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ORIGINAL ARTICLE

Associations of sleep and circadian phenotypes with COVID-19 susceptibility and hospitalization: an observational cohort study based on the UK Biobank and a two-sample Mendelian randomization study

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Abstract

Study Objectives: Sleep and circadian phenotypes are associated with several diseases. The present study aimed to investigate whether sleep and circadian phenotypes were causally linked with coronavirus disease 2019 (COVID-19)-related outcomes.

Methods: Habitual sleep duration, insomnia, excessive daytime sleepiness, daytime napping, and chronotype were selected as exposures. Key outcomes included positivity and hospitalization for COVID-19. In the observation cohort study, multivariable risk ratios (RRs) and their 95% confidence intervals (CIs) were calculated. Two-sample Mendelian randomization (MR) analyses were conducted to estimate the causal effects of the significant findings in the observation analyses. Odds ratios (ORs) and the corresponding 95% CIs were calculated and compared using the inverse variance weighting, weighted median, and MR-Egger methods.

Results: In the UK Biobank cohort study, both often excessive daytime sleepiness and sometimes daytime napping were associated with hospitalized COVID-19 (excessive daytime sleepiness [often vs. never]: RR = 1.24, 95% CI = 1.02–1.5; daytime napping [sometimes vs. never]: RR = 1.12, 95% CI = 1.02–1.22). In addition, sometimes daytime napping was also associated with an increased risk of COVID-19 susceptibility (sometimes vs. never: RR = 1.04, 95% CI = 1.01–1.28). In the MR analyses, excessive daytime sleepiness was found to increase the risk of hospitalized COVID-19 (MR IVW method: OR = 4.53, 95% CI = 1.04–19.82), whereas little evidence supported a causal link between daytime napping and COVID-19 outcomes.

Conclusions: Observational and genetic evidence supports a potential causal link between excessive daytime sleepiness and an increased risk of COVID-19 hospitalization, suggesting that interventions targeting excessive daytime sleepiness symptoms might decrease severe COVID-19 rate.

Statement of Significance

The present study explored the association of five major sleep and circadian phenotypes with COVID-19 susceptibility and hospitalization based on both epidemiological and genetic evidence. From the UK Biobank, a large population-based observation cohort, we found that daytime napping and excessive daytime sleepiness were associated with a higher risk of severe COVID-19 while no sleep or circadian phenotypes were associated with COVID-19 susceptibility. By applying Mendelian randomization analyses using SNPs as instrumental variables, we further demonstrated that there may be a causal link between excessive daytime sleepiness and COVID-19 hospitalization might be causal. Interventions targeting excessive daytime sleepiness symptoms may decrease the likelihood of severity of COVID-19.

Key words: Mendelian randomization; cohort study; COVID-19; sleep

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Introduction

Sleep is a naturally recurring phenomenon of the brain and body that is mediated by the central nervous system through a series of psychophysiological processes and is associated with the normal regulation of the immune system [1]. Sleep disturbances affect approximately one-quarter of the population in the United States and are often associated with increased risks of cardiometabolic risks, psychiatric disorders, and infectious diseases [2]. Studies have revealed that the association between elevated disease susceptibility and sleep disturbance might be mediated by the dysregulation of sleep-immune bidirectional crosstalk [3].

Coronavirus disease 2019 (COVID-19), which is triggered by infection with severe acute respiratory syndrome coronavirus 2, has caused a global crisis with both economic and health impacts. The susceptibility to COVID-19 and rates of hospitalization differ among individuals, with the severity ranging from asymptomatic infections, dry cough, and fever to multiple organ dysfunction and even death [4]. Evidence suggests that the severity of COVID-19 might be affected by the acceleration of immune senescence, which has been found to be related to insomnia [5, 6]. Furthermore, a high body mass index (BMI), which is strongly associated with sleep disturbances [7], might cause an increase in COVID-19 susceptibility and hospitalization rates [8]. Previous studies have revealed that insomnia, severe sleep problems, and burnout might increase the risk of COVID-19 in healthcare workers [9]. However, whether this association remains consistent in a general population with European ancestry has not been properly investigated.

Considering the existing evidence, it is logical to infer that abnormal sleep and circadian phenotypes might be associated with high susceptibility or worse clinical outcomes of COVID-19. The present study aimed to reveal the associations of sleep and circadian phenotypes with COVID-19 susceptibility and hospitalization rates by using a community-based UK Biobank cohort and to estimate their potential causal effects using two-sample Mendelian randomization (MR) analyses.

Methods

UK Biobank cohort

The UK Biobank is a large-scale population-based prospective cohort with more than 500,000 participants aged 40–69 years from 22 assessment centers across the United Kingdom recruited between 2006 and 2010. The details of the UK Biobank have been described previously [10]. Phenotypic and genotypic details of each participant were acquired from baseline questionnaires, face-to-face interviews, body measurements, and genome-wide genotyping. Follow-up information was acquired from multiple data linkages to national datasets and records [11]. Inpatient hospital data from England, Scotland, and Wales were acquired from Hospital Episode Statistics in England, the Scottish Morbidity Record, and the Patient Episode Database for Wales. The COVID-19 test data were first available on January 31, 2020 and last updated on December 30, 2020, and were acquired from Public Health England's Second Generation Surveillance System microbiology database with linkage to the UK Biobank participants [12].

All the UK Biobank participants gave written informed consent before data collection. The UK Biobank has full ethics approval from the NHS National Research Ethics Service (16/NW/0274). Part of this research was performed using the UK Biobank Resource under Application 69718.

Study Design and Statistical Analyses in the Cohort Study

The overall study design in the cohort study is presented in Figure 1. Participants were excluded if they died before January 31, 2020 (i.e. the date on which the first COVID-19 case was diagnosed in the UK). In the primary analyses, we restricted our analyses to Caucasian individuals to make the observational results comparable to those of the subsequent MR analyses. Additionally, we only included participants with laboratory test results for COVID-19, given that the estimation might be biased in the general population because a large number of patients with COVID-19 could have been asymptomatic or have died before undergoing COVID-19 testing.

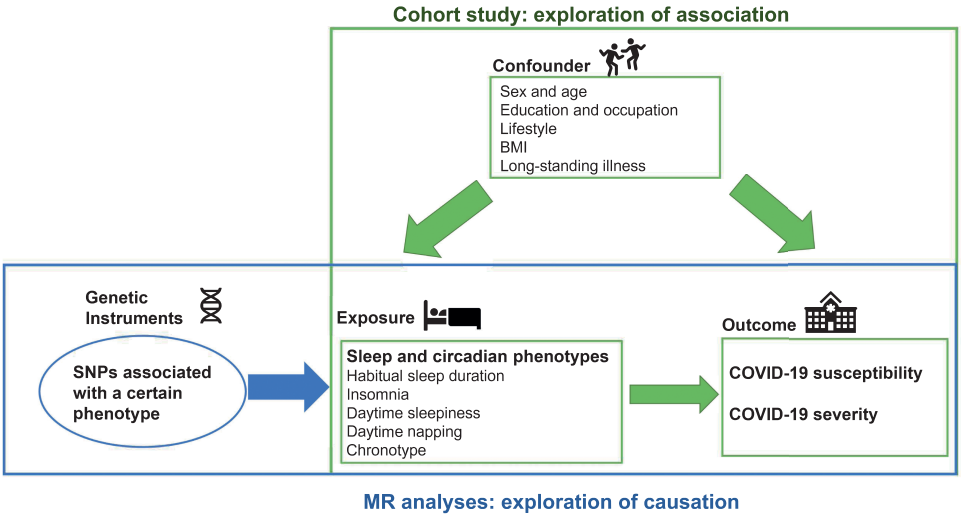

Figure 1. Diagrams illustrating the general design of the observational study (A) and Mendelian randomization study (B).

Sleep and circadian phenotypes in the UK Biobank were selected as exposures, including habitual sleep duration, insomnia, excessive daytime sleepiness, daytime napping, and chronotype (Supplementary Method). Two outcomes were used: (1) COVID-19 positivity and (2) COVID-19 hospitalizations. COVID-19 positive cases were defined as participants who had at least one positive COVID-19 test result, while hospitalized COVID-19 cases were defined as participants who were admitted to the hospital with COVID-19 as the primary diagnosis, received critical care treatments, or died from COVID-19 [13]. For COVID-19 susceptibility, the control group was the participants who had negative laboratory test results for COVID-19 while for COVID-19 hospitalizations, the control group was the participants who had positive COVID-19 testing results without hospitalizations.

Covariates include sex (female and male), age on January 31, 2021 (continuous variable), scores on the Townsend deprivation index (TDI, categorized into quintiles, i.e. Q1, Q2–Q4, Q5), occupation (employed, retired, and other), smoking status (current, previous, and never), alcohol consumption (current, previous, and never), BMI (normal/underweight, overweight, and obese), and obstructive sleep apnea (yes and no, according to the diagnoses coded by the International Classification of Disease version 10). History of severe somatic comorbidity before COVID-19 testing for each participant was chosen to represent a broad spectrum of common diseases and the participants' general health (i.e. diabetes; vascular/heart problems diagnosed by a doctor; chronic lower respiratory disease; disease of the esophagus, stomach and duodenum; hepatic failure; fibrosis and cirrhosis of the liver; and dementia). Risk ratios (RRs) were calculated using a generalized linear model. Three models were constructed to estimate the association between the selected exposure and the outcome. Model 1 was adjusted for sex, age at the time of COVID-19 testing, TDI, occupation, smoking status, and alcohol consumption. Model 2 was additionally adjusted for BMI because BMI has been showed to be associated with both sleep phenotypes and COVID-19 [7, 14]. Model 3 was additionally adjusted for a history of severe somatic comorbidity. Model 4 was additionally adjusted for obstructive sleep apnea.

Subsequential analyses were only conducted on the sleep and circadian phenotypes that were significantly associated with COVID-19 outcomes in the cohort study (i.e. excessive daytime sleepiness and daytime napping). In the subgroup analyses, each selected sleep and circadian phenotype was stratified by age, sex, BMI, history of severe somatic comorbidity, and obstructive sleep apnea to demonstrate the potential modification effects. Sensitivity analyses were conducted by extending the criteria for the included population. We reanalyzed our results expanding our sample to include participants from all ethnicities (n = 70,557). All analyses were conducted using R 3.6.3 (R Development Core Team, Vienna, Austria). The UKB.COVID19 package was used to process the COVID-19 hospitalizations data [13]. A two-sided $p < 0.05$ was considered statistically significant.

Study Design of the MR Analyses

The principle and mechanism of the MR study have been explained previously [15]. Briefly, MR is a method that uses genetic variants as instrumental variables to estimate the potential causal effects of exposure on the outcome. Three requirements must be satisfied to perform MR. (1) The relevance assumption states that the genetic variants must have a strong association with the selected exposure. (2) The independence assumption states that no confounder can exist between the genetic variants and the outcome. (3) The exclusion restriction assumption states that the genetic variants can only affect the outcome through the selected exposure. Once the three assumptions are met, a valid causal inference can be made through MR. The general study design of the MR analyses is presented in Figure 1.

Summary Statistics of Sleep, Circadian Phenotypes and COVID-19

Five sleep and circadian phenotypes, namely, habitual sleep duration [16], insomnia [17], daytime sleepiness [7], daytime napping [18], and chronotype [19], were selected as exposures. Summary-level data on sleep and circadian phenotypes were obtained from five published large genome-wide association (GWAS) studies including participants of European ancestry in the UK Biobank. The characteristics of the included GWAS results are listed in Table 1. Candidate genetic variants were included if they reached genome-wide significance ($p < 5 \times 10^{-8}$) and were uncorrelated (10,000 kbp apart from each other with linkage disequilibrium $R^2 \leq 0.001$). To avoid weak instrument bias, instrument strength was evaluated by F-statistics. An F-statistic > 10 is considered sufficient for the magnitude of association between instrument variables and the exposure of interest [20].

Summary-level data on COVID-19 susceptibility and severity were obtained from the COVID-19 Host Genetics Initiative (Supplementary Method, Supplementary Table S1), and the details were previously described [21]. Since the exposure data were derived from the UK Biobank, we restricted the analysis to individuals of European ancestry and excluded those from the UK Biobank to avoid potential instrument bias in the MR analyses introduced by sample overlap. In the primary analysis, COVID-19 susceptibility was measured based on the group with laboratory-confirmed or self-reported cases of COVID-19 (n = 32,494) versus the rest of the population (which was composed of all the individuals who were not in the case group, n = 1,316,207). COVID-19 hospitalization was measured based on the group hospitalized for COVID-19 (n = 8316) versus the rest of the population (n = 1,549,095, Supplementary Figure S1).

Two-sample MR Analyses

Two-sample MR analyses were performed to estimate the potential causal effects between sleep phenotype and each COVID-19 outcome using the twosamplemr package [15]. In the primary MR analyses, daytime napping and daytime sleepiness, which were significantly associated with COVID-19 outcomes in the observational analyses, were included separately. A random-effects inverse-variance weighted (IVW) method was used for the main MR analyses, as it is one of the most statistically powerful methods of estimating effects when all single nucleotide polymorphisms (SNPs) are valid instrumental variables [22]. Since the pleiotropy of SNPs has been considered universal in most cases, weighted median [23] and MR-Egger regression [24] were used depending on different assumptions of pleiotropy. The weighted median method can provide a causal estimate when at least 50% of genetic variants are valid instrumental variables, while MR-Egger regression can be used for causal estimation when

Table 1. The information of candidate genetic instruments of sleep and circadian phenotypes

Exposure	Author	Year	Sample size	Phenotype processing	Candidate genetic instruments, N	Reported variance explained (%)	Genetic instruments included in the analyses, N	F statistics
Habitual sleep duration	Dashti et al.	2019	446,118	Sleep duration was treated as a continuous variable	78	0.69%	64	46.4
Insomnia	Lane et al.	2019	453,379	Insomnia symptoms were dichotomized into controls ("never/rarely") and cases with any symptoms ("sometimes" and "usually").	57	1%	38	42.744
Excessive daytime sleepiness	Wang et al.	2019	452,071	Four categories corresponding to the severity of daytime sleepiness were ("never", "sometimes", "often", or "all of the time") were used as a continuous variable	42	6.90%	35	42.086
Daytime napping	Dashti et al.	2021	452,633	Three categories corresponding to the degree of daytime napping ("never/rarely", "sometimes", or "usually") were used as a continuous variable	123	1.10%	92	47.838
Chronotype	Jones et al.	2019	449,734	"Definitely a 'morning' person", "More a 'morning' than 'evening' person", "More an 'evening' than a 'morning' person", "Definitely an 'evening' person", "Do not know" or "Prefer not to answer" were coded as 2, 1, –1, –2, 0 and missing, respectively	351	13.70%	146	46.403

all SNPs are invalid instrumental variables [23, 24]. Odds ratios and 95% CIs for each comparison were calculated to estimate the causal effects. Cochran's Q was calculated for each comparison, and funnel plots were drawn to examine potential heterogeneity [25]. The MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to correct for the influential outliers by removing them in order and re-estimating the exposure-outcome relationships [26]. The causal directions between exposure and outcomes were evaluated using the MR Steiger directionality test [27].

Secondary MR analysis was conducted to test the robustness of our results. We changed our definition of COVID-19 severity and performed our MR analyses again. The additional outcome that represented COVID-19 severity was critical respiratory illness, which was defined by death or respiratory support in patients hospitalized for COVID-19 (n = 4792) versus the rest of the population (n = 1,054,664).

Furthermore, we applied MR-MoE, which is a method to choose the most appropriate MR tests using a mixture of experts' machine learning approach, as a sensitivity analysis for our results. The detailed mechanism and description of MR-MOE was presented by Hemani et al. [28]. In general, it first performs MR using 11 MR methods and then performs 14 MR methods again using the subset of SNPs after filtering using the Steiger method [27]. Finally, pretrained random forest method is used to select the most reliable MR method depending on the area under the receiver operating characteristic curve.

Additionally, MR analyses on other sleep and circadian phenotypes were conducted to add supplemental evidence to our study. A two-sided $p < 0.05$ was considered statistically significant for all MR analyses.

Results

Observed associations based on the UK Biobank cohort

The details of the participants' characteristics at recruitment are shown in Table 2. A total of 65,576 participants were included in the present study, including 13,959 participants with COVID-19; among them, 2171 participants were identified as patients hospitalized with COVID-19. Compared with non-hospitalized COVID-19 positive participants, patients hospitalized with COVID-19 were more likely to have insufficient or excessive sleep duration, suffer from insomnia, experience excessive daytime sleepiness, have a habit of daytime napping, and have at least one somatic severe comorbidity.

As shown in Figure 2, in model 4, sometimes having daytime napping was associated with both increased COVID-19 susceptibility (RR = 1.04, 95% CI = 1.01–1.08) and hospitalization (RR = 1.12, 95% CI = 1.02–1.22) compared with never having daytime napping. Often having excessive daytime sleepiness was associated with an increased risk of COVID-19 hospitalizations (RR = 1.24, 95% CI = 1.02–1.5). These associations were largely consistent within models, except only a marginally significant association was found between sometimes daytime napping and COVID-19 susceptibility (RR = 1.03, 95% CI = 1–1.07, Supplementary Table S2).

Subgroup and Sensitivity Analyses in the Observational Cohort

In the subgroup analyses, no significant interaction was found after stratification of excessive daytime sleepiness and daytime

Table 2. The information of candidate genetic instruments of sleep and circadian phenotypes

	COVID-19 susceptibility			COVID-19 severity		
	COVID-19 negative	COVID-19 positive	All	Non-hospitalized COVID-19 positive	Hospitalized COVID-19 positive	All
Cases	51,617	13,959	65,576	11,788	2171	13,959
Chronotype						
Morning	28,648 (55.5%)	7465 (53.5%)	36,113 (55.1%)	6326 (53.7%)	1139 (52.5%)	7465 (53.5%)
Evening	17,072 (33.1%)	4892 (35.0%)	21,964 (33.5%)	4143 (35.1%)	749 (34.5%)	4892 (35.0%)
Missing	5897 (11.4%)	1602 (11.5%)	7499 (11.4%)	1319 (11.2%)	283 (13.0%)	1602 (11.5%)
Insomnia						
Never/rarely	11,383 (22.1%)	3496 (25.0%)	14,879 (22.7%)	3043 (25.8%)	453 (20.9%)	3496 (25.0%)
Sometimes	24,021 (46.5%)	6369 (45.6%)	30,390 (46.3%)	5407 (45.9%)	962 (44.3%)	6369 (45.6%)
Usually	16,180 (31.3%)	4083 (29.2%)	20,263 (30.9%)	3330 (28.2%)	753 (34.7%)	4083 (29.2%)
Missing	33 (0.1%)	11 (0.1%)	44 (0.1%)	8 (0.1%)	3 (0.1%)	11 (0.1%)
Daytime sleepiness						
Never/rarely	38,272 (74.1%)	10,570 (75.7%)	48,842 (74.5%)	9136 (77.5%)	1434 (66.1%)	10,570 (75.7%)
Sometimes	11,510 (22.3%)	2887 (20.7%)	14,397 (22.0%)	2291 (19.4%)	596 (27.5%)	2887 (20.7%)
Often/All of the time	1620 (3.1%)	437 (3.1%)	2057 (3.1%)	311 (2.6%)	126 (5.8%)	437 (3.1%)
Missing	215 (0.4%)	65 (0.5%)	280 (0.4%)	50 (0.4%)	15 (0.7%)	65 (0.5%)
Daytime napping						
Never/rarely	27,742 (53.7%)	7787 (55.8%)	35,529 (54.2%)	6856 (58.2%)	931 (42.9%)	7787 (55.8%)
Sometimes	20,704 (40.1%)	5407 (38.7%)	26,111 (39.8%)	4370 (37.1%)	1037 (47.8%)	5407 (38.7%)
Usually	3139 (6.1%)	753 (5.4%)	3892 (5.9%)	552 (4.7%)	201 (9.3%)	753 (5.4%)
Missing	32 (0.1%)	12 (0.1%)	44 (0.1%)	10 (0.1%)	2 (0.1%)	12 (0.1%)
Habitual sleep duration						
<6 h	3090 (6.0%)	873 (6.3%)	3963 (6.0%)	691 (5.9%)	182 (8.4%)	873 (6.3%)
6–9 h	47,106 (91.3%)	12,688 (90.9%)	59,794 (91.2%)	10,817 (91.8%)	1871 (86.2%)	12,688 (90.9%)
>9 h	1113 (2.2%)	288 (2.1%)	1401 (2.1%)	204 (1.7%)	84 (3.9%)	288 (2.1%)
Missing	308 (0.6%)	110 (0.8%)	418 (0.6%)	76 (0.6%)	34 (1.6%)	110 (0.8%)
Obstructive sleep apnea						
No	50,097 (97.1%)	13, 624 (97.6%)	63,721 (97.2%)	11,568 (98.1%)	2056 (94.7%)	13,624 (97.6%)
Yes	1520 (2.9%)	335 (2.4%)	1855 (2.8%)	220 (1.9%)	115 (5.3%)	335 (2.4%)
Sex						
Male	23,985 (46.5%)	6570 (47.1%)	30,555 (46.6%)	5256 (44.6%)	1314 (60.5%)	6570 (47.1%)
Female	27,632 (53.5%)	7389 (52.9%)	35,021 (53.4%)	6532 (55.4%)	857 (39.5%)	7389 (52.9%)
Age						
Mean (SD)	69.0 (7.88)	64.8 (8.63)	68.1 (8.23)	63.7 (8.35)	70.5 (7.88)	64.8 (8.63)
Median [Min, Max]	70.7 [49.6, 85.2]	63.9 [49.6, 82.9]	69.7 [49.6, 85.2]	62.6 [49.6, 82.7]	72.5 [49.7, 82.9]	63.9 [49.6, 82.9]
Townsend deprivation index						
High	9722 (18.8%)	3276 (23.5%)	12,998 (19.8%)	2625 (22.3%)	651 (30.0%)	3276 (23.5%)
Median	31,207 (60.5%)	8322 (59.6%)	39,529 (60.3%)	7122 (60.4%)	1200 (55.3%)	8322 (59.6%)
Low	10,623 (20.6%)	2344 (16.8%)	12,967 (19.8%)	2026 (17.2%)	318 (14.6%)	2344 (16.8%)
Missing	65 (0.1%)	17 (0.1%)	82 (0.1%)	15 (0.1%)	2 (0.1%)	17 (0.1%)
Occupation						
Employed	28,061 (54.4%)	9459 (67.8%)	37,520 (57.2%)	8517 (72.3%)	942 (43.4%)	9459 (67.8%)
Retired	19,250 (37.3%)	3210 (23.0%)	22,460 (34.3%)	2247 (19.1%)	963 (44.4%)	3210 (23.0%)
Other	4142 (8.0%)	1239 (8.9%)	5381 (8.2%)	982 (8.3%)	257 (11.8%)	1239 (8.9%)
Missing	164 (0.3%)	51 (0.4%)	215 (0.3%)	42 (0.4%)	9 (0.4%)	51 (0.4%)
Alcohol consumption						
Current	47,764 (92.5%)	12,976 (93.0%)	60,740 (92.6%)	11,047 (93.7%)	1929 (88.9%)	12,976 (93.0%)
Previous	2005 (3.9%)	547 (3.9%)	2552 (3.9%)	401 (3.4%)	146 (6.7%)	547 (3.9%)
Never	1782 (3.5%)	428 (3.1%)	2210 (3.4%)	336 (2.9%)	92 (4.2%)	428 (3.1%)
Missing	66 (0.1%)	8 (0.1%)	74 (0.1%)	4 (0.0%)	4 (0.2%)	8 (0.1%)
Smoking status						
Current	5458 (10.6%)	1609 (11.5%)	7067 (10.8%)	1319 (11.2%)	290 (13.4%)	1609 (11.5%)
Previous	19,771 (38.3%)	5188 (37.2%)	24,959 (38.1%)	4187 (35.5%)	1001 (46.1%)	5188 (37.2%)
Never	26,146 (50.7%)	7110 (50.9%)	33,256 (50.7%)	6248 (53.0%)	862 (39.7%)	7110 (50.9%)
Missing	242 (0.5%)	52 (0.4%)	294 (0.4%)	34 (0.3%)	18 (0.8%)	52 (0.4%)
Body mass index						
Normal/under	15,255 (29.6%)	3688 (26.4%)	18,943 (28.9%)	3360 (28.5%)	328 (15.1%)	3688 (26.4%)
Obese	14,084 (27.3%)	4295 (30.8%)	18,379 (28.0%)	3349 (28.4%)	946 (43.6%)	4295 (30.8%)
Overweight	22,004 (42.6%)	5890 (42.2%)	27,894 (42.5%)	5025 (42.6%)	865 (39.8%)	5890 (42.2%)
Missing	274 (0.5%)	86 (0.6%)	360 (0.5%)	54 (0.5%)	32 (1.5%)	86 (0.6%)
Severe somatic comorbidity history						
No	143,94 (27.9%)	5353 (38.3%)	19,747 (30.1%)	5054 (42.9%)	299 (13.8%)	5353 (38.3%)
Yes	37,223 (72.1%)	8606 (61.7%)	45,829 (69.9%)	6734 (57.1%)	1872 (86.2%)	8606 (61.7%)

napping by predefined confounders including sex, age, BMI, obese status, history of somatic comorbidities, and obstructive sleep apnea (Supplementary Figure S2).

In the sensitivity analyses, when we included all participants in our analyses instead of only including Caucasian participants, additional associations were found between short sleep

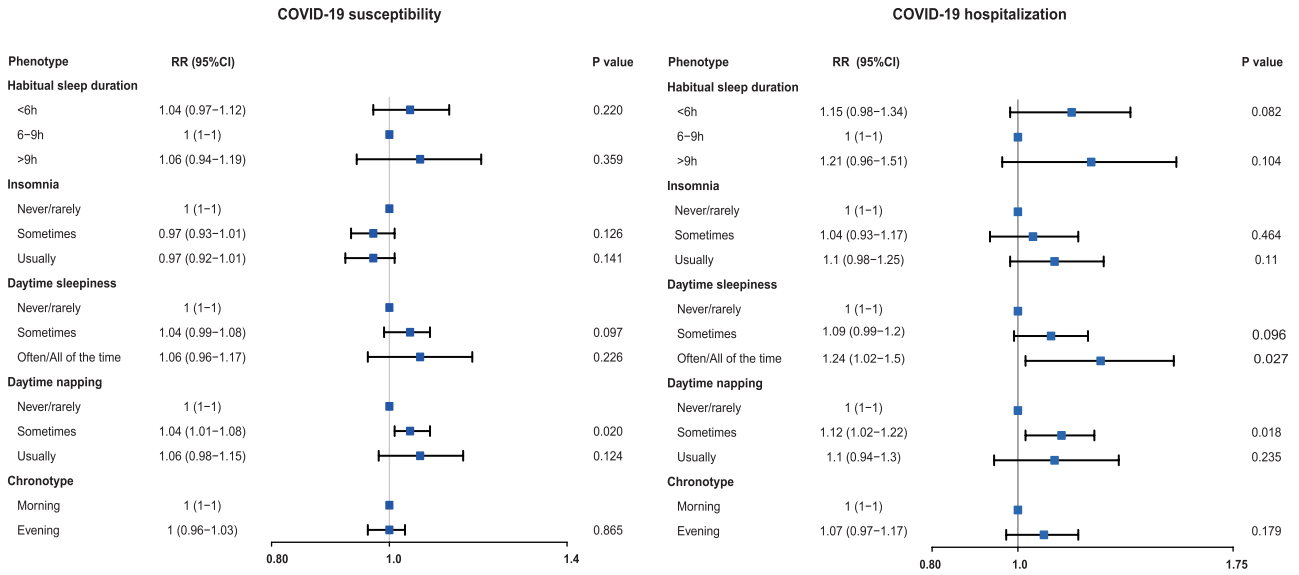

Figure 2. Forest plots showing the association between sleep and circadian phenotypes and COVID-19 susceptibility (A) and severity (B). Models were adjusted for sex, age at COVID-19 test, Townsend deprivation index, occupation, smoking status, and alcohol consumption, body mass index, history of severe somatic comorbidity, and obstructive sleep apnea.

duration and COVID-19 severity (RR = 1.16, 95% CI = 1.01–1.34, Supplementary Table S3).

Associations Based on Two-Sample MR Analyses

MR analyses were conducted to further explore the potential casualty between daytime napping with COVID-19 susceptibility and hospitalization and excessive daytime sleepiness with COVID-19 hospitalizations. Information on variant-exposure and variant-outcome associations is presented in Supplementary Tables S4 and S5. We found significant evidence that daytime sleepiness was associated with a higher risk of COVID-19 hospitalizations across the IVW, WME, and MR-Egger methods (odd ratio: OR = 4.53, 95% CI = 1.04-19.82, $p = 0.04$, Figure 3A). Although the MR-Egger intercept test (Egger-intercept = –0.042, standard error [SE] = 0.024, $p = 0.095$) demonstrated no evidence of directional pleiotropy, heterogeneity tests for the IVW and MR-Egger methods suggested potential heterogeneity (Table 3). Two influential outliers that may cause heterogeneity were detected by the MR-PRESSO method, and after excluding those outliers, the association remained (MR-PRESSO with outlier correction: OR = 4.36, 95% CI = 1.20–15.77, $p = 0.03$). The MR Steiger directionality test showed excessive daytime sleepiness was upstream of COVID-19 hospitalizations (Steiger p value < 0.001).

No causal evidence was found supporting the relationship of daytime napping with either COVID-19 susceptibility or hospitalization (Figure 3B and C), and MR-PRESSO did not identify outliers (p-value for global test: 0.466 for variants to COVID-19 susceptibility, and 0.823 for variants to COVID-19 hospitalizations).

Additional Analyses

In the secondary MR analyses, we changed the definitions of the case and control groups. The results showed that when changing the definition of severe COVID-19 from hospitalization for COVID-19 to COVID-19 with critical respiratory illness, daytime sleepiness was still associated with severe COVID-19 by using the IVW method (Supplementary Table S6). The direction of the association estimated by the MR-Egger method was consistent with the association estimated by the IVW method; however, it was no longer statistically significant in the MR-Egger method (Supplementary Table S5). Since no evidence of the presence of directional horizontal pleiotropy (Egger intercept = –0.009, $p = 0.786$) and no influential outliers were detected, it was reasonable to assume that the IVW method in MR analyses could offer a more accurate estimation. The heterogeneity test also found limited evidence of heterogeneity (IVW: Q = 46.89, df = 34, $p = 0.07$; MR Egger: Q = 46.78, df = 33, $p = 0.06$, Supplementary Table S6).

The MR-MOE machine learning method was used to further test the robustness of MR analyses. The top three MR methods selected by MR-MOE further confirmed the association between excessive daytime sleepiness and COVID-19 hospitalizations while the association between daytime napping and COVID-19 outcomes remain nonsignificant (Supplementary Tables S7–S9).

MR analyses of other sleep phenotypes (i.e. habitual sleep duration and insomnia) were also conducted (Supplementary Figure S3, Table S10). The results largely followed the observational findings, demonstrating that none of these sleep phenotypes was associated with the COVID-19 outcome. For the circadian phenotype, although the morning chronotype was associated with a higher risk of COVID-19, the associations disappeared when the WME and MR-Egger methods were used (Supplementary Figure S3).

Discussion

In the present study, we revealed associations between sleep phenotypes and COVID-19 susceptibility and severity based on a prospective cohort study using the UK Biobank. The results demonstrated that often excessive daytime sleepiness and

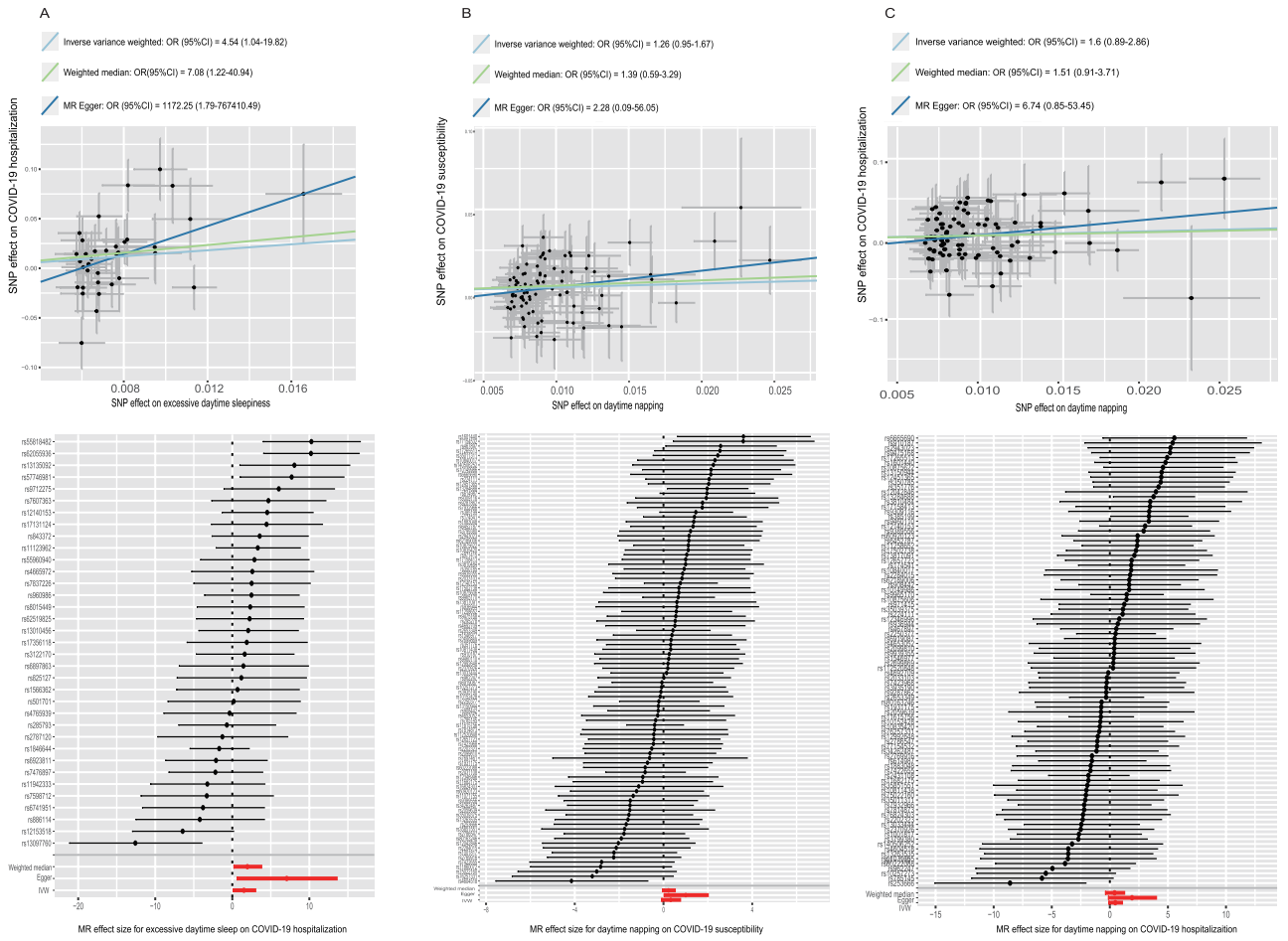

Figure 3. The results of causal estimates using Mendelian randomization. The forest plot of single SNP Mendelian randomization and scatter plots comparing the results of different Mendelian randomization methods in the association between (A) daytime sleepiness and COVD-19 hospitalization; (B) excessive daytime napping and COVD-19 susceptibility; (C) excessive daytime napping and COVD-19 hospitalization.

Table 3. Assessing heterogeneity and directional horizontal of pleiotropy of single nucleotide polymorphism effect in the Mendelian randomization analyses of excessive daytime sleepiness and daytime napping with COVID-19 outcomes

		Heterogeneity tests		Test for directional horizontal pleiotropy		
Covid-19 outcome	**Variables**	Q statistics	*P* value of Q statistics	Intercept of MR-Egger	Standard error	*P* value
COVID-19 susceptibility	**Daytime napping**					
	MR Egger	90.76	0.55	-0.008	0.005	0.11
	Inverse variance weighted	93.3	0.5			
COVID-19 hospitalization	**Excessive daytime sleepiness**					
	MR Egger	50.96	0.02	-0.042	0.02	0.09
	Inverse variance weighted	55.54	0.01			
	Daytime napping					
	MR Egger	76.12	0.85	-0.01	0.01	0.16
	Inverse variance weighted	78.14	0.83			

sometimes daytime napping were associated with an increased incidence of COVID-19 hospitalizations and sometimes daytime napping was also associated with COVID-19 susceptibility. Potential causal effects of excessive daytime sleepiness and daytime napping were further investigated using two-sample MR analyses, showing that individuals who had excessive daytime sleepiness more readily developed hospitalized COVID-19.

The association between excessive daytime sleepiness and COVID-19 severity was confirmed in our observational study. Excessive daytime sleepiness was defined as the inability to remain awake and alert during the main wakeful period of the day, resulting in unexpected drowsiness or sleep. It is a sign of chronic insufficient sleep as well as multiple sleep disorders [29]. Studies have shown that excessive daytime sleepiness is associated with higher risks of depression, coronary heart disease, and stroke [30,31]. Obstructive sleep apnea is often regarded as the main cause of excessive daytime sleepiness. The association of obstructive sleep apnea and severe COVID-19 has been reported

in several studies; despite the different end-point definitions, all of them showed a significant association between severe COVID-19 and obstructive sleep apnea [32]. Our results were in line with these findings and had the largest sample size, showing that the association of excessive daytime sleepiness and severe COVID-19 was independent of other sleep disorders, lifestyle, and BMI. Furthermore, none of the previous research could reveal the causal effects between excessive daytime sleepiness and severe COVID-19 because observational research cannot support causal inferences. By using univariable MR analysis, we revealed that daytime sleepiness could increase the risk of severe COVID-19.

According to Wang et al., *KSR2*, which was most significantly associated with five loci related to daytime sleepiness, was responsible for regulating multiple pathways (e.g. the ERK/MEK pathway) linked to cellular fatty acid metabolism and glucose oxidation that implicated in obesity and insulin resistance [7]. A previous study demonstrated that the synergy of obesity, insulin resistance and COVID-19 could increase the severity of COVID-19 [33]. Thus, it is logical to infer that daytime sleepiness might be linked to COVID-19 hospitalizations through multiple metabolism-related pathways.

We found that daytime napping was associated with both COVID-19 susceptibility and hospitalization based on the UK Biobank cohort. Although both sometimes and usually daytime napping have similar directions of effects, we did not find a significant association between usually daytime napping and both COVID-19 susceptibility and hospitalization, which implies that these associations might not depend on the frequency of daytime napping. Daytime napping is part of the cultural norm in China, Latin America, and the Mediterranean but not in the UK [34]. It is also often thought to be a countermeasure for shortened sleep duration and insomnia and a result of daytime sleepiness, which might be an early manifestation of diseases [35]. Li et al. found that longer daytime napping was associated with an increased risk of incident heart failure [36]. A large prospective cohort that included 116,632 participants across 12 countries demonstrated that daytime napping could lead to an increased risk of all-cause mortality and major cardiovascular events [37]. These results have also been confirmed by meta-analyses, showing that the duration of daytime napping and cardiovascular disease might have a J-shaped association [38]. The unique characteristics of daytime napping make causal inferences difficult to draw in traditional cohort studies because it could either be a cultural influence or an early marker of potential health problems and reverse causation [39]. In addition, it should be noted that daytime sleepiness and napping might share the same mechanisms and have some overlap with people with daytime sleepiness. Here, we clarify that daytime napping was only a sign, rather than a cause, of severe COVID-19 by conducting MR analyses using SNPs related to daytime napping as instrumental variables.

The association of poor sleep behaviors and COVID-19 hospitalizations and mortality in the UK Biobank cohort has been investigated before by Li et al. [40]. In addition to daytime sleepiness, Li et al. also found that long sleepers and usually having insomnia were significantly associated with COVID-19 hospitalizations. However, some differences between Li et al.'s and our study should be noticed. First, we have different definitions of COVID-19 cases. Li et al. included all hospitalized patients with positive COVID-19 tests in the past 7 days, while ours contained patients who were admitted to the hospital with COVID-19 as the primary diagnosis, received critical care treatments, or died from COVID-19. Our criterion, although it included fewer patients, was more accurate and more aligned with the definition included in the subsequent MR analyses [13]. Second, we used the risk ratio (RR) instead of the odds ratio (OR) to estimate the association between exposures and outcome. As the events increased, these two results cannot be used interchangeably, and ORs might exaggerate the association, as Ranganathan et al. suggested [41].

The key strength of this study is the integrated approaches we used to assess the associations of sleep and circadian traits with COVID-19. The individual-level data in the UK Biobank were used to explore the observed associations, while the summary-level data derived from the UK Biobank and the COVID-19 Host Genetics Initiative were used to estimate the potential causal effects. In the multivariable generalized linear model, we adjusted for several hypothesized confounders, and thus, the key source of biases was restricted. However, the nature of the prospective cohort limited further analyses of residual bias, selection bias, and measurement error. By using two-sample MR analyses, we directly measured the causal effects between exposure and outcome and minimized the possibility of reverse causation and those biases that were unavoidable in the observation cohort study because the exposure and outcome data were from two different cohorts with limited overlap. Furthermore, the results of the sensitivity analyses evaluating the generalizability of the observed associations showed that the observed association could be extended to populations with any ethnic background. Additionally, sensitivity analysis testing the core assumptions of MR analyses revealed that in most cases, the basic assumptions of MR analyses were not violated.

Our results should be interpreted with consideration of several limitations. A major limitation was that Mendelian analyses were conducted using summary-level data rather than individual level data, which prevented us from confirming that associations were independent of some known confounding variables [42]. Further studies using one-sample analysis adjusting known confounders and exploiting potential collider bias in sensitivity analyses are warranted [43]. Then, the low precision of the estimates in MR analyses because of the low variance explained by the genetic instruments in each sleep-related exposure, especially for the analyses of daytime sleepiness. Although several statistical tools were used to evaluate instrument strength, the modest instrument strength could not exclude the possibility that undetected subtle causal effects may exist. Third, although we minimized the possibility of sample overlap between exposure datasets and outcome datasets by excluding data from participants in the UK Biobank from our COVID-19 outcome dataset, hidden relatedness and potential sample overlap may have caused some instrument bias. In addition, in the observational study, although we adjusted for obstructive sleep apnea in our final models, the events of obstructive sleep apnea might be underreported. Finally, our study only included individuals of European descent; therefore, the results might not be generalizable to other populations.

The present study is comprehensively explored the relationship of sleep and circadian phenotypes with COVID-19 susceptibility and severity. To the best of our knowledge, it broadened the existing evidence supporting sleep-disease associations and potential causal effects. Excessive daytime sleepiness and daytime napping were associated with COVID-19 outcomes. However, only

daytime sleepiness showed evidence of being causally related to COVID-19 hospitalizations in MR analysis. The findings of our study highlight that daytime sleepiness should be recognized as one of the independent risk factors for COVID-19-induced hospitalization and that targeting excessive daytime sleepiness might be beneficial for preventing COVID-19 hospitalizations.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Table S1.1 Cohort contributing to the COVID-19 Host Genetics Initiative assessing study outcomes for COVID-19 susceptibility.

Table S1.2 Cohort contributing to the COVID-19 Host Genetics Initiative assessing study outcomes for COVID-19 hospitalization.

Table S1.3 Cohort contributing to the COVID-19 Host Genetics Initiative assessing study outcomes for COVID-19 with death or respiratory support outcome.

Table S1.4 Full names and abbreviations of contributing cohort in COVID19-hg GWAS meta-analyses round 5 conducted by COVID-19 Host Genetics Initiative.

Table S2. The association between sleep and circadian phenotypes and COVID-19 susceptibility (A) and hospitalization (B).

Table S3. The association of sleep and circadian phenotypes with COVID-19 susceptibility and hospitalization in a population without any ethnic background restriction.

Table S4. The association of each selected genetic instrument with excessive daytime sleepiness, daytime napping and COVID-19 susceptibility.

Table S5. The association of each selected genetic instrument with excessive daytime sleepiness, daytime napping and COVID-19 hospitalization.

Table S6. Mendelian randomization analyses of excessive daytime sleepiness and daytime napping with COVID-19 with critical respiratory illness.

Table S7 The association between excessive daytime sleepiness and COVID-19 hospitalization using 44 MR methods and selected by MR-MOE.

Table S8 The association between daytime napping and COVID-19 hospitalization using 44 MR methods and selected by MR-MOE.

Table S9 The association between daytime napping and COVID-19 susceptibility using 44 MR methods and selected by MR-MOE.

Table S10 The association of each selected genetic instrument with habitual sleep duration, insomnia, and chronotype.

Figure S1. The flow chart of two-sample Mendelian randomization analysis.

Figure S2 The subgroup analyses of the association of excessive daytime sleepiness and daytime napping with COVID-19 susceptibility (A) and hospitalization (B, C). Models were adjusted for sex, age at COVID-19 test, Townsend deprivation index, occupation, smoking status, and alcohol consumption, body mass index, history of severe somatic comorbidity, and obstructive sleep apnea.

Figure S3 Forest plots showing the association of habitual sleep duration, insomnia, and chronotype with COVID-19 susceptibility (A) and severity (B) using three Mendelian randomization methods.

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Disclosure Statement

None declared.

Ethics Approval and Consent to Participate

All the UK Biobank participants gave written informed consent before data collection. UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274).

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Data Availability

This work has been conducted using the UK Biobank Resource. The UK Biobank is an open access resource and bona fide researchers can apply to use the UK Biobank dataset by registering and applying at http://ukbiobank.ac.uk/register-apply/. Further information is available from the corresponding author upon request.

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