0.46–0.59)	
Missing: 10,535				
MET Scores	10.7 (4.80)	9.32 (5.22)	0.94 (0.94–0.95)	<0.001
MET Status, n (%)				<0.001
<3	281,865 (80.4)	3,283 (70.1)	REF	
Between 3 and 6	52,706 (15.0)	869 (18.6)	1.42 (1.31–1.53)	
>6	15,881 (4.5)	529 (11.3)	2.86 (2.60–3.14)	
Diabetes, n (%)				<0.001
No	333,826 (95.3)	3,968 (84.8)	REF	
Yes	16,626 (4.7)	713 (15.2)	3.61 (3.32–3.91)	
Hypertension, n (%)				<0.001
No	252,223 (72.0)	1,623 (34.7)	REF	
Yes	98,229 (28.0)	3,058 (65.3)	4.84 (4.55–5.14)	
Sleep time, n (%)				<0.001
(7–8 h)	242,756 (69.3)	2,648 (56.6)	REF	
(≤6 h)	81,136 (23.2)	1,462 (31.2)	1.65 (1.55–1.76)	
(≥9 h)	25,927 (7.4)	541 (11.6)	1.91 (1.74–2.10)	
Missing: 663				
Daytime dozing/sleeping, n (%)				<0.001
Never/rarely	272,620 (77.8)	2,656 (56.7)	REF	
Sometimes	69,070 (19.7)	1,511 (32.3)	2.25 (2.11–2.39)	
Often	8,104 (2.3)	486 (10.4)	6.16 (5.57–6.79)	
All the time	12 (0.00)	1 (0.02)	9.67 (0.40–49.4)	
Missing: 673				
Chronotype, n (%)				<0.001
Morning	84,239 (24.0)	1,128 (24.1)	REF	
Morning more than evening	115,968 (33.1)	1,337 (28.6)	0.86 (0.80–0.93)	
Evening more than morning	89,383 (25.5)	1,266 (27.0)	1.06 (0.98–1.15)	
Evening	27,243 (7.8)	532 (11.4)	1.46 (1.31–1.62)	
Missing: 34,037				

(*Continued*)

Table 1 (Continued).

	Non-OSA (n = 350,452)	OSA (n = 4,681)	OR (95% CI)	p (t/U/χ^2)
Snoring, n (%)				<0.001
Yes	120,330 (34.3)	3,249 (69.4)	REF	
No	208,395 (59.5)	1,163 (24.8)	0.21 (0.19–0.22)	
Missing: 21,996				
Getting up in the morning, n (%)				<0.001
Not at all easy	11,977 (3.42)	379 (8.10)	REF	
Not very easy	46,199 (13.2)	875 (18.7)	0.60 (0.53–0.68)	
Fairly easy	176,230 (50.3)	2,038 (43.5)	0.37 (0.33–0.41)	
Very easy	115,855 (33.1)	1,381 (29.5)	0.38 (0.34–0.42)	
Missing: 198				
Sleeplessness/insomnia, n (%)				<0.001
Never/rarely	86,707 (24.7)	963 (20.6)	REF	
Sometimes	167,138 (47.7)	1,809 (38.6)	0.97 (0.90–1.05)	
Usually	96,467 (27.5)	1,905 (40.7)	1.78 (1.64–1.92)	
Missing:144				
Nap during the day, n (%)				<0.001
Never/rarely	202,018 (57.6)	1,711 (36.6)	REF	
Sometimes	130,809 (37.3)	2,349 (50.2)	2.12 (1.99–2.26)	
Usually	17,568 (5.01)	620 (13.2)	4.17 (3.79–4.57)	
Missing: 58				

Abbreviations: OSA, obstructive sleep; BMI, body mass index; and MET, metabolic equivalent intensity.

Association Between Sleep Patterns and OSA

The incidence density of OSA in those with poor sleep patterns (≤1) (5.14/1000 person-years) was 5.5 times that in those with optimal sleep patterns (≥6) (0.93/1000 person-years) (Table 3). A high healthy sleep score reduced the OSA risk (Supplementary Table 1). Compared with a poor sleep pattern, an optimal sleep pattern can reduce the disease risk by 85.0% (HR: 0.15, 95% CI: 0.12–0.18). Normal sleep patterns (HR: 0.42, 95% CI: 0.38–0.46) and ideal sleep patterns (HR: 0.21, 95% CI: 0.19–0.24) could also reduce the disease risk.

The subgroup analysis revealed that for every 1-point increase in the healthy sleep score, there was a significant difference in the occurrence of OSA events in the sex, BMI, waist circumference, and high blood pressure subgroups (p interaction <0.05) (Supplementary Table 2).

A weighted optimal sleep pattern also significantly reduced the risk of OSA (HR: 0.12, 95% CI: 0.11–0.14) (Supplementary Table 3). Regarding weighted sleep patterns, the cumulative risk of poor sleep patterns increased significantly with increasing follow-up time ($p < 0.001$) (Supplementary Figure 2).

Another sensitivity analysis eliminated 1582 people with snoring, comprising 294 patients with OSA and 1288 without, and the results remained robust (Supplementary Table 4).

PRS and Sleep Patterns in Patients with OSA

The GWAS conducted on the basic dataset (210,181 participants; 114,175 women: 54.3%) revealed four SNPs below the 5.0×10^{-7} threshold significantly associated with OSA (Supplementary Table 5). The GWAS results are summarized in a Manhattan plot (Supplementary Figure 3). The genome-wide significant findings from these studies and the corresponding associations in our study are shown in the Supplementary Materials (Supplementary Table 6). A total of 210,105 participants (114,128 women: 54.3%) from the target dataset were used to calculate the PRS, and 173,239 underwent Cox proportional risk regression.

After adjusting for variables, the results showed no significant differences between the seven sleep phenotypes and the genetic information of OSA patients (Supplementary Table 7). Compared with those with a sleep score of 4–7 and in

Table 2 Multivariable-Adjusted HRs (95% CIs) for OSA by Low-Risk Sleep Phenotypes Among 355,133 Participants

	Model 1*			Model 2†			Model 3‡		
	β	HR (95% CI)	PAR%	β	HR (95% CI)	PAR%	β	HR (95% CI)	PAR%
Sleep 7–8 h/day	−0.20	0.82 (0.77–0.88)	5.0 (3.70–6.9)	−0.17	0.84 (0.79–0.90)	4.6 (2.9–6.3)	−0.07	0.94 (0.88–1.00)	1.8 (−0.1–3.6)
Early chronotype	−0.18	0.83 (0.79–0.88)	9.4 (6.7–12.2)	−0.15	0.86 (0.81–0.91)	7.7 (4.8–10.6)	−0.08	0.92 (0.87–0.98)	4.4 (1.3–7.6)
Never/rarely experience insomnia	−0.24	0.79 (0.73–0.84)	5.2 (3.9–6.6)	−0.38	0.69 (0.64–0.74)	7.8 (6.5–9.0)	−0.19	0.83 (0.77–0.89)	4.3 (2.8–5.8)
No self-reported snoring	−1.48	0.23 (0.21–0.24)	46.1 (45.1–47.0)	−1.36	0.26 (0.24–0.27)	44.4 (43.4–45.5)	−1.02	0.36 (0.34–0.39)	38.6 (37.2–40.1)
No frequent daytime sleepiness	−1.57	0.21 (0.19–0.23)	77.2 (75.3–79.1)	−1.53	0.22 (0.20–0.24)	76.5 (74.5–78.5)	−1.06	0.35 (0.31–0.38)	66.0 (62.8–69.3)
No nap	−0.87	0.42 (0.39–0.44)	33.2 (31.8–34.7)	−0.80	0.45 (0.42–0.48)	31.6 (30–33.2)	−0.50	0.61 (0.57–0.65)	22.7 (20.5–24.9)
Easily getting up early	−0.61	0.54 (0.51–0.58)	38.2 (35.3–41.2)	−0.77	0.46 (0.43–0.49)	44.7 (42.1–47.3)	−0.55	0.58 (0.54–0.62)	36.0 (32.7–39.3)

Notes: *Model 1: unadjusted; †Model 2: adjusted for sex and age; and ‡Model 3: adjusted for sex, age, BMI, TDI, MET, smoking status, drinking status, diabetes status, and hypertension.

Table 3 Multivariable-Adjusted HR (95% CI) for Incident OSA by Sleep Patterns Among 355,133 Participants

Sleep Pattern	All	Case	Control	Cases/1000 PYs	Model 1*		Model 2†		Model 3‡	
					β	HR (95% CI)	β	HR (95% CI)	β	HR (95% CI)
Poor	7,476	465	7,011	5.14	REF	REF	REF	REF	REF	REF
Normal	212,878	3,496	209,382	2.32	−1.37	0.25 (0.23–0.28)	−1.39	0.25 (0.23–0.27)	−0.87	0.42 (0.38–0.46)
Ideal	92,688	569	92,119	1.49	−2.37	0.09 (0.08–0.11)	−2.33	0.10 (0.09–0.11)	−1.55	0.21 (0.19–0.24)
Optimal	42,091	151	41,940	0.93	−2.91	0.05 (0.05–0.07)	−2.85	0.06 (0.05–0.07)	−1.92	0.15 (0.12–0.18)

Notes: *Model 1: unadjusted; †Model 2: adjusted for sex and age; and ‡Model 3: adjusted for sex, age, BMI, TDI, MET, smoking status, alcohol consumption status, diabetes status, and hypertension status.

the low-susceptibility group, those with a normal sleep pattern had a 55.0% greater risk (HR: 1.55, 95% CI: 1.17–2.05), and those with poor sleep patterns (16 OSA and 242 non-OSA) had a 388% greater risk (HR: 4.88, 95% CI: 2.95–8.05) in the context of intermediate susceptibility to OSA. A normal sleep pattern increased disease risk by 89.0% (HR: 1.89, 95% CI: 1.66–2.16); a poor sleep pattern increased disease risk by 267.0% (HR: 3.67, 95% CI: 2.95–4.57) in the high-susceptibility group (Figure 2).

Discussion

To our knowledge, few studies have investigated how combinations of low-risk sleep phenotypes affect the risk of OSA. However, these phenotypes may act synergistically to decrease OSA risk and could be useful in identifying at-risk populations and promoting health management. In this large prospective cohort study, we examined the associations between OSA and seven low-risk sleep phenotypes (morning chronotype, 7–8 hours of sleep per day, never/rarely experience insomnia, no snoring, no frequent daytime sleepiness, never/rarely nap, and easily getting up early) compiled as a sleep pattern, also considering genetic susceptibility to the disease. Our new sleep pattern analysis reflects the comprehensive influence of these seven low-risk sleep phenotypes on OSA. Participants with an ideal sleep pattern had an 85% lower risk of developing OSA than those with a poor sleep pattern. The evidence suggesting that an ideal sleep pattern could reduce disease risk in various populations with varying degrees of genetic susceptibility.

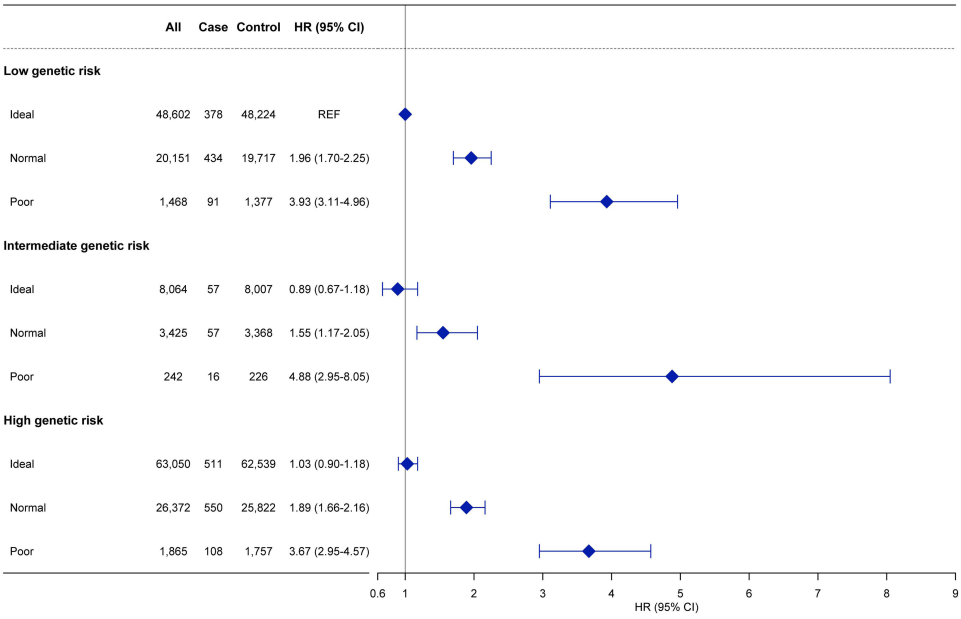

Figure 2 Joint association of genetic risk and sleep pattern with OSA among 173,239 participants.
Note: Adjusted for sex, age, BMI, TDI, MET, smoking status, drinking status, diabetes status, and hypertension status.

A short sleep duration increases OSA risk at least 0.27 times compared with that observed with a normal sleep duration and 0.43 times compared with a longer sleep duration. Other studies have shown that short sleep durations are associated with OSA.[34] Additionally, the percentage of rapid eye movement (REM) sleep time during short sleep has been found to be lower in OSA patients than common population.[35] Short REM may exacerbate the severity of OSA and may represent a brain defense mechanism.[36] Snoring events have been observed during ~60% of OSA events involving apnea–terminating hyperpnea,[37] and the intensity and frequency of snoring have been found to be independent predictors of OSA, at 77% and 81%, respectively, with age and sex increasing these values to 87% and 89%, respectively.[38] Daytime sleepiness is a common symptom in obese patients with OSA, suggesting that objective daytime sleepiness is a more severe type of OSA phenotype with greater sympathetic drive, greater blood pressure, and possibly greater cardiovascular morbidity and mortality.[39] One study of 23 patients revealed that more OSA patients with mild apnea had a morning chronotype,[40] and the process of chronotype change is closely related to the prevalence of OSA.[41] Thus, it might be valuable to identify the chronotype associated with the onset of OSA in adults. Our study revealed that the risk of OSA in the evening chronotype group was significantly greater than that of the morning chronotype group, consistent with the findings of a previous study.[42] The effects of naps on nocturnal sleep health and sleep dependence have been reported, and adverse health effects of naps have been confirmed.[43–45] Our study highlighted the effects of daytime naps on the incidence of OSA, providing an important reference for early-onset predictions of OSA.

Our analysis demonstrated that improving sleep phenotypic behaviors may significantly lower disease risk. Short sleep duration or insomnia symptoms are linked to endocrine or metabolic disorders, increased sympathetic activity, or inflammatory pathways,[46] while an evening chronotype can result in bipolar disorder.[47] Habitual snoring is often associated with sleep apnea, and severe snoring is linked to increased thickness of the carotid endometrium and plaque and atherosclerosis.[48] The benefits of reducing OSA and other disease risks by improving sleep behaviors, such as reducing sleep duration, changing chronotype, and limiting daytime naps, are substantial.

This study provides novel empirical evidence for the predictive value of seven low-risk sleep phenotypes and introduces a new healthy sleep pattern. This study offers clinical insights into the genetic factors contributing to susceptibility to OSA, paving the way for personalized treatment approaches. Clinicians can identify individuals at greater risk based on their genetic characteristics and tailor interventions accordingly. Assessing and intervening in sleep phenotypes in clinical practice allows more targeted and effective OSA prevention strategies and treatment.

Despite these strengths and implications for future research, several limitations should be considered when interpreting our results. First, since our study relied solely on diagnostic information related to OSA provided by the UK Biobank, we could not ascertain the diagnostic accuracy or severity classification. The sleep phenotype data were self-reported, which introduces the possibility of information bias, potentially limiting the interpretation of sleep phenotypes in relation to OSA severity. Second, our study is observational; therefore, caution should be exercised in interpreting the results. Third, this study was restricted to white British individuals, which may limit the generalizability of the findings to the overall population. Given these limitations, it is important to validate our findings in subsequent studies using an independent large sample, employing rigorous sleep phenotyping and outcome assessment to establish robust and applicable results across diverse populations. These future studies represent a crucial step in elucidating the comprehensive effect of phenotypic and genetic variations associated with OSA across different ethnicities. We believe that the results presented here provide a reference for future phenotypic and genetic functional studies on OSA.

Conclusion

This study presents new empirical evidence on the predictive value of seven low-risk sleep phenotypes and a new healthy sleep pattern may protect against OSA in individuals with varying degrees of genetic susceptibility. The results indicate that prioritizing management strategies to achieve a healthy sleep pattern may reduce the risk of OSA among individuals with low, intermediate, or high genetic susceptibility. These findings have important implications for reducing the burden of OSA in the population.

Abbreviations

OSA, obstructive sleep apnea; GWAS, genome-wide association study; SNPs, single nucleotide polymorphisms; BMI, body mass index; ACE, Assessment Centre Environment; ICD-10, International Statistical Classification of Diseases and

Related Health Problems 10th version; PRS, polygenic risk score; PRS, polygenic risk score; SAIGE, scalable and accurate implementation of generalized mixed model; SPA, saddle point approximation; PC, principal component; C+T, standard clumping + thresholding; TDI, Townsend deprivation index; MET, metabolic equivalent intensity; PAR%, population attributable risk percent; and REM, rapid eye movement.

Data Sharing Statement

All supporting data in this study were obtained from the UK Biobank (http://www.ukbiobank.ac.uk/), which is available to all researchers upon request. This study was conducted using the UK Biobank Resource (Application No. 77803). Our team welcomes potential collaborations to maximize the use of the data. The detailed data extraction protocol is available upon reasonable request from the corresponding author Guoqing Zhang (gqzhang@sinh.ac.cn).

Ethics Statement

UK Biobank data use was approved by the North West Multi-centre Research Ethics Committee (MREC) (REC Reference: 21/NW/0157) Ethics (ukbiobank.ac.uk). In addition, article 32 of China's Notice on the Issuance of Ethical Review Measures for Life Science and Medical Research Involving Humans: The use of human information data or biological samples to carry out life science and medical research involving human beings, does not cause harm to human beings, does not involve personal sensitive information or commercial interests, can be exempted from ethical review, in order to reduce the unnecessary burden on researchers and promote the development of life science and medical research involving human beings. Therefore, we also provide this document for reference.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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