Current Psychiatry Reports (2022) 24:635–643
https://doi.org/10.1007/s11920-022-01371-y

SLEEP DISORDERS (P GEHRMAN, SECTION EDITOR)

Sleep During the COVID-19 Pandemic

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Accepted: 25 August 2022 / Published online: 4 October 2022

Abstract
Purpose of Review We reviewed current evidence on the impact of coronavirus disease 2019 (COVID-19) pandemic on sleep of different populations.
Recent Findings Several studies demonstrated that sleep deprivation may cause immune system dysregulation, which deteriorates the course of COVID-19. The increased prevalence of sleep disorders among COVID-19 patients has been associated with more severe disease and worse clinical outcomes. Healthcare workers who were subjected to atypical workload and more nightshifts developed sleep disorders which associated with work-related errors and COVID-19 infection susceptibility. In general population, circadian misalignment and excessive stressors impaired sleep quality.
Summary Sleep dysfunction has been recorded due to the pandemic. It is essential to implement interventions in order to alleviate pandemic-related sleep disorders. Telemedicine, cognitive behavioral therapy, and sleep hygiene practices appear to be helpful. Psychotropic medication should be cautiously administered, while other pharmacological agents, such as melatonin, have shown promising results.

Keywords COVID-19 · Sleep · Patients · Healthcare workers · General population

Introduction

In December 2019, a new coronavirus, which causes respiratory infection in humans (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)), was reported in Wuhan, China [1]. The virus was spread worldwide, leading to the coronavirus disease 2019 (COVID-19). On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic, and until July 2022, over 547 million confirmed cases and over 6 million deaths have been reported worldwide [2, 3]. Due to the initial absence of vaccines and specific treatment, measures such as use of masks, social distancing, quarantine, and isolation were imposed to prevent virus transmission [4]. As a consequence, this public health issue had a serious impact on several daily life aspects.

Sleep is a vital physiological process, associated with essential functions, required for maintaining physical and mental health [5, 6]. Sleep plays an important role in homeostasis, immune system, cognitive function, neural plasticity, memory, energy maintenance, macromolecular biosynthesis, and metabolism regulation [7, 8], while sleep deprivation leads to impaired physical and mental performance and has been associated with obesity, diabetes, hypertension, and cardiovascular disease [9].

Previous studies have shown that COVID-19 has a negative impact on public mental health, as it is linked to fear, anxiety, depression, and sleep disorders [10•]. Sleep was affected by several factors during the pandemic such as isolation, stress, fear of infection, reduced physical activity,

This article is part of the Topical Collection on *Sleep Disorders*

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and exposure to daylight [5]. Moreover, sleep dysfunction was prevalent not only in the general population, but also in infected patients and healthcare workers [6]. The aim of this review is to make an overview about the link between sleep deprivation, immune system, and COVID-19 severity, to present the prevalence of sleep disorders in different populations during the pandemic (i.e., patients with COVID-19, healthcare professionals, and general population) and to summarize the risk factors and the management options to alleviate sleep disorders in these populations.

Sleep Disorders in COVID-19 Patients

Prevalence

Numerous studies were conducted during the pandemic, focusing on sleep disorders in COVID-19 patients. The prevalence of sleep disorders was found to range between 34 and 82% [6, 10•, 11, 12••, 13–16]. In a recent systematic review with meta-analysis, which included 250 studies from 49 countries, patients with COVID-19 were the most affected, with a pooled estimated prevalence of sleep problems at 52.39% [12••]. In another meta-analysis, which included studies solely from China, the prevalence of insomnia in COVID-19 patients was 48.7% [11]. It was also exhibited that patients with COVID-19 or other chronic medical problems had higher risk to develop insomnia [11]. In a large-scale meta-analysis, Dragioti et al. demonstrated that disturbed sleep was one of the most frequent mental health issues in COVID-19 patients, with a prevalence of 63% [13]. On the other hand, another meta-analysis reported lower prevalence of sleep disturbances, with only 34% of patients with SARS-CoV-2 exhibiting sleep disorders [15]. Concerning symptom severity, it was mild in 20%, moderate in 16%, and severe in only 2% [15]. As of gender, Alimoradi et al. found that the prevalence of sleep problems was 39% in male and 51% in female patients [14]. It was assumed that this difference could be attributed to the different brain structures and functions among sexes, as it was demonstrated in previous studies [14]. The highest prevalence of sleep disturbance in COVID-19 patients was reported in the meta-analysis of Krishnamoorthy et al., who found poor sleep quality in the 82% of these patients [10•]. An overview of available meta-analyses, referring to sleep disorders in COVID-19 patients, is presented in Table 1.

Table 1 Prevalence of sleep disorders in COVID-19 patients across meta-analysis

Study	Sample	Assessment tools	Pooled prevalence	Limitations
Li et al. [11]	6 studies, 1780 patients	• ISI • PSQI • ASI • SRSS	48.7% (95% CI 21.6–75.8%, $I^2=99.5\%$)	• High heterogeneity • Studies only from China
Jahrami et al. [12••]	16 studies, 6821 patients	• ISI • PSQI • ASI • Research developed	52.39% [41.69; 62.88%], $I^2=98.10\%$	• High heterogeneity
Dragioti et al. [13]	15 studies	• ISI	63% [95% CI 23–94%]	• Focusing on general mental health impact • Heterogeneity not applicable
Alimoradi et al. [14]	7 studies	• ISI • PSQI	Males: 39% [95% CI 27–50%, $I^2=97.58\%$] Females: 51% [95% CI 42–60%, $I^2=99.43\%$]	• High heterogeneity
Jahrami et al. [6]	3 studies, 1884 patients	• ISI • PSQI • ASI • Research developed	74.8% [95% CI, 28.7–95.6%, $I^2=96\%$]	• High heterogeneity • Sleep disorders not the primary focus in some studies
Deng et al. [15]	10 studies, 1795 patients	• ISI • PSQI • Research developed • Clinical interview	34% [95% CI: 19–50%, $I^2=98\%$]	•High heterogeneity • Most studies from China
Alimoradi et al. [16]	10 studies	• ISI • PSQI • Others not referred	57% [95% CI: 42–72%, $I^2=98.5$]	• High heterogeneity • Most studies cross-sectional

ISI Insomnia Severity Index, *PSQI* Pittsburgh Sleep Quality Index (PSQI), *ASI* Athens Insomnia Scale, *SRSS* Self-Rating Scale of Sleep

Pathophysiology and Risk Factors

The new coronavirus leads to sleep disruption either directly, by infecting the central nervous system (CNS), or indirectly, through COVID-19 provoked cytokine storm [5]. More specifically, coronavirus can enter CNS through nasal mucosa and olfactory pathway or through blood–brain barrier, by infecting the endothelium and the leucocytes [17]. By using ACE-2 receptors, the virus can invade in cerebral structures, including brainstem and hypothalamus, resulting in dysregulation of sleep–wake cycle [17, 18]. In addition, COVID-19 triggers extensive inflammatory response and cytokine storm, that increases blood–brain barrier accessibility and induces immunologic tissue insult, neuropsychiatric symptoms, and sleep disorders [5, 17].

Other factors resulting in sleep disorders in COVID-19 patients are related to symptoms and psychological impact caused by the infection, as well as to social changes provoked by the pandemic. COVID-19 patients experience intense stress related to uncertainty on the course of the illness, fear of adverse outcome, and isolation from loved ones [5, 10•]. In addition, they have to be confined in isolation wards or in their home, facing, sometimes, discrimination, and social stigma [5, 10•]. Anxiety and depression, due to the above circumstances, are strongly associated with sleep disturbance [5]. The core symptoms of COVID-19, i.e., cough, fever, pain, and dyspnea, have, also, negative impact on sleep quality [11]. Moreover, hospitalization could further impair sleep quality due to noise, exposure to lights, alerted sleep routine, clinical interventions, and medication's side effects [12••, 19]. A summary of the factors relating to sleep disorders in COVID-19 patients are presented in Fig. 1.

Sleep and Immune Response to COVID-19

As mentioned above, sleep plays an essential role in physical and mental health. Sleep is an important regulating factor of immune system [20], while, by influencing the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, mediates in the circadian expression of cells, including cells of the innate and adaptive immune system [21–23]. Therefore, sleep deprivation could modify this function, inducing immunosuppression [24]. In particular, sleep deprivation leads to

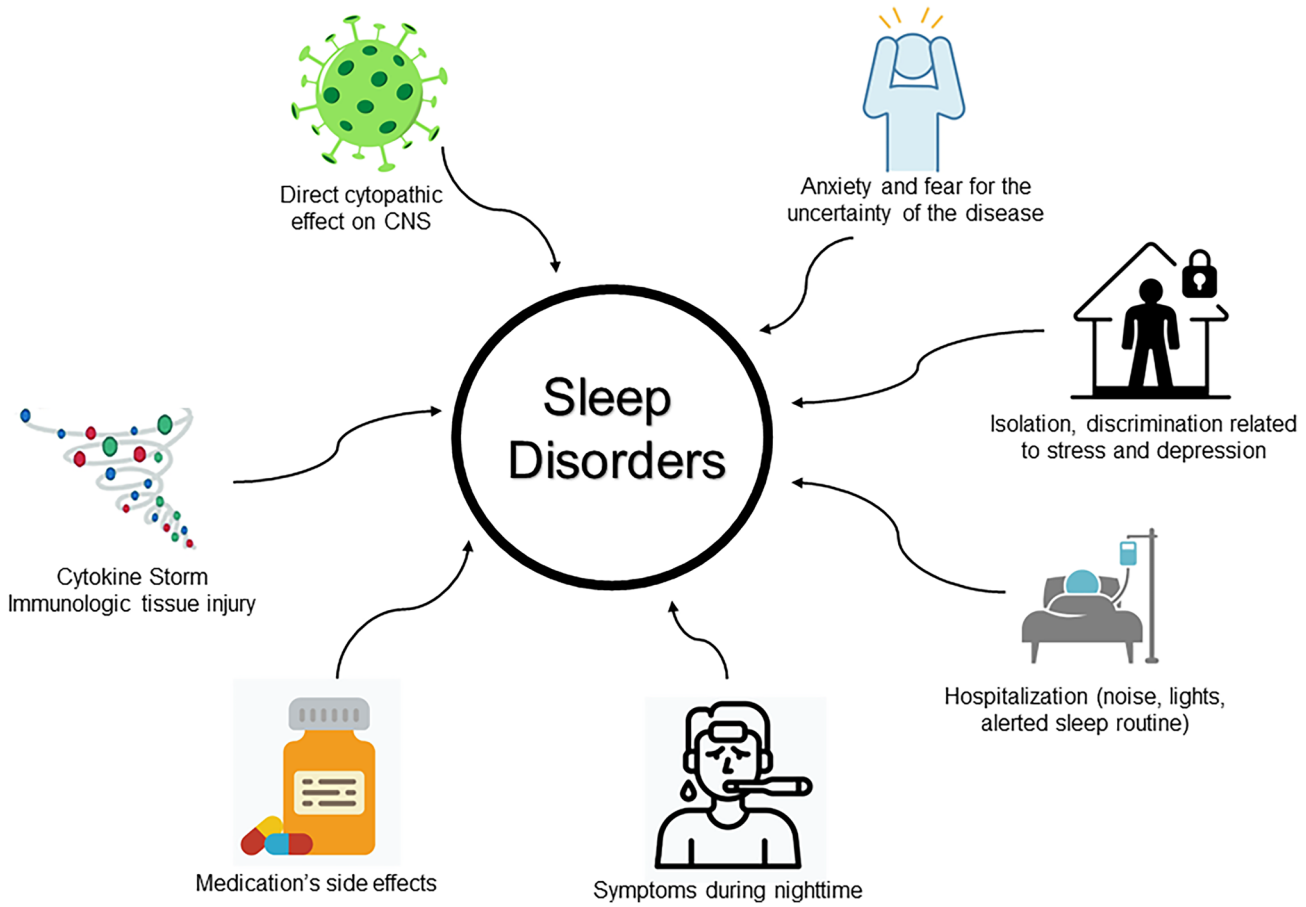

Fig. 1 Factors resulting to sleep disorders in patients with COVID-19

increased production of pre-inflammatory cytokines; increased activity of CD4+and CD8+lymphocytes; decreased activity of natural killer cells of CD16+, CD56+, and CD57+cells; and decreased levels of interleukin-2 [21, 22]. Moreover, chronic insomnia has been associated with alteration in Th1 and Th2 immune balance, favoring Th2 activity [21, 22]. Thus, it is not unreasonable to assume that these alterations in immune system predispose to susceptibility in infections, including COVID-19.

Several studies have demonstrated a relationship between lack of sleep in COVID-19 patients and worse clinical outcomes. Zhang et al. found that poor sleep quality in infected patients was associated with increased neutrophil-to-lymphocyte ratio (NLR), lower recovery from lymphopenia, longer hospitalization, and higher risk of ICU admission [25•]. Li et al. exhibited that NLR was increased in patients with poor sleep quality and sleep deprivation was positively correlated with virus negative conversion time [26]. In a prospective cohort study, poor sleep quality in COVID-19 patients was significantly associated with prolonged hospitalization, major dysregulation of immune system, indicated by several biomarkers, and increased risk of developing severe or critical pneumonia [27••]. Similar results were demonstrated by Akinci et al. and Jiang et al.; patients with poor sleep quality had longer hospitalization and more severe symptoms [28, 29]. Furthermore, Jones et al. conducted a longitudinal cohort study and found that insomnia predispose to COVID-19 infection and high risk of hospitalization [30].

Post-COVID-19 and Sleep Disorders

Post-COVID-19 condition (or long COVID-19) was defined by WHO as a set of symptoms that emerged during or after SARS-CoV-2 infection, persists more than 2 months and cannot be explained by another diagnosis [31]. The new coronavirus may cause persistent physical and mental deficits, affecting the quality of sleep [5]. Despite the fact that the most common symptom in long COVID-19 is fatigue, a high prevalence of sleep disorders has been described in numerous studies [19]. In several systematic reviews and meta-analyses, sleep disturbance in post-COVID-19 patients ranged between 27.4 and 47% [32–39]. Premraj et al. found that the prevalence of insomnia increased from mid- to long-term follow-up, assuming that sleep deprivation is more likely to develop rather than persist after the infection [38••]. Malik et al. suggested that increased stress levels, psychological problems, and increased cough reflex sensitivity are accountable factors for disturbed sleep in post-COVID-19 period, while Badenoch et al. assumed that persisting symptoms may result due to direct tissue injury caused by the virus [35, 37]. Future studies are necessary to further delineate these complex interactions for the benefit of post-COVID-19 patients.

Types of Sleep Disorders

Regarding sleep disorders during COVID-19 pandemic, the majority of studies focused on insomnia [10•, 11, 12••, 14]. However, multiple types of sleep disorders, such as narcolepsy, restless leg syndrome (RLS), parasomnias, and nightmares have also constituted a health problem in this period [40]. To the best of our knowledge, little evidence exists on individual sleep disorders in COVID-19 patients. Narcolepsy, characterized by excessive daytime sleepiness and rapid eye movement (REM)-sleep associated symptoms (i.e., sleep paralysis and cataplexy), derives from the interaction of genetic and triggering environmental factors which dysregulate neurons in hypothalamus [41]. Since the virus can affect neurons in the hypothalamus, it is reasonable to hypothesize that COVID-19 may act as a triggering factor leading to narcolepsy [41]. With regard to RLS, in a cross-sectional study, the prevalence of RLS was higher in long COVID-19 female patients compared to uninfected females, indicating that post-infection immunological processes predispose to this situation [42]. Furthermore, Liu et al. demonstrated that COVID-19 patients had higher prevalence of dream-enactment behaviors (DEB) and DEB was positively associated with COVID-19 severity, concluding that more studies are needed to shed light on potential neurodegenerative role of COVID-19 [43].

Obstructive sleep apnea (OSA) is the most prevalent sleep-related breathing disorder [44]. Numerous studies have shown an association between OSA and worse COVID-19 outcomes, while others did not confirm this correlation [45–48]. However, Hariyanto et al. conducted a meta-analysis of 21 studies and found that OSA is associated with poor COVID-19 outcomes and, more specifically, with ICU admission, mechanical ventilation, and mortality [49••]. This association could be explained by several factors. First of all, patients with OSA may have a number of comorbidities, such as obesity, hypertension, diabetes, and cardiovascular disease, which are strongly related with worse clinical outcome in COVID-19 patients and could act as confounding factors [44]. However, apart from that, OSA leads to sleep deprivation, due to frequent awakenings during sleep, resulting in dysregulation of immune system and vulnerability to COVID-19 infection, as analyzed before [49]. Moreover, hypoxia provoked by OSA may further deteriorate the hypoxia caused by COVID-19 and increase the risk of more severe disease [49••]. Finally, disruption of renin-angiotensin system (RAS), with increased activity of angiotensin-converting enzyme (ACE) and increased levels of angiotensin II, was observed in OSA patients. Since the virus uses angiotensin-converting enzyme 2 to invade into host cells, it is not unreasonable to assume that the dysregulation of RAS in OSA may predispose to more severe COVID-19 infection [49••].

Management of Sleep Disorders in COVID-19 Patients

Given that sleep deprivation has been associated with psychological distress and poor COVID-19 outcomes, there is a need for implementation of appropriate management strategies and interventions [44]. Concerning hospitalized patients, it is important to provide sufficient psychological and emotional support, to improve the ward environment (i.e., by reducing noise and light, and ensuring patient's privacy) and to adopt measures in order to reduce physical discomfort, such as adequate analgesia and proper sedation [25•]. Psychotropic medication should be cautiously administered, and healthcare professionals should take into account any potential interactions with the drugs used in COVID-19 treatment [50]. Melatonin and melatonin agonist receptor, ramelteon, have been used in ICU patients and have shown to improve sleep, decrease delirium, and possibly even alleviate respiratory failure [51]. Due to its safety, melatonin may replace, when feasible, other medications such as benzodiazepines and antipsychotics, that may exaggerate delirium and cause central respiratory depression [51]. Further studies are needed to clarify the impact of melatonin in COVID-19 patients.

Cognitive behavioral therapy (CBT) is the gold standard for the treatment of insomnia, according to the European Sleep Research Society and the American Academy of Sleep Medicine guidelines [44]. In cases of home-quarantined COVID-19 patients during the pandemic, CBT can be implemented via telemedicine (using telephone and videoconferencing) [44]. Other non-pharmacologic measures, such as progressive muscular relaxation, have also been shown to be effective in alleviating insomnia [44]. Moreover, it seems to be essential for COVID-19 patients to keep a regular wake-up time and nighttime schedule in order to regulate their circadian rhythm [52••].

In addition to that, COVID-19 patients with suggesting clinical features should be screened for OSA, as OSA has been linked to more severe COVID-19 infection [44]. Telemedicine may be useful for the evaluation, diagnosis, and follow-up of these patients. Home sleep testing may be preferable and treatment with positive airway pressure (PAP) could be applied and evaluated via telemonitoring [44]. When urgent evaluation of a patient with laboratory polysomnography is needed, medical stuff should use all the appropriate personal protective measures and disinfect carefully all the equipment used, according to current guidelines [44].

Sleep Disorders in Healthcare Professionals During COVID-19 Pandemic

Based on previous experience from SARS and Ebola epidemics, an unexpected and life-threatening disease could provoke excessive pressure and stress in healthcare workers (HCWs) [53]. Due to the nature of their work, HCWs were placed in the center of the pandemic, confronted with the effects of the virus and managed heavy workloads; thus, their physical and mental well-being was negatively affected [54•]. Existing evidence suggests that the prevalence of psychological morbidity in HCWs during COVID-19 pandemic is higher than that of previous epidemics [55].

Several studies investigated the effect of COVID-19 pandemic in sleep quality of HCWs. The prevalence of sleep disorders ranged between 23.1 and 64.3% [56••]. In a recent umbrella review of 26 meta-analyses, the prevalence of sleep disorders in hospital staff during the pandemic was 39.45% [56••]. The authors also demonstrated that nurses suffered more from sleep problems/insomnia compared to doctors, probably because of different responsibilities, tasks, and working hours [56••]. On the other hand, Salari et al., in their meta-analysis, found that sleep disorders are greater in physicians compared to nurses [57]. Numerous studies suggested that, irrespective of their profession, frontline HCWs were more prone to develop sleep disorders due to close contact with patients, anxiety, fear, and exhaustion [56••, 58–60].

Assorted causes are implicated in the development of sleep disorders in HCWs. First of all, HCWs are subjected to heavy workload, unusual work schedules, and more night shifts because of the increased requirements in hospitals during the pandemic [61]. Moreover, they have to change their lifestyle routine and minimize daytime activity [54•]. As a consequence, these alterations may dysregulate circadian rhythm leading to sleep disorders [22]. Furthermore, they frequently face changes in hospital role and work team, factors that may cause uncertainty and anxiety [54•]. In addition, HCWs in COVID-19 wards and ICUs are exposed to stress factors such as patients' fears and expectations, high fatality rates, shortages of personal protective equipment, and fear of being infected [54•, 62]. Moreover, they are isolated from their loved ones as they worry not to spread the virus [62]. Stress, provoked by those factors, may disrupt hypothalamic-pituitary adrenal axis and autonomic nervous system and, thus, result in sleep disturbance [63].

Sleep deprivation in HCWs not only affects negatively their work performance but also their well-being. Lack of sleep has been associated with work-related errors and lower quality of care [62, 64]. Additionally, shift workers are more susceptible in developing both mental and physical diseases. More specifically, insufficient sleep has been related with higher risk of cardiovascular disease, obesity, stroke, gastrointestinal disorders, anxiety, loss of interest, and depression [64]. Concerning COVID-19, shift workers are more vulnerable to respiratory infections, including SARS-CoV-2, and probably to more severe course of disease [65].

Therefore, it is crucial to adopt appropriate interventions to confront sleep problems among HCWs in order to prevent physical and mental disorders and improve their resilience. Supportive measures include the development of a suitable work environment by reducing shifts, hiring new staff, providing adequate protective personal equipment, and improving team cohesion [54•, 63]. HCWs should have access to mental health professionals and be encouraged to express their feelings and their fears [63]. Other practical recommendations encompass relaxing by reading, exercising, taking naps, setting a sleep-friendly environment, and following a regular sleep routine when it is feasible [54•, 64].

Sleep Disorders in General Population During COVID-19 Pandemic

Apart from COVID-19 patients and HCWs, the pandemic has also affected the general population. COVID-19-related sleep dysfunction has been established in many scientific papers. In a recent global meta-analysis, the prevalence of sleep disorders in general population was 36.73% [12••]. Similar results were also published in previous meta-analyses [10•, 13, 16]. However, other studies found lower prevalence of sleep disorders, ranging between 26 and 29% [11, 14•, 66]. The heterogeneity in the results could be explained by the different tools which were used to assess sleep across the studies, as the majority of them used self-reported data. Conflicting results have been reported when comparing sleep habits before and during the pandemic. More specifically, some studies demonstrated that sleep duration remained constant, while others reported increased sleep time due to changes in daily and working routine [67–70]. The flexibility in work time and the work-from-home may provide the opportunity for longer sleep duration. However, negative emotions and stress may affect other sleep characteristics (i.e., awakenings during the night and frequent nightmares) impairing the overall sleep quality [67]. Wang et al., found an increase in sleep duration (with delayed bed and wake times) and a decrease in sleep quality during the pandemic, by using wrist actigraphy and self-reported data [71].

As far as other sleep characteristics, Vladutu et al. demonstrated that, among 328 university students, the prevalence of sleep bruxism was 16.28%, and it was significantly associated with COVID-related stress, while Winocur-Arias et al. found that sleep bruxism was more prevalent exclusively in women during the pandemic [72, 73]. In addition to that, oneiric activity was also modified during the pandemic. Higher frequency of nightmares and increased dream recall were observed, a fact that was related with parasomnia [74, 75]. Dream content also changed, becoming more negative (i.e., dreaming about diseases, war, and death) [74]. Gorgoni et al. reported that dream frequency, vividness, bizarreness, lucid dreams, and emotional load reduced after lockdown [76].

Circadian misalignment, developed during the pandemic, could explain the aforementioned sleep disturbances. Lockdown and atypical work/school schedules resulted in reduced sunlight exposure and daily physical activity [52••, 77]. Additionally, increased screen time (i.e., increased use of smartphones and social media) has been shown to impair the secretion of melatonin [77]. The flexibility of work/school schedule could allow individuals to sleep more in synchrony with their circadian tendency, promoting greater circadian alignment. However, as mentioned above, literature suggests the opposite. This could be explained by the fact that many people with fixed daily schedule before the pandemic developed a stable sleep schedule and sleep habits, something that promoted circadian alignment. On the other hand, the greater flexibility during the pandemic disrupted their sleep schedule, promoting circadian misalignment. Therefore, their circadian rhythm might have been disrupted, leading to sleep disorders [52••, 77]. Furthermore, people were extensively exposed to stressful situations during the pandemic. Fear of being infected, lack of knowledge about the disease, misinformation, and rumors generated increased worry and stress [10•]. Moreover, isolation and separation from loved ones, restrictions, and uncertainty about employment and financial state resulted in excessive anxiety [10•]. These factors reflect the psychological sphere and might deteriorate sleep quality.

The optimal strategy for treating COVID-related sleep disorders remains unclear. CBT is the gold standard in the case of insomnia, and during a lockdown, it could be implemented via telemedicine [44]. Furthermore, it seems essential to adopt sleep hygiene practices. Following a regular sleep program, exercising enough, subjecting to light during daytime, minimizing screen time, and avoiding caffeine and other stimulants may improve sleep quality [77].

Conclusions

COVID-19 pandemic has increased the prevalence of sleep disorders in different populations. Sleep problems appear to be considerably common in COVID-19 patients and have been associated with more severe disease and poor clinical outcome. HCWs, subjected to heavy workload and night-shifts, also suffer from sleep disturbances, provide lower quality of care, and are more susceptible to infection and physical disorders. General population was also affected in terms of sleep quality, being exposed to many stressors. Effective interventions and measures should be implemented in order to improve sleep quality and reduce the mental and physical consequences from its disturbance. Further studies are needed to provide high-quality information on the effectiveness of the implemented interventions.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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