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REVIEW

Sleep Disturbance and Immunological Consequences of COVID-19

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Abstract: The overarching importance of sleep was further emphasized during the pandemic of COVID-19. The subjects infected by COVID-19 frequently experience sleep disturbances; some are long-lasting problems and decrease the quality of life. Insomnia is the most studied sleep disorder associated with COVID-19. Insomnia affects patients who have experienced an infection and the general population. Good sleep is important in maintaining mental and physical health, including immune system functions. The interconnections between insomnia, the immune system, and COVID-19 are complex. Insomnia triggers numerous immune system dysregulations and makes individuals more vulnerable to respiratory infections. This narrative review overviews the influence of the COVID-19 pandemic on the immune system through sleep disorders.

Keywords: insomnia, COVID-19, circadian rhythms, immunity, sleep deprivation, mental disorders

Introduction

The illness caused by the SARS-CoV-2 virus has become a pandemic disturbing the health and mental well-being of the entire population. In addition to the somatic, economic, and social consequences, this pandemic's psychological effects are increasingly reported in the professional literature.[1–3] Current research findings indicate that individuals affected by COVID-19 may be more likely to experience mental health issues. Possible psychological problems include depression, anxiety disorders (eg, panic attacks), excessive irritability, increased impulsivity, somatoform disorders, increased suicidality, and sleep disorders.[3–6]

Healthy sleep is important for many physiological processes. Besides affecting mood regulation and cognitive functions, sleep helps regulate the immune system.[7,8] There is pre-pandemic evidence that sleep disorders increase the risk of infectious diseases and the progression of many physical illnesses.[7] Sleep is essential in homeostasis, muscle recovery, energy metabolism, and neuroplasticity.[9] Good quality sleep positively affects well-being and mental health.[10]

Sleep disorders arise as a result of the malfunctioning of numerous regulatory mechanisms. Insomnia, the most common sleep-related problem, is defined as difficulty initiating, maintaining, and consolidating sleep or a poor overall sleep quality leading to a somatic and psychical impairment.[11–13] Depression and an extensive increase in anxiety are risk factors for insomnia.[14,15] Sleep deprivation also increases the risk of cerebrovascular accidents, obesity, diabetes mellitus, cancer, osteoporosis, and cardiovascular diseases.[16,17] Associated health problems (such as osteoarthritis) have been seen in various sleep disorders (eg., insomnia, restless legs syndrome, obstructive sleep apnea).[16,18] In the same way, lack of sleep can significantly negatively impact everyday behaviour and mental health.[3,19]

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The connection between COVID-19 infection and the psychosocial impact of the pandemic on sleep intrigued many researchers. Studies performed during the pandemic found sleep-related problems in many forms. There is an indication of a bidirectional relationship between COVID-19 and sleep.[20] Many patients experience insomnia during the infection and covid post-period.[21,22] Insomnia and lack of good quality sleep led to dysregulations in several immune functions.[23–29] It takes several days to restore normal immune system function even after short sleep deprivation. Sleep deprivation similarly leads to increased levels of stress and cortisol.[30] Surprisingly, even immune response after vaccination is decreased in sleep-deprived individuals.[31] Therefore, many patients may be infected due to sleep deprivation.[20] (Figure 1).

This review was designed to summarise the current knowledge of the complex interconnections between sleep, the immune system and the COVID-19 pandemic via an assessment of contemporary literature and scientific databases. We established the following hypotheses:

1. Does the covid-19 pandemic increase the prevalence of insomnia?
2. Is insomnia often sign in patients with post-COVID-19 syndrome?
3. Does the COVID-19 pandemic changed the circadian rhythm?
4. Can lack of sleep lead to an alteration of the immune system?
5. Is there a link between insomnia and changes in the immune system in COVID-19 patients?

Method

Articles for this narrative review were acquired via PubMed, Scopus, and Web of Science, with publishing dates between January 1990 and September 2022. The applied search terms were: insomnia, sleep disturbances, COVID-19, and immune system. The selected articles met the following inclusion criteria: (1) studies in humans; (2) published in peer-reviewed journals; (3) reviews on the related topic; (4) English language. The exclusion criteria were: (1) abstracts from conferences, (2) commentaries, and (3) subjects younger than 18 years. Also, additional works were chosen from the references of the primary articles. A total of 1292 articles were nominated by primary collection using the search terms in different combinations. After the assortment according to the inclusion and exclusion criteria, 186 articles were chosen. After a complete examination of the full texts, 43 papers were nominated. Secondary papers from the references of the

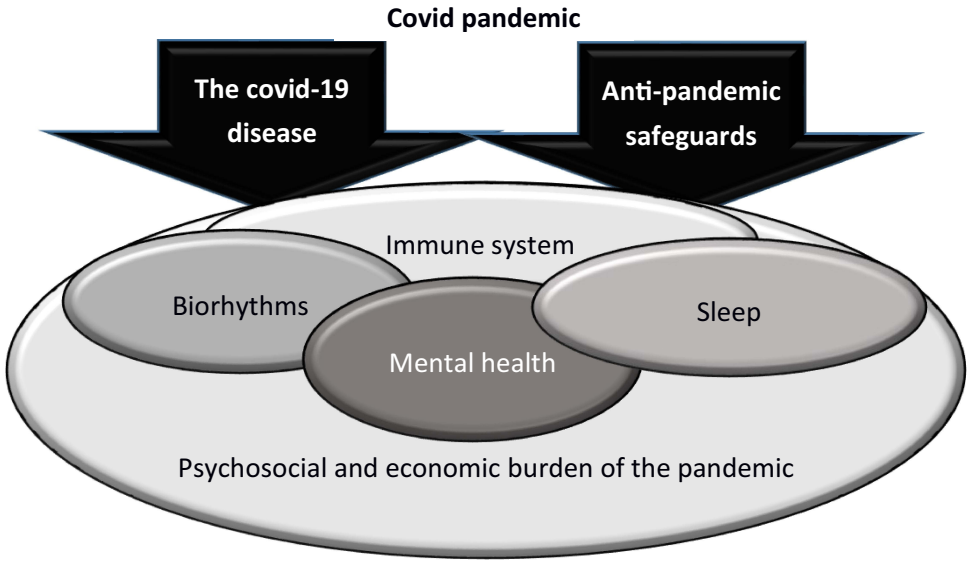

Figure 1 Diagram of the connections between the COVID-19 pandemic and its effects on sleep.
Notes: The connection between COVID-19 infection, anti-pandemic safeguards and sleep are mediated by many influences, such as immunity, biorhythms, and mental health. These factors interact with each other and with sleep.

primary papers were searched, assessed for suitability, and supplemented the list of the papers (n = 51). Ninety-three papers were included in the review process.

Results

This review article aims to summarize knowledge about the effect of the COVID-19 pandemic on sleep and map the effects of insomnia during this pandemic.

Does the COVID-19 Pandemic Increase the Prevalence of Insomnia?

The COVID-19 pandemic has affected numerous aspects of contemporary life, including sleep.[6,32] The measures that were supposed to prevent the spread of the pandemic disrupted most people's daily functioning, which indirectly affected their physiological processes.[5,12,33–35] Since the pandemic's beginning, the population has been exposed to various periods of social isolation with restrictions on going out.[36] During these periods, the lifestyles of most individuals have significantly changed, and some studies report additional consequences in the form of reduced sleep quality.[6,37,38] The underlying causes of sleep impairment include stress, increased exposure to artificial light (including nocturnal exposure to light-emitting diodes), and reduced exposure to sunlight during the day.[39,40]

Excessive worries about the course of the pandemic, the individual's or loved one's health, and financial aspects contribute to the deterioration of sleep.[8,42] The pandemic of other illnesses has also been connected with sleep problems. Adler et al focused on US soldiers quarantined in West Africa during the Ebola outbreak. Approximately one in three (specifically 29.8%) reported difficulty sleeping.[43] Deterioration of sleep quality during social contact restrictions adopted due to the COVID-19 pandemic should therefore be expected globally. Although it is difficult to measure the prevalence of insomnia under these circumstances, there is expected to be a great number of underreported cases.

The effects of the COVID-19 pandemic and related restrictions on sleep difficulties were also felt in the population. Table 1 summarizes recent meta-analyses dealing with the prevalence of insomnia during the pandemic in non-COVID patients. From the available results, we can conclude that insomnia or sleep problems are more common during the covid-19 pandemic.

In their study, Cellini et al[93] compared the sleep pattern and quality of sleep in patients during and before the lockdown. During the lockdown, sleep timing was significantly delayed, time spent in bed increased, and sleep quality

Table 1 Meta-Analyses Dealing with the Prevalence of Insomnia During COVID-19 Pandemic

Meta-Analysis	N of Studies	N of Patients	Insomnia/Sleep Disturbances Prevalence	Other Relevant Key Findings
AlRasheed et al[87]	48	133,006	52.6% (CI 47.4–57.7%)	Significant insomnia occurred only in 16.7% of subjects. The COVID-19 pandemic was associated with a significant rise in subthreshold insomnia symptoms but not moderate or severe insomnia.
Yuan et al[89]	283	948,882	29.7% (CI 24.4–34.9%)	Higher prevalence of insomnia symptoms in university students (58.4% with CI 28.1–88.6).
Cevik et al[90]	48	77,299 (pregnant women)	88.8% (CI 82.1–92.1%)	The COVID-19 pandemic increased insomnia.
Ahmadi et al[91]	33	573,665 (PTSD)	63% (CI: 45–78%)	The prevalence of insomnia in PTSD/PTSS was moderated by the type of trauma and the PTSD/PTSS assessment scale.
Alimoradi et al[42]	54	67,722	Females: 24% (CI 19–29%) Males: 27% (CI 24–30%)	Both gender groups had a higher prevalence of sleep problems during the lockdown period.

was markedly impaired. The most vulnerable individuals appeared to be women, subjects experiencing a more negative mood, and those perceiving the pandemic situation as highly stressful.[93]

Sleep disorders can be associated with various risk factors. During the pandemic, we encountered significant stress, which could be reflected in the quality of sleep in the general population. In Table 2, we include a short overview of some studies that specifically deal with risk factors. The results are not completely clear. One factor is probably age, the presence of another mental illness or some changes in leukocytes. A more detailed explanation of the risk factor and, thus, the correct treatment management should be the subject of further research.

Is Insomnia Often Sing in Patients with Post-COVID-19 Syndrome?

Scarpelli et al[41] explored the Pittsburgh Sleep Quality Index score (PSQI) in 139 studies involving post-COVID-19 patients. The insomnia severity index was reported in 50 studies with a pool mean of 8.4 (95% CI 7.5–9.3). A longer duration of severe restrictions and female gender were associated with poor sleep quality, according to PSQI.

An assessment of the emotional and psychological impact of the COVID-19 pandemic on the Chinese population during January and February 2020 demonstrated the effects produced by the spread of the illness on the mental health of individuals.[33] As the number of COVID-19 cases has increased, anxiety, stress, depression increased, and decreased sleep quality have also been noted.[12,32,44] Online psychosocial interventions may ameliorate this harmful effect, which has been especially useful during restrictions causing social isolation.[45]

The recent meta-analyses dealing with the prevalence of insomnia in post-COVID-19 patients are in Table 3.

As part of the association of sleep disorders with COVID-19, we must not forget the relatively widespread sleep and breathing disorders often associated with insomnia and depression.[46] These diseases (mainly obstructive sleep apnea-OSA) worsen with obesity, and changes in lifestyle during the pandemic also led to weight gain in many people.[47] Although there are no relevant studies tracking obesity in these cases during the pandemic, it can be assumed that weight gain led to the progression of sleep disordered breathing symptoms in patients with known (but also undiagnosed) OSA.[12] Nevertheless, we can confidently say that sleep quality worsened during the pandemic, not only in the general population but also in patients with severe OSA already treated with continuous positive airway pressure (CPAP).[48] OSA is one of the most common diseases of the respiratory tract. Hu et al,[94] in their meta-analyses (n=31,933), compared the association between OSA and COVID-19 infection. They demonstrated that OSA was independently associated with a significantly elevated risk for death among patients with COVID-19.[94] A similar finding was the results of a meta-analysis from Harivanto et al. The authors found that

Table 2 Studies Discussing Sleep Disorders During the COVID-19 Pandemic and Their Associated Risk Factors

Study	Design	General Population or COVID-19 Patients	Associated Risk Factors of Sleep Disorders
Pataka et al[96]	Review	COVID-19 patients	Duration of hospitalization, pre-existing mental health concerns, lower absolute lymphocyte count, and increased neutrophil-to-lymphocyte.
Alimoradi et al[97]	A systematic review and meta-analysis	Both	Anxiety and depression.
Cha et al[98]	Infodemiological study	General population	Age 60 and above.
Alshumrani et al[99]	Cross-sectional	Both	Male gender, young and middle aged, being a health worker and location of treatment.
Jahrami et al[86]	A systematic review and meta-analysis	Both	Being children and adolescents, and university students.

Table 3 Meta-Analyses Dealing with the Prevalence of Insomnia in Post-COVID-19 Patients

Meta-Analysis	N of Studies	N of Patients	Insomnia/Sleep Disturbances Prevalence	Other Relevant Key Findings
Badenoch et al[44]	51	18,917	27.4% (CI 21.4–31.4%)	Neuropsychiatric symptoms were common in post-COVID-19 patients, but the disease severity did not predict them.
Han et al[85]	18	8591	12% (CI 7–17%)	Female subjects were more likely to have long-term psychiatric sequelae of COVID-19.
Jahrami et al[86]	250	493,475	52.4% (CI 41.7–62.9%)	0
Li et al[88]	6	1780	48.7% (CI 21.6–75.8%)	COVID-19 patients showed a higher prevalence of insomnia symptoms than the general population.
Elhiny et al[92]	69	146, 725	40% (CI not available)	The prevalence of insomnia was higher in patients with a history of mental disorders.

patients with OSA were associated with severe COVID-19, ICU admissions, the need for mechanical ventilation and mortality from COVID-19.[95] In addition, the pandemic and the limitation of health care led to a deterioration in the availability of OSA diagnostics, further worsening patients' health.[49]

Does the COVID-19 Pandemic Changed the Circadian Rhythm?

The perception of time is critical for the organism's adaptation to everyday functioning. Based on this perception, cycles associated with temperature fluctuations, hormones, and other homeostatic processes occur in the body.[39] If these physiological processes are unbalanced, they can negatively affect health. Disturbances of the circadian cycles influence the development of metabolic diseases such as obesity, diabetes, cardiovascular disease and cancer.[50] Likewise, a lifestyle that does not follow the circadian rhythm or has sudden changes in the daily rhythm resulting from the COVID-19 pandemic promotes these disorders and is a risk factor for developing diseases.[3,5] Non-standard working hours or other external influences can also cause pathophysiological changes and lead to disturbances in circadian rhythms, as is common in shift workers.[16,18]

The pandemic has often brought lifestyle changes, including increased sleep time.[51–53] However, excessive sleep (more than 10 hours a day) is also harmful, and excessively long sleep is connected with an increased risk of metabolic syndrome or cardiovascular diseases. In addition, excessive sleep was linked with lower levels of circulating 25-hydroxyvitamin D (25OHD) compared to the average sleep duration (6–7 h).[54] Vitamin D (1,25-(OH)2D3) and its metabolites (especially 25-hydroxyvitamin D) also play a role in immune regulation, and its deficiency is linked with a higher incidence of pathological conditions such as infections, autoimmune diseases and allergies.[55] Isolation in home quarantine can lead to reduced exposure to sunlight, affecting vitamin D metabolism, the biological clocks, and the immune system.[7] Thus, it is not surprising that in hospitalized patients with COVID-19, vitamin D serum levels were low and inversely correlated with the severity of the infection.[56] Furthermore, as it has been shown in recent years, although vitamin D supplementation does not reduce the risk of infection with the SARS-COV2 virus itself, it is associated with a lower risk of a severe course of COVID-19 and lower mortality rates.[57]

Since 2019, COVID-19 has spread globally and significantly affected peoples' daily lifestyles. Chen et al[58] explored the effect of the COVID-19 pandemic on circadian rhythm changes and the presence of negative emotions in the Chinese population. A third of the participants presented circadian rhythm disturbance; moreover, 67.2% presented negative emotions. Gender and age were significant features for changes in the circadian phases and emotions. The effects of the lockdown on sleep quality in the general French population were examined by Bertrand et al. More than half of the participants experienced a deterioration in their sleep quality, and half of the entire patient sample had an irregular sleep pattern – women reported poorer sleep quality during the pandemic than men.[59]

Phillips et al exposed individuals with irregular sleep patterns to a variable light regime inducing a delay in the circadian cycle. Participants subsequently experienced sleep delays and irregularities, suggesting a mutual association.[60] Changes in the normal daily rhythm thus increase the likelihood of fluctuations in sleep time and worse sleep quality. In addition, an imbalance between the 24-hour environmental cycle and the endogenous circadian rhythm system is a risk factor for inflammatory and cardiovascular diseases.[61]

The sleep-wake cycle functions as the "internal clock" of the human body, which regulates processes directly related to it.[52] There is growing evidence that typical symptoms of depression may, in some cases, be related to disturbances in circadian rhythms, supporting the notion that changes in sleep or other cycles may affect mental health.[5,62] Some of the strategies adopted to reduce contamination with the coronavirus during the pandemic, such as social distancing and isolation, significantly altered lifestyles, which may have affected some learned behaviours (regular alarm clocks, exposure to sunlight, eating and social interactions), all of which help to maintain the circadian rhythm. As a result, these strategies can disrupt sleep quality.[63]

The pandemic has forced many employees to work from home, leading to changes in the sleep and wake cycle. A large study shown among 3787 healthy volunteers during lockdown showed that the most significant changes occurred during the first ten days when the differences between weekday and weekend sleep-wake cycles disappeared, and there was a tendency towards eveningness and daytime napping.[12,64]

The pineal hormone melatonin is significant in the sleep-wake cycle and essential to a person's circadian rhythms. Melatonin is secreted mostly at night, and its production depends on light, but it is also influenced by other factors such as physical activity, social interaction, and diet. Exposure to artificial light during the night hours leads to the suppression of melatonin secretion, disruption of the circadian rhythm, and sleep deprivation. In the long term, this disruption can increase the risk of several illnesses, such as cancer, cardiovascular disease, diabetes, obesity, and mood disorders.[52]

Melatonin is commonly known and used to treat insomnia. However, in addition to improving sleep quality, its effects are complex and include regulation of the immune system, inflammation, and oxidative stress.[65] Melatonin supplementation in the context of COVID-19 infection has been monitored in several randomized clinical trials, where the effect on improving the symptoms of the infection, shortening the hospitalization and overall improvement of the health status of the patients was demonstrated.[66–68]

As mentioned above, diet is also important for proper functioning melatonin secretion. A study by Binks et al describes the effect of diet on sleep. Consuming foods containing carbohydrates, tryptophan, melatonin, and phytonutrients suggests an improvement in the quality and quantity of sleep. We can positively influence both modalities if we select the right diet.[69]

Can Lack of Sleep Lead to an Alteration of the Immune System?

Sleep plays a unique role in maintaining a normal immune response. In an unprecedented long-lasting stress situation - such as the COVID-19 pandemic - individuals become exposed to an increase in anxiety and stress, which lead to lower quality sleep, dysregulation of immunity, and greater susceptibility to viral infections.[37] Circumstances affecting sleep quality have reduced vaccine response and increased vulnerability to infectious diseases. In the current scenario caused by the coronavirus disease pandemic, sleep is important in maintaining a functional immune system and the population's health.[7]

Innate and acquired immunity is an important component of humoral communication.[70] Cytokines are proteins formed by the immune system cells that regulate intra- and intercellular immune responses.[71] Cytokines involved in sleep and the innate immune response include, for example, interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-a).[7] IL-6 is a pro-inflammatory cytokine that reduces anabolic pathways and increases catabolic pathways, leading to increased energy turnover and, thus, reduced weight gain.[72] In contrast, the function of TNF-α, which is also a pro-inflammatory cytokine, dominantly stimulates lipolysis and adipose tissue changes, immunomodulation, apoptosis, proliferation and pathological reactions.[72,73]

Previous studies with groups of participants with a short duration of sleep (<6 hours) revealed a decrease in T-lymphocytes, lower natural killer cell activity, increased inflammatory markers (C-reactive protein, IL-6), and shorter

T-cell telomere length.[74] Compared to individuals who slept seven to eight hours a day, individuals who slept less than five hours reported more cases of nasopharyngitis and acute bronchitis.[75]

Mechanisms that are likely directly related to increased susceptibility to infections after sleep deprivation include: decreased lymphocyte proliferation, decreased HLA-DR expression, upregulation of CD14+ and variation in CD4+ and CD8+ T-.[76] In addition, it has also been shown that the physiological response to psychological stressors that can affect sleep can negatively affect the immune system, which illustrates how sleep, immunity, and mental health are linked.[77]

In connection with the factors of immunity, sleep and depression, patients with depression who go through significant psychological stress have increased pro-inflammatory markers, especially the C protein marker (CRP) and IL-6. Additionally, an increase in inflammation amplifies symptoms of depression. In addition, sleep disturbances such as insomnia are also associated with depression and increased inflammation.[5,78]

There is an increasing body of evidence about sleep deprivation (both chronic and acute) and its effect on the immune system. After the short sleep deprivation, increased levels of interferon-γ, tumor necrosis factor-alpha (TNF-α), and interleukin-1-beta (IL-1-beta) are observed after short sleep deprivation.[79] Even a night with a sleep of three and a half hours or shorter can bring a measurable effect on the immune system. The lymphocyte levels are slightly increased, and neutrophils and natural killer levels decrease.[29,30] Ruiz et al[25] divided their participating patients into two parallel arms. In the first arm, subjects were completely sleep deprived for two nights, and in the second arm, subjects, for two consequent nights, woken up every time shortly after rapid-eye-movement (REM) sleep started. In both arms were observed increased levels of T-lymphocytes and significant drops in neutrophils count. The number of neutrophils normalized after a single night of normal sleep, and increased lymphocytes were present even after three normal nights after the intervention. Moreover, in an animal model, a single night of REM sleep deprivation leads to increased levels of TNF-α and IL-17 for at least one week despite normal sleep.[23]

Chronic insomnia might negatively impact the immune system even more. Savard et al[26] found in subjects with insomnia depletion of lymphocytes in classes of a cluster of determination (CD) 3, 4 and 8 in subjects with insomnia. This depletion contrasts with acute sleep deprivation leading to increased levels of lymphocytes. Carroll et al[28] found that the lymphocytes are of higher epigenetic age in a female with chronic insomnia (ie they have a higher level of methylation). Interestingly, the length of sleep was not as important as daytime symptoms of insomnia, especially chronic fatigue.

Is There a Link Between Insomnia and Changes in the Immune System in COVID-19 Patients?

The psychosocial impact of pandemics changed the daily routine in some individuals and may have led to impaired immune functions.[39,52,74] Increased susceptibility to respiratory infections (including COVID-19) may be one of the impacts. Patel et al performed a large observational study involving 56,953 nurses, and the main conclusion was an increased chance of developing pneumonia in nurses with chronic sleep deprivation.[80] Prather et al found that the common cold was more common in subjects with chronic sleep deprivation.[81] Finally, Huang et al found that sleep quality and length are important, as subjects with shorter or impaired sleep had more severe COVID-19 courses than individuals with good sleep quality.[20]

The SARS-CoV-2 virus causes sleep disturbances in two ways. The first one is direct, where the virus directly attacks the CNS. Indirectly, we understand brain damage caused by cytokine storms.[82] The virus uses the ACE-2 (angiotensin-converting enzyme 2) receptor in the CNS to enter cells. In this way, it attacks the brain structure, leading to sleep dysregulation. COVID-19 causes excessive activation of the immune system and a cytokine storm in the body, which leads to an increased immune response of brain tissue, neuropsychiatric manifestations and sleep disorders.[13]

In their study, Zhang et al[83] compared the levels of inflammatory parameters in patients hospitalized for COVID-19. Sleep quality was assessed using the PSQI, and the PSQI value divided them into four groups: good, fairly good, general and poor sleep quality. Patients in the group with poor sleep quality had significantly increased levels of inflammatory markers compared to the other three groups.

A cohort study compared the effect of sleep quality on recovery from lymphopenia in patients hospitalized for COVID-19. Individuals were divided into two groups, according to sleep quality, assessed by PSQI. Poor sleep was related to slow recovery from lymphopenia, increased ICU requirements, and prolonged hospital stays.[84]

Conclusion

The COVID-19 pandemic has been one of the biggest challenges for global healthcare in the last decades. The pandemic has significantly changed the daily lives of individuals over the world. Stopping the spread of viral infection and somatic treatment of infected persons are priorities. However, it is also necessary to deal with significant secondary consequences of the pandemic and the measures leading to its management. One of these impacts is a sleep quality change affecting the immune response and related to mental health. There is strong evidence of the increased prevalence of insomnia during the COVID-19 pandemic. Insomnia is one of the most common psychiatric manifestations of post-COVID syndrome. Risk factors for insomnia after infection include female gender and mental illness in medical history. The pandemic has altered the circadian rhythm of many people. Lack of sleep is linked to the alteration of the immune system. The most common is the increased production of pro-inflammatory indicators. COVID-19 infection itself can be neurotoxic through direct and indirect pathways. Involvement of the immune system in the cascade of events during infection with the SARS-CoV-2 virus may cause sleep disorders.

Disclosure

The authors have no conflict of interest.

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