Pre-existing sleep disturbances and risk of COVID-19: a meta-analysis

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Summary

Background Sleep disturbances are widespread but usually overlooked health risk factors for coronavirus disease 2019 (COVID-19). We aimed to investigate the influence of pre-existing sleep disturbances on the susceptibility, severity, and long-term effects of COVID-19.

Methods We searched PubMed, Web of Science, and Embase for relevant articles from inception to October 27, 2023 and updated at May 8, 2024. Sleep disturbances included obstructive sleep apnea (OSA), insomnia, abnormal sleep duration, night-shift work, and any other sleep disturbances. Outcomes were COVID-19 susceptibility, hospitalization, mortality, and long COVID. The effect sizes were pooled odds ratios (ORs) and 95% confidence intervals (95% CIs). This study is registered with PROSPERO (CRD42024503518).

Findings A total of 48 observational studies (n = 8,664,026) were included. Pre-existing sleep disturbances increased the risk of COVID-19 susceptibility (OR = 1.12, 95% CI 1.07–1.18), hospitalization (OR = 1.25, 95% CI 1.15–1.36), mortality (OR = 1.45, 95% CI 1.19–1.78), and long COVID (OR = 1.36 95% CI 1.17–1.57). Subgroup analysis showed that younger individuals with sleep disturbances were associated with higher susceptibility and hospitalization and a lower risk of mortality than older individuals. Males with sleep disturbances were associated with higher mortality. For specific sleep disturbances, the susceptibility and hospitalization of COVID-19 were associated with OSA, abnormal sleep duration, and night-shift work; mortality of COVID-19 was linked to OSA; risk of long COVID was related to OSA, abnormal sleep duration and insomnia.

Interpretation Pre-existing sleep disturbances, especially OSA, increased the risk of COVID-19 susceptibility, hospitalization, mortality, and long COVID. Age and sex played important roles in the effect of sleep disturbances on COVID-19.

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Keywords: Pre-existing sleep disturbances; COVID-19; Long COVID; OSA

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has threatened global healthcare systems and brought about substantial morbidity and mortality for years. Although we are in the post-pandemic period, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) still persists, and the long-term sequelae of acute infection, known as long COVID, also need to be considered. At least 65 million individuals might have developed long COVID worldwide.[1] Long COVID is associated with a wide spectrum of symptoms, sometimes accompanying new-onset diseases.[1] It implied that substantial disease and economic burden caused by COVID-19 will be imposed on individuals and society in the foreseeable future.

Sleep disturbances, including insomnia, obstructive sleep apnea (OSA), poor sleep quality, and abnormal sleep duration, are ubiquitous yet widely neglected health risk factors for COVID-19. The global prevalence of sleep disturbances during the COVID-19 pandemic was 40.49%.[2] Jahrami et al.[2] further classified the population into six groups (patients with COVID-19, children and adolescents, healthcare workers, special populations with healthcare needs, university students,

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Research in context

Evidence before this study

Sleep disturbances, including insomnia, obstructive sleep apnea (OSA), poor sleep quality, and abnormal sleep duration, are ubiquitous yet widely neglected health risk factors for coronavirus disease 2019 (COVID-19). Several studies have investigated the impact of the COVID-19 pandemic on sleep disturbances. Inversely, little literature summarized whether and to what extent pre-existing sleep disturbances influenced COVID-19, especially long COVID. Till now, only two meta-analyses have reported that OSA increased the severity and mortality of COVID-19. These meta-analyses only focused on one specific type of sleep disturbances and neglected other important sleep disturbances, such as insomnia. Furthermore, it was still debatable whether patients with COVID-19 and pre-existing sleep disturbances were more vulnerable to developing long COVID. We searched PubMed, Web of Science, and Embase for relevant articles from inception to October 27, 2023 and updated at May 8, 2024, using the search terms ("sleep" OR "sleep disorders" OR "sleep duration" OR "sleep quality" OR "OSA") AND ("COVID-19" OR "SARS-CoV-2" OR "long COVID"). Observational studies reporting the association between pre-existing sleep disturbances and COVID-19 susceptibility, hospitalization, mortality, and long COVID were included.

Added value of this study

A total of 48 observational studies (n = 8,664,026) were included. Compared with previous studies that only focused on OSA, our study enrolled different kinds of sleep disturbances and systematically demonstrated the relationship between pre-existing sleep disturbances and COVID-19, especially long COVID. Pre-existing sleep disturbances increased the risk of COVID-19 susceptibility, hospitalization, mortality, and long COVID. Subgroup analysis showed that younger individuals with sleep disturbances were associated with higher susceptibility and hospitalization and a lower risk of mortality than older individuals. Males with sleep disturbances were associated with higher mortality. This study further investigated specific types of sleep disturbances and found that various sleep disturbances had different influences. OSA played a vital role not only in the whole clinical course of COVID-19 but also in the long COVID. Abnormal sleep duration elevated the risk of COVID-19 susceptibility, hospitalization, and long COVID. Insomnia escalated the risk of long COVID. Night-shift work increased the risk of COVID-19 susceptibility and hospitalization.

Implications of all the available evidence

By including all types of sleep disturbances, our meta-analysis comprehensively illustrated the influence of pre-existing sleep disturbances on the entire clinical course of COVID-19. It emphasized that sleep disturbances, especially OSA, significantly increased the risk of COVID-19 susceptibility, hospitalization, mortality and long COVID. These influences could be affected by age and gender. These findings urge the general population and healthcare workers to conduct early evaluation and intervention for individuals with sleep disturbances to mitigate the short- and long-term effects of COVID-19.

and the general population) and found that patients with COVID-19 had the highest prevalence, up to 52.39%. Sleep disturbances not only cause daytime drowsiness, work burnout, and low spirits but also induce immune deficiency and systematic inflammation.[3]

Several studies have investigated the impact of the COVID-19 pandemic on sleep disturbances.[2] Inversely, little literature summarized whether and to what extent pre-existing sleep disturbances influenced COVID-19, especially long COVID. Till now, only two meta-analyses have reported that OSA increased the severity and mortality of COVID-19.[4,5] These meta-analyses only focused on one specific type of sleep disturbances and neglected other important sleep disturbances, such as insomnia. Furthermore, it was still debatable whether patients with COVID-19 and pre-existing sleep disturbances were more vulnerable to developing long COVID. For example, in a comprehensive analysis of three large cohorts (two adult cohorts and one pediatric cohort), L Mandel et al.[6] suggested a positive association between OSA and long COVID; however, this association was attenuated in two adult cohorts and disappeared in the pediatric cohort after adjusting confounders. An international cross-sectional study, ICOSS-II, showed that insomnia was associated with an increased risk of long COVID,[7] whereas no significant association was detected in another study.[8]

Therefore, our meta-analysis aimed to (1) investigate the association between pre-existing sleep disturbances and COVID-19, including susceptibility, hospitalization, mortality, and long COVID-19; (2) calculate the effects of specific sleep disturbances on four outcomes and explore the potential associated factors.

Methods

Search strategy and selection criteria

We searched PubMed, Web of Science, and Embase for relevant articles from inception to October 27, 2023, and an updated search was done on May 8, 2024, using the search terms ("sleep" OR "sleep disorders" OR "sleep duration" OR "sleep quality" OR "OSA") AND ("COVID-19" OR "SARS-CoV-2" OR "long COVID") (Supplementary Appendix 1). Additionally, an extra manual search was conducted by screening the references of relevant articles and reviews to identify

additional studies that met the selection criteria. The exposure variables were pre-existing sleep disturbances, including OSA, insomnia, abnormal sleep duration (defined as sleep duration of less than 6 h or more than 9 h), night-shift work, evening chronotype, poor sleep quality, restless legs syndrome and so on, and recorded by electronic health records (polysomnography or International Classification of Diseases-10), interview, or self-report. Observational studies reporting the association between pre-existing sleep disturbances and COVID-19 susceptibility, hospitalization, mortality, or long COVID were included. Articles were excluded if they were: (1) unreported outcomes of interest, (2) case reports, letters, brief communications, or reviews, and (3) preprint studies. If the same cohort or data was reported in more than one study, we included only the one with the most comprehensive and recent information to avoid data duplication. Two investigators independently assessed the eligibility of the retrieved articles for inclusion, and any discrepancies were resolved by negotiation with a third investigator.

Procedures

Two experienced researchers conducted the data extraction and quality assessment under the supervision of a third investigator. We extracted the following: (1) basic information: author, year of publication, region, study design, sample size, age, and male ratio; (2) exposures: type of sleep disturbances and corresponding measurements; and (3) outcomes: COVID-19 susceptibility, hospitalization, mortality, or long COVID and corresponding measurements. If odds ratio (OR) was unavailable, hazard ratio, relative risk ratio, or raw data were extracted to calculate the corresponding ORs. We used the Agency for Healthcare Research and Quality to assess the quality of the cross-sectional studies and the Newcastle–Ottawa Scale (NOS) to assess the quality of the cohort and case–control studies (Table S1). Ethical approval and informed consent were not applicable for this study.

Statistical analysis

All analyses were performed with Stata 16.0 software. The effect sizes were pooled ORs and corresponding 95% confidence intervals (95% CIs) and the adjusted one was superior to the unadjusted one. High heterogeneity was defined as I^2 ≥50%. If I^2 ≥50%, a random-effects model was selected for pooled estimates, otherwise a fixed-effects model was adopted. Subgroup analysis, including age (<60 years old vs. ≥60 years old), income level (high vs. low and middle),[9] male proportion (<50% vs. ≥50%), exposure measurement (self-report vs. interview vs. electronic health records), outcome measurement (self-report vs. electronic health records), study design (cohort vs. case–control vs. cross-sectional), adjusted for OR (yes vs. no), literature quality (cohort: NOS <7 vs. NOS ≥7), and long COVID definition (≥1-month vs. ≥3-month) were performed to explore the source of heterogeneity. Heterogeneity in the subgroups was evaluated by the I^2 statistic (%). Between-subgroup heterogeneity was assessed by a P value. We calculated pooled estimates only if there were at least four studies in a category in order to reduce the potential bias caused by the low number of studies. The leave-one-out sensitivity analysis was used to evaluate the robustness of the pooled estimates. We performed additional sensitivity analyses to determine the influence of specific populations on the robustness of the pooled estimates by excluding (1) studies executed in women, (2) studies conducted in children, (3) studies performed in patients with diabetes, (4) studies with health worker proportion >50%, (5) studies with all the bias mentioned above. Egger's test was used to evaluate the symmetry of the funnel plot. If the funnel plot was asymmetrical, we conducted the trim-and-fill method to identify whether the source of asymmetry was from publication bias or not.[10] Statistical significance was set at $P < 0.05$. This study is registered with PROSPERO (CRD42024503518).

Role of the funding source

The funding source had no role in the design, execution, analyses, interpretation of the data, or decision to submit results.

Results

A total of 9835 records were retrieved, 95 full-text articles were evaluated, and 48 studies with 8,664,026 participants met the inclusion and exclusion criteria (Fig. 1). We included 22 studies (5,416,808 participants) for susceptibility, 12 studies (5,110,351 participants) for hospitalization, 16 studies (5,573,387 participants) for mortality, and 11 studies (2,367,827 participants) for long COVID. The sample size ranged from 118 to 4,912,229, and the proportion of males ranged from 0% to 72%. The regions were spread over USA (n = 19), multinational (n = 5), UK (n = 5), China (n = 2), India (n = 2), Netherlands (n = 2), Switzerland (n = 2), Norway (n = 2), Finland (n = 2), Canada (n = 1), France (n = 1), Germany (n = 1), Japan (n = 1), Poland (n = 1), South Korea (n = 1), and Turkey (n = 1). These studies mainly included four types of sleep disturbances (OSA, insomnia, abnormal sleep duration, night-shift work) (Table 1).

Susceptibility

Individuals with pre-existing sleep disturbances were more susceptible to COVID-19 (OR = 1.12, 95% CI 1.07–1.18) (Table 2). For specific sleep disturbances, OSA, abnormal sleep duration, and night-shift work increased the occurrence of COVID-19 (Table 2). Subgroup analysis showed that the increased susceptibility of COVID-19 was more significant in the population

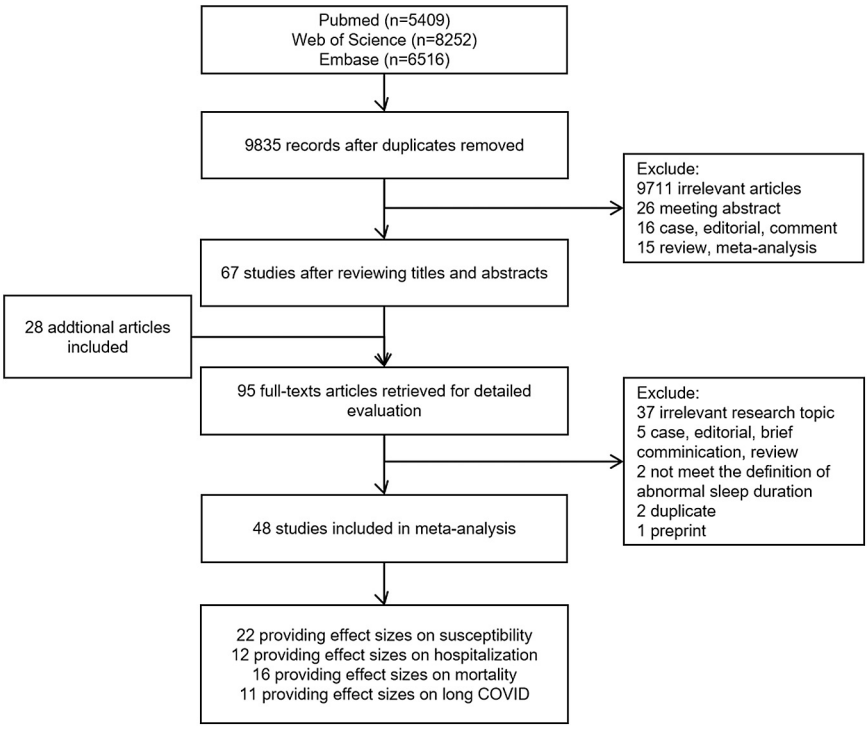

Fig. 1: Flow chart of study.

from low- and middle-income countries (high-income: 1.11, 95% CI 1.05–1.16 vs. low- and middle-income: 3.63, 95% CI 2.58–5.78; P < 0.001) and in studies with unadjusted ORs (adjusted: 1.12, 95% CI 1.06–1.17 vs. unadjusted: 1.78, 95% CI 1.17–2.70; P = 0.030). In addition, younger individuals with pre-existing sleep disturbances were associated with an increased susceptibility to COVID-19 (OR = 1.20, 95% CI 1.11–1.30), while older individuals were not (Fig. 2).

Clinical courses of COVID-19

The odds of COVID-19 hospitalization were significantly higher in patients with pre-existing sleep disturbances (OR = 1.25, 95% CI 1.15–1.36) (Table 2). Except for insomnia, the other three types of sleep disturbances were associated with an increased probability of hospitalization. The association between pre-existing sleep disturbances and COVID-19 hospitalization was stronger in younger patients (age <60 years: 1.43, 95% CI 1.26–1.61 vs. ≥60 years: 1.10, 95% CI 1.05–1.15; P < 0.001) (Fig. 2).

Pre-existing sleep disturbances increased the mortality of COVID-19 (OR = 1.45, 95% CI 1.19–1.78), mainly attributable to OSA (Table 2). The increased mortality of COVID-19 was more significant in the older patients (age <60 years: 1.22, 95% CI 0.91–1.62 vs. ≥60 years: 2.07, 95% CI 1.59–2.68; P = 0.007) and in males (male ratio <50%: 1.09, 95% CI 0.94–1.27 vs. ≥50%: 1.79, 95% CI 1.31–2.45; P = 0.005) (Fig. 2). Sensitivity analysis showed that after removing the study performed in patients with diabetes, the heterogeneity turned into low, which meant the population was the source of heterogeneity. Therefore, we extra performed a subgroup analysis and found that the association between pre-existing sleep disturbances and COVID-19 mortality was stronger in patients with diabetes than in the general population (diabetes: 2.80, 95% CI 1.46–5.38 vs. general population: 1.16, 95% CI 1.05–1.28; P = 0.009) (Figure S5).

Long COVID

Pre-existing sleep disturbances promoted the occurrence of long COVID (OR = 1.36, 95% CI 1.17–1.57) (Table 2). Subgroup analysis reported that the association between pre-existing sleep disturbances and long COVID was more significant in those whose definition of long COVID was symptoms ≥3-month (3-month: 1.53, 1.24–1.91 vs. 1-month: 1.18, 1.09–1.29; P = 0.029) (Fig. 2). Abnormal sleep duration and insomnia increased the odds of long COVID. L Mandel et al. reported a strong association between OSA and long COVID (OR = 1.75, 95% CI 1.71–1.80). However, this association disappeared in the pooled estimates. High heterogeneity was caused by different definitions of long COVID between the study by L Mandel et al. and the other three studies. Therefore, we divided the studies into two groups based on the definition of COVID-19 and found that OSA increased the risk of long COVID

Study	Region	Study design	Sample size	Age (years)	Males (%)	Type of sleep disturbances	Outcomes
Ahmadi et al., 2021	UK	cohort	468,569	57^{mean}	45	Poor sleep quality	③
Bjorvatn et al., 2023	Norway	cross-sectional	988	49^{mean}	40	Sleep debt, abnormal, sleep duration, insomnia	①
Bjorvatn et al., 2023	Multinational	cross-sectional	7141	44^{mean}	35	Night-shift work	①②④
Bjorvatn et al., 2024	Norway	cross-sectional	893	49^{mean}	40	Evening chronotype, night-shift work	①
Bushman et al., 2022	USA	case–control	1029	56^{median}	66	OSA	③
Cariou et al., 2020	France	cohort	1317	70^{mean}	65	OSA	③
Chen et al., 2023	Multinational	cross-sectional	1891	44^{mean}	48	Insomnia	④
Chung et al., 2023	Multinational	cross-sectional	20,598	42^{mean}	35	OSA	①②
Durstenfeld et al., 2023	USA	cohort	1480	53^{mean}	31	OSA	④
Goldstein et al., 2021	USA	cohort	572	63^{median}	56	OSA, insomnia, restless legs syndrome.	③
Gottlieb et al., 2020	USA	cohort	8673	41^{median}	47	OSA	②
Halalau et al., 2021	USA	cohort	821	49^{mean}	47	OSA	②
Hejazian et al., 2024	USA	cross-sectional	108,455	NA	47	Abnormal sleep duration	④
Holt et al., 2022	UK	cohort	15,227	59^{mean}	30	Abnormal sleep duration	①
Ioannou et al., 2020	USA	cohort	10,131	NA	36	OSA	②③
Jones et al., 2023	Finland	cohort	392,396,	60^{mean}	44,	Insomnia	①
Kar et al., 2021	India	cohort	213	55^{median}	68	OSA	③
Kendzerska et al., 2023	Canada	cohort	4,912,229	47^{median}	53	OSA	①②③
Kim et al., 2021	Multinational	case–control	2884	48^{mean}	72	Sleep disturbance	①
L Mandel et al., 2023	USA	cohort	1,783,940^{N3C}, 333,642^{PCORnet}, 106,262^{PETSnet}	NA	38^{N3C}, 40 ^{PCORnet}, 51 ^{PETSnet}	OSA	④
Li et al., 2021	cohort	cohort	1125	58^{mean}	50	OSA	③
Liu et al., 2022	UK	cohort	65,576	68^{mean}	47	Abnormal sleep duration, insomnia, excessive daytime sleepiness, and evening chronotype	①②
Loef et al., 2022	Netherlands	cohort	26,051	51^{mean}	38	Night-shift work	①
Lohia et al., 2021	USA	cohort	1871	64^{mean}	52	OSA	③
Maidstone et al., 2021	UK	cohort	120,307	NA	NA	Night-shift work	①
Mashaqi et al., 2021	USA	cohort	1738	58^{median}	49	OSA	③
Nakashima et al., 2022	Japan	cross-sectional	8837	43^{mean}	49	OSA	①
Oh et al., 2021	South Korea	cohort	122,040	NA	39	OSA	①③
Palaiodimos et al., 2020	USA	cohort	200	64^{median}	49	OSA	③
Paul et al., 2022	UK	cohort	1581	NA	49	Poor sleep quality	④
Peker et al., 2021	Turkey	cohort	320	53^{mean}	54	OSA	②
Pellaud et al., 2020	Switzerland	cohort	196	70^{median}	61	OSA	③
Pływaczewska-Jakubowska et al., 2022	Poland	cohort	1847	51^{median}	34	Insomnia	④
Punj et al., 2023	USA	cohort	49,434	59^{mean}	37	Sleep disorders	①②③
Quan et al., 2023(1)	USA	cross-sectional	15,057	46^{mean}	49	OSA	①②
Quan et al., 2023(2)	USA	cross-sectional	19,926	46^{mean}	49	Insomnia, poor sleep quality, abnormal sleep duration	①②
Quan et al., 2024	USA	cross-sectional	19,821	46^{mean}	49	Evening chronotype, night-shift work	①
Schilling et al., 2023	Germany	cross-sectional	11,710	44^{mean}	41	Sleep problems	④
Shah et al., 2022	India	cross-sectional	150	38^{mean}	0	Abnormal sleep duration, night-shift work	①
Strausz et al., 2021	Finland	cohort	445	53^{mean}	37	OSA	②
Swanson et al., 2023	USA	cross-sectional	750	39^{mean}	8	Night-shift work	①
Tessitore et al., 2021	Switzerland	cohort	839	67^{median}	54	OSA	③
Vargas et al., 2023	USA	cohort	2974	47^{mean}	19	Insomnia	①
Voncken et al., 2022	Netherlands	cohort	1884	69^{mean}	57	OSA	①③
Wang et al., 2020	China	cohort	118	31^{mean}	36	Night-shift work	①
Wang et al., 2023(1)	USA	cohort	1981	65^{mean}	0	Abnormal sleep duration	④

(Table 1 continues on next page)

Study	Region	Study design	Sample size	Age (years)	Males (%)	Type of sleep disturbances	Outcomes
(Continued from previous page)							
Wang et al., 2023(2)	USA	cohort	1979	65^{mean}	0	Evening chronotype, insomnia, daytime dysfunction	④
Xue et al., 2023	Multinational	cross-sectional	5918	45^{mean}	37	Abnormal sleep duration	④

Abbreviation: OSA, obstructive sleep apnea. ①susceptibility, ②hospitalization, ③ mortality, ④ long COVID.

Table 1: **Basic characteristics of included studies.**

in both groups (3-month: 1.75, 1.71–1.80 vs. 1-month: 1.12, 1.08–1.16; P < 0.001) (Figure S6). These results suggested that OSA was a risk factor for susceptibility to long COVID, but the results should be interpreted with caution.

Publication bias, quality control and sensitivity analysis

Asymmetric funnel plots had been observed in studies on COVID-19 susceptibility (P = 0.007), hospitalization (P = 0.033), and mortality (P = 0.008), indicating potential risks of publication bias (Figures S1.9, S2.9, and S3.9). In studies on COVID-19 susceptibility and hospitalization, the results from the trim-and-fill method indicated that the asymmetry in the funnel plot was more likely to be introduced by other reasons, such as poor study quality and selection bias (Figures S1.11 and S2.11), instead of publication bias (Table S2). In terms of COVID-19 mortality, there was a suggestion of publication bias (Table S2), which might lead to the asymmetry in the funnel plot. No evidence for publication bias was detected for long COVID (P = 0.364) (Figure S4.10). Three subgroups representing good quality (cohort study, adjusted ORs, and NOS ≥ 7) illustrated that the associations between pre-existing sleep disturbances and the four outcomes were consistent with the main analyses (Fig. 2). In addition, the results of leave-one-out sensitivity analyses

Sleep disturbances	Sample size	Number	OR (95% CI)	I^2(%)
COVID-19 susceptibility				
Any sleep disturbances	6,297,547	40	**1.12 (1.07–1.18)**	84.6
OSA	5,079,484	6	**1.64 (1.28–2.10)**	90.7
Abnormal sleep duration	203,434	8	**1.07 (1.02–1.13)**	17.9
Insomnia	547,436	6	0.98 (0.96–1.00)	0
Night-shift work	195,052	9	**1.49 (1.13–1.96)**	74.7
Other sleep disturbances	272,141	11	**1.09 (1.12–1.16)**	77.5
COVID-19 hospitalization				
Any sleep disturbances	5,563,585	21	**1.25 (1.15–1.36)**	71.7
OSA	4,968,274	8	1.49 (1.23–1.80)	57.2
Abnormal sleep duration	171,004	4	**1.20 (1.09–1.33)**	0
Insomnia	151,078	3	1.08 (1.00–1.17)	0
Night-shift work	7141	1	**5.66 (1.89–16.95)**	NA
Other sleep disturbances	266,088	5	**1.17 (1.06–1.30)**	56.3
COVID-19 mortality				
Any sleep disturbances	5,573,370	18	**1.45 (1.19–1.78)**	55.5
OSA	5,054,223	14	**1.52 (1.20–1.94)**	64.7
Insomnia	572	1	1.64 (0.75–3.57)	NA
Other sleep disturbances	518,575	3	1.16 (0.79–1.72)	0
Long COVID				
Any sleep disturbances	2,285,227	20	**1.36 (1.17–1.57)**	96.5
OSA	2,225,324	4	1.25 (0.90–1.74)	99.3
Abnormal sleep duration	128,215	7	**1.25 (1.05–1.47)**	66.5
Insomnia	5717	3	**1.17 (1.06–1.30)**	0
Night-shift work	7141	1	1.08 (0.43–2.70)	NA
Other sleep disturbances	18,830	5	**1.92 (1.24–2.97)**	94.9

Abbreviation: OSA, obstructive sleep apnea. Bold means that the result was statistically significant (P < 0.05).

Table 2: **Subgroup analysis of odds ratios across specific types of sleep disturbances.**

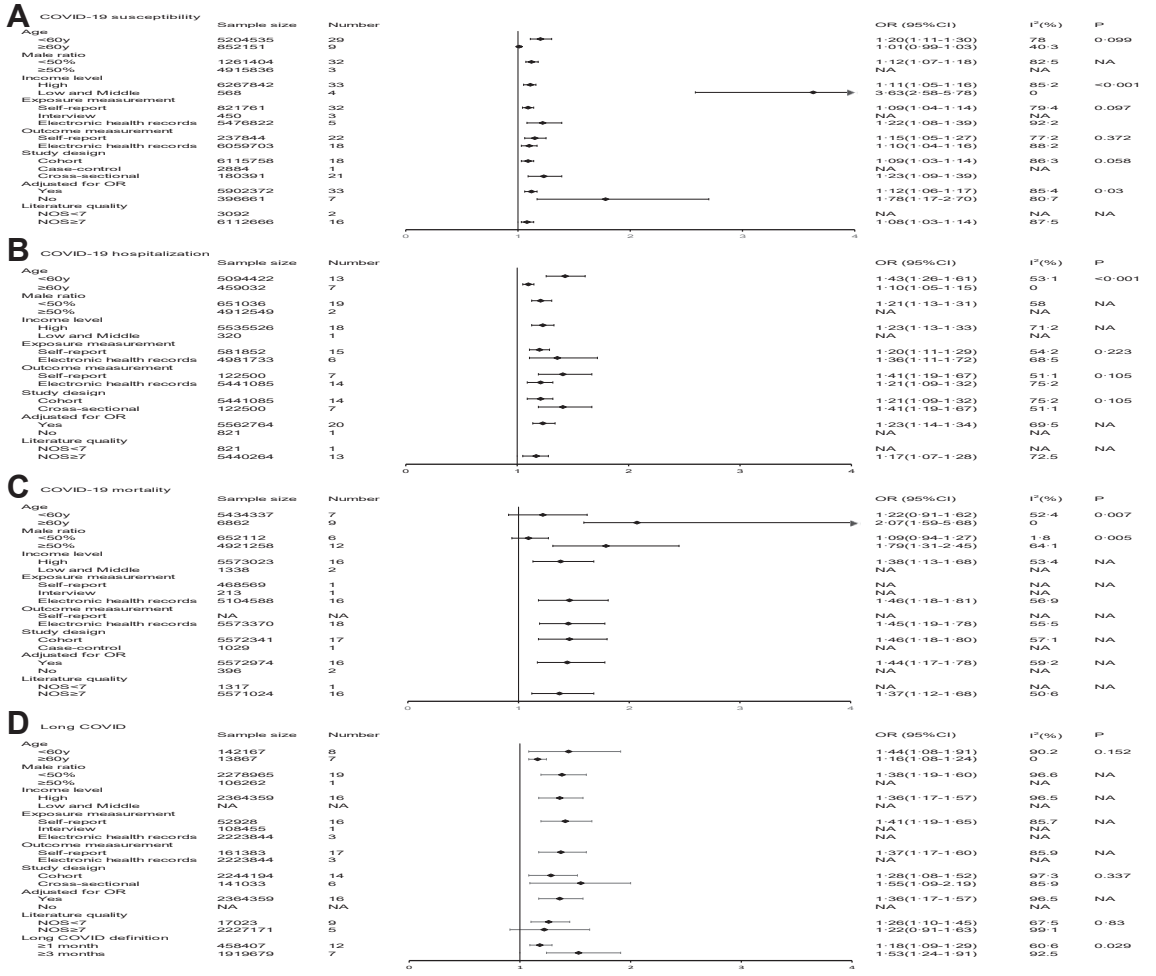

Fig. 2: **Forest plot that demonstrates the association of pre-existing sleep disturbances with four types of outcomes**. Abbreviation: NOS, Newcastle–Ottawa Scale.

(Figures S1.12, S2.12, S3.12, and S4.11) and those removing specific population sensitivity analyses (Table 3) were consistent with the main analyses, confirming the robustness of our results.

Discussion

Compared with previous studies that only focused on OSA, our study enrolled different kinds of sleep disturbances and systematically demonstrated the relationship between pre-existing sleep disturbances and COVID-19, especially long COVID. Our results indicated that pre-existing sleep disturbances increased the risk of COVID-19 susceptibility, hospitalization, mortality, and long COVID. Subgroup analysis showed that younger individuals with sleep disturbances were associated with a higher risk of COVID-19 susceptibility and hospitalization and a lower risk of mortality than older individuals. Males with sleep disturbances were associated with higher risks of COVID-19 mortality than females. We further investigated specific types of sleep disturbances and found that various sleep disturbances had different influences. OSA played a vital role not only in the whole clinical course of COVID-19 but also in the long COVID. Abnormal sleep duration elevated the risk of COVID-19 susceptibility, hospitalization, and long COVID. Insomnia escalated the risk of long COVID. Night-shift work increased the risk of COVID-19 susceptibility and hospitalization. These findings urge the general population and healthcare workers to conduct early evaluation and intervention for individuals with sleep disturbances to mitigate the short- and long-term effects of COVID-19.

Insomnia and sleep-related breathing disorders are the top two types of sleep disorders. Their common manifestation is insufficient sleep duration. We observed that pre-existing sleep disturbances increased the risk of COVID-19 susceptibility, hospitalization,

Components	Sample size	Number	OR (95% CI)	I^2 (%)
COVID-19 susceptibility				
Main analysis	6,297,547	40	1.12 (1.07–1.18)	84.6
Women studies removal	6,298,583	37	1.11 (1.06–1.16)	84.3
Health worker proportion >50% studies removal	6,268,780	33	1.11 (1.06–1.16)	85.2
All the biased studies removal	6,268,780	33	1.11 (1.06–1.16)	85.2
COVID-19 mortality				
Main analysis	5,573,370	18	1.45 (1.19–1.78)	55.5
Diabetes study removal	5,572,053	17	1.37 (1.33–1.66)	49.0
Long COVID				
Main analysis	2,285,227	20	1.38 (1.19–1.60)	96.6
Children studies removal	2,278,965	19	1.36 (1.18–1.57)	95.9
Women studies removal	2,371,366	13	1.40 (1.24–1.81)	97.6
All the biased studies removal	2,265,104	12	1.55 (1.27–1.90)	97.7

Table 3: **Sensitivity analysis by removing biased studies.**

mortality, and long COVID. One study administered nasal drops containing rhinovirus to 164 healthy adults and found that those with shorter sleep duration were more vulnerable to viral infection than those who slept for over 7 h.[11] Lin et al.[12] illustrated that patients with insufficient sleep had a longer duration of virus shedding than those who slept over 6 h. A 72-h sleep deprivation experiment showed that natural killer cells continuously declined with prolonged sleep deprivation.[13] Bollinger et al.[14] investigated serum T cell levels of seven healthy young men during normal sleep and sleep deprivation, and observed that sleep deprivation significantly inhibited CD4(+) and CD25(–) T cell proliferation. In addition, persistent sleep deprivation could promote the accumulation of pro-inflammatory cytokines and chemokines[15] and manifest as elevated C-reactive protein (CRP) and interleukin-6 (IL-6) levels,[16] which were also the hallmarks of severe COVID-19. Overall, the compromised innate and adaptive immune functions combined with a persistent inflammatory state may explain the higher risk of susceptibility, severity, and longer recovery time observed in patients with sleep disturbances. Fortunately, early intervention for sleep disturbances could attenuate the adverse effects of COVID-19. Clinical evidence has shown that patients with melatonin administration, a drug for improving sleep efficiency, significantly reduced the severity and shortened recovery time of COVID-19.[17] Genzor et al.[18] recruited 273 patients with OSA and found that patients with sufficient continuous positive airway pressure adherence, defined as more than 4 h per night over the past ten years, experienced a less severe course of COVID-19 compared with non-users, although the adherent group had more severe OSA at the baseline. The above studies highlighted the importance of early screening and targeted interventions for sleep disturbances.

The effect of pre-existing sleep disturbances on COVID-19 varies at different ages. We found that young individuals with pre-existing sleep disturbances had a higher susceptibility and hospitalization for COVID-19 than those without. This finding further confirmed the compromised immune function induced by sleep disturbances. Hence, early detection of sleep disturbances was crucial in young populations. In old individuals, those with pre-existing sleep disturbances elevated the hospitalization and mortality of COVID-19 but did not increase the susceptibility compared with those without. Zheng et al.[19] compared the distribution of immune cell types between old and young in healthy groups and patients with COVID-19. They found that in healthy groups, aging promoted the transition of T cells from naïve and memory to extreme effector phenotypes such as effector, exhausted, cytotoxic, and regulatory cell subsets and increased inflammatory monocytes. In addition, old individuals are usually associated with various pre-existing comorbidities such as chronic obstructive pulmonary disease, diabetes, cardiovascular disease, and so on. These comorbidities make them predisposed to COVID-19. Therefore, the effect of age on susceptibility might be counteracted by other risk factors. Considering the poor prognosis in old patients with sleep disturbances, intervention should be initiated as soon as possible.

It is interesting that the effect of sleep disturbances on COVID-19 was different between males and females. Male patients with sleep disturbances had higher mortality of COVID-19. It could be explained from two aspects. Regarding the host factors, the humoral and cellular immune responses of females to the viral infection were stronger than those of males due to inherent immune response.[20] In a murine model of the 2009 H1N1 influenza virus infection, female mice showed higher serum IgG antibody titers and IgA antibody titers of bronchoalveolar lavage fluid and elicited more potent CD4+ T and CD8+ T cell activity compared with male mice.[21] Besides, sex-specific

expression of angiotensin-converting enzyme 2 (ACE-2), a receptor for SARS-CoV-2, may explain the increased severity reported in male patients with COVID-19. Viveiros et al.[22] explored the expression and activity of ACE-2 in different organs in both mice and humans. They observed that ACE-2 was higher in the kidneys, hearts, and lungs of males than that of females in different age groups. Data from the protein atlas database also demonstrated that both ACE-2 RNA and protein were highly expressed in the human testes.[23] All these results showed that ACE-2 expressed higher in males than females. In terms of environmental factors, males are more likely to have unhealthy lifestyles and comorbidities (smoking, cardiovascular disease, etc.), which predispose them to adverse COVID-19 outcomes.

Of note, our subgroup analysis showed that only OSA played an essential role in the whole clinical course of COVID-19. Previous meta-analyses demonstrated that OSA was linked to poor outcomes in patients with COVID-19 (intensive care unit admission, severity, mechanical ventilation and mortality),[4,5] which was consistent with our results. We further elaborated that the susceptibility to COVID-19 was increased in patients with OSA. However, its mechanism was unclear. A Mendelian randomization study showed no casual association between OSA and COVID-19, which meant that other factors instead of genetic influenced the susceptibility.[24] The main pathophysiological features of OSA were sleep fragmentation and nocturnal chronic intermittent hypoxia. As mentioned before, insufficient sleep duration induced by sleep fragmentation was associated with impaired immune function and promoted inflammatory response. In addition, chronic intermittent hypoxia was also a significant risk factor for COVID-19. Cubillos-Zapata et al.[25] reported that chronic intermittent hypoxia could reduce the CD8+ T-cell activation and cytotoxicity by upregulating the programmed death cell receptor and its ligand crosstalk. An in vivo mouse model showed that both intermittent hypoxia and sleep fragmentation reduced intra-tumoral CD8+ T-cell cytotoxicity.[26] The above pathophysiology of OSA may be responsible for the increased susceptibility to COVID-19.

At least 10% of patients with COVID-19 experienced persistent symptoms after infection.[1] Long COVID could involve multisystem and last for more than three years, imposing a huge threat to global health. To date, the mechanism of long COVID is unclear, and no intervention is proved to be effective in the prophylactic or therapeutic field. We found that patients with OSA were vulnerable to long COVID. Cortellini et al.[27] recruited 1339 survivors of COVID-19 to investigate the association between inflammatory biomarkers collected at diagnosis and long COVID. They suggested that elevated CRP levels and neutrophil-to-lymphocyte ratios were the predictors of long COVID. Schultheiß et al.[28] included 318 participants and found that high levels of IL-6, IL-1β, and tumor necrosis factor (TNF) increased the risk of long COVID, and this finding was verified in a validation cohort of 333 participants. It indicated that long COVID was linked to pro-inflammatory status. Coincidentally, OSA is a chronic low-grade inflammatory disease. A meta-analysis enrolled 51 studies and found that patients with OSA had higher serum levels of CRP, TNF-α, IL-6 and IL-8 than those without.[29] Chronic intermittent hypoxia could activate immune cellular pathways, such as nuclear factor-kappa B and toll-like receptor-4 to increase TNF-α, IL-6, and many other inflammatory mediators.[30] Therefore, we supposed that long COVID in patients with pre-existing OSA was caused by chronic inflammation. It is elusive whether continuous positive airway pressure could protect patients with OSA from long COVID, and future studies are needed.

To our knowledge, this is the first meta-analysis focusing on all sleep disturbances, rather than OSA alone, to illustrate the influence of pre-existing sleep disturbances on the entire clinical course of COVID-19. It emphasized that sleep disturbances, especially OSA significantly influenced COVID-19. These influences could be affected by age and gender. This study had some limitations. First, high heterogeneity was observed in all outcomes. We used random-effect models to alleviate the influence of high heterogeneity on the results. Second, owing to the outbreak of COVID-19, all included studies were observational. Thus, no causal relationships could be confirmed. We have performed three subgroup analyses representing good quality, and the results showed that the associations between pre-existing sleep disturbances and the four outcomes were consistent with the main analyses. Future randomized controlled trials are expected to investigate the prophylactic and therapeutic effects of timely sleep interventions on the susceptibility and severity of COVID-19.

In conclusion, sleep disturbances, especially OSA, significantly increased the risk of COVID-19 susceptibility, hospitalization, mortality and long COVID. These influences could be affected by age and gender. Early evaluation and prompt intervention for sleep disturbances are necessary to alleviate the short-term and long-term effects of COVID-19.

Contributors

Jiawei Zhou developed the concept, designed the study, conducted statistical analysis, interpreted data, and drafted the article. Xia Li, Ting Zhang, Ziyan Liu, and Peng Li provided the study selection, data extraction, and quality assessment. All authors had full access to all the data, and authors (Jiawei Zhou, Xia Li, Ting Zhang, Ziyan Liu, and Peng Li) have verified the underlying data. Na Yu and Wei Wang made equal contributions to manuscript revision and supervision and had final responsibility for the final decision. All authors helped to interpret data and revise the draft of the article. All authors read and approved the final article.

Data sharing statement

Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as Supplementary Information.

Declaration of interests
None.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102719.

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