Chapter 213

COVID-19 and Sleep

Meir Kryger; Cathy A. Goldstein

Chapter Highlights

- The COVID-19 pandemic resulted in an increase in sleep disorders and complaints such as insomnia, nightmares, and posttraumatic stress disorder (PTSD)–like syndrome among uninfected caregivers and the public.
- Restrictions to mitigate the spread of COVID-19 often resulted in increased time use flexibility and later, longer, and more consistently timed sleep.
- COVID-19 infection affecting the respiratory, neurologic, and cardiovascular systems can result in downstream effects on sleep.
- Obesity and associated metabolic comorbidities common in obstructive sleep apnea were recognized as risk factors for patients severely affected with COVID-19.
- Knowledge about the long-term impact of the COVID-19 pandemic on the sleep of the public and those with sleep disorders is evolving.
- COVID-19 has had a dramatic impact on the practice of sleep medicine throughout the world with the adoption of telemedicine and an increasing focus on home testing. Some of these changes are likely permanent.

INTRODUCTION

The world first encountered the coronavirus, SARS-CoV-2, in December 2019. Infection by this virus is called *COVID-19*. By mid-2021 a pandemic of COVID-19 had affected almost the entire planet, and successive waves of infection had immeasurable effects on nations' health, economies, and political systems. The successive waxing and waning rates of infection were impacted by properties of the virus (virulence, transmissibility, emergence of variants, medical risk factors), attempts at mitigation (masking, social distancing, lockdowns, vaccination), and other factors (vaccine hesitancy, political systems, and socioeconomics). By late 2021, about 5 million people worldwide had died of COVID-19.

Initially, the focus of the medical profession was on the severe respiratory infections, which often led to respiratory failure and death. It soon became apparent that other organ systems were affected[1] and that long-term sequelae were frequently present. Shortness of breath, fatigue, and brain "fog" were common persistent symptoms in some post–COVID-19 patients.[2] People with persistent symptoms sometimes describe themselves as "long haulers," and the condition in the medical literature is often called "post–COVID-19 syndrome" or "long COVID-19." Clinics were established to follow post–COVID-19 patients.[3] Almost a year after the first cases were reported, the first vaccines were approved for use.

The pandemic resulted in a change in the practice of sleep medicine—telemedicine was rapidly adopted in many parts of the world and greater reliance was placed on out-of-center testing and remote monitoring to protect patients and caregivers.[4] The pandemic has affected the mental health of the population.[5] The anxiety and stress related to the pandemic had profound effects on the sleep of the uninfected general population. However, remote work and learning allowed many individuals to sleep for longer durations and with more regular timing. A great deal of sleep research focused on the effect of the pandemic.[6] Additionally, many patients who recovered from infection were left with chronic sleep disorders. Patients with known sleep disorders (such as obstructive sleep apnea [OSA]) were at risk for complications when infected with SARS-CoV-2.

In this chapter, we review what is known about COVID-19 and sleep. Research is continuing at a rapid pace to further elucidate the many unanswered or inadequately answered questions.

SLEEP IN THE UNINFECTED POPULATION

Sleep Disturbances

Anxiety, stress, changes in life (e.g., illness, employment, food security, education, lockdown) and evening increase in use of electronic devices[6a] related to the pandemic have led to a dramatic surge in people around the world becoming interested in[7] and reporting sleep problems.[8-11] The prevalence of disturbed sleep was cited at about 40% to 60% in general populations around the world.[8,11]

Nightmares (with negative content) were reported to be more frequent, especially in women, younger adults, and those with anxiety and depressive symptoms.[12] Mandatory lockdowns resulted in a severe impact on sleep quality, especially in females, individuals with a low educational level, and those with financial problems.[13-15] There was an increase in hypnotic use in the general population.[8,16] With successive waves of the pandemic, disturbed sleep persisted, and more evidence revealed that female gender, advanced age, low education, lower socioeconomic status, and evening

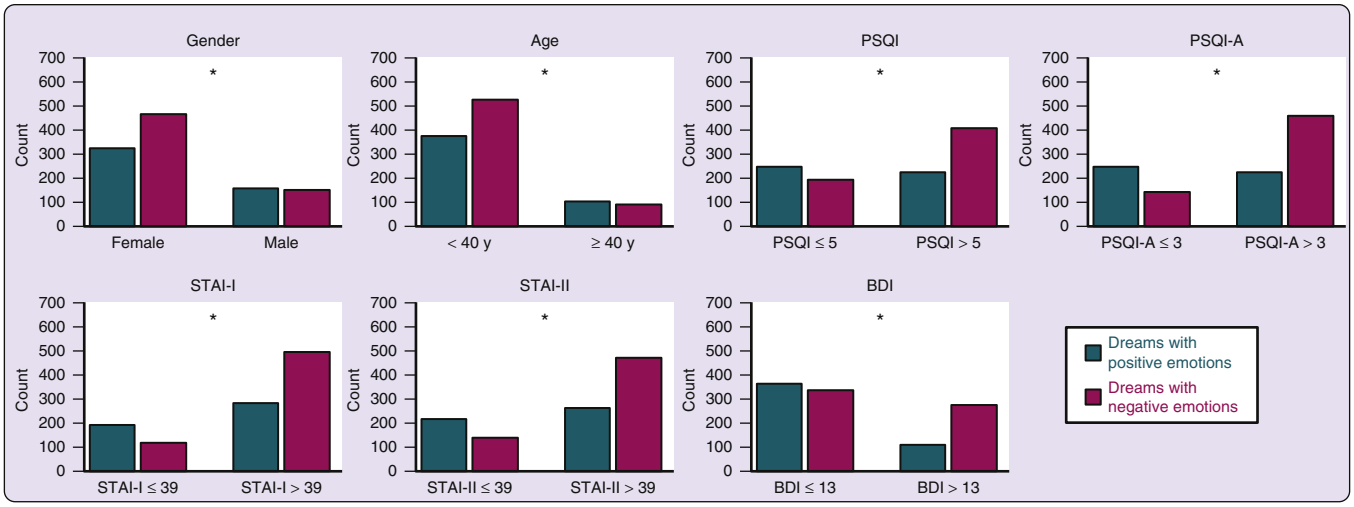

Figure 213.1 Number of subjects reporting a positive *(blue bars)* or a negative *(red bars)* emotion in dreams during the lockdown in Italy. Nightmares (with negative content) were more frequent, especially in women, younger adults, and those with anxiety and depressive symptoms *Asterisks* indicate significant chi-squares ($P < 0.05$). A Pittsburgh Sleep Quality Index (PSQI) global score larger than 5 indicates a subjectively perceived poor sleep quality. The PSQI-A assesses nocturnal behaviors common in PTSD. A PSQI score greater than or equal to 4 suggests PTSD. State-Trait Anxiety Inventory (STAI-I, II) assesses anxiety symptoms. Scores greater than or equal to 40 indicate significant anxiety levels. The Beck Depression Inventory-II (BDI-II; scores >13 are indicative of the presence of depressive disorder. (Adapted from Gorgoni M, Scarpelli S, Alfonsi V, et al. Pandemic dreams: quantitative and qualitative features of the oneiric activity during the lockdown due to COVID-19 in Italy. *Sleep Med*. 2021;81:20-32.)

smartphone overuse predicted a higher risk of insomnia symptoms.[17] Being high-risk for COVID-19 infection, living with a high-risk person for COVID-19 infection, and having a relative/friend infected with COVID-19 were risk factors for poor sleep quality.[10,17] Sleep disturbances during the COVID-19 pandemic were associated with a variety of negative symptoms such as depression, anxiety, psychosis, rumination, and somatic symptoms.[17a,b] Poor sleep and mental health problems were alarmingly prevalent in evening chronotypes.[17c]

Sleep problems were present across age groups and affected children[18,19] and college students[20] in addition to adults. Children with attention deficit hyperactivity disorder appeared particularly vulnerable to sleep disturbances during COVID-19 social isolation and experienced psychological symptoms related to sleep problems.[20a,b]

There are documented positive effects of physical activity on sleep symptoms.[21] Additionally, maintaining regular daytime naps was an effective way to stabilize biologic rhythms, sleep patterns, and mental disorders.[22] Fortunately, a reduction in sleep disturbances has been observed when confinement restrictions were lifted (Figure 213.1).[23]

Health Care Workers

Not surprisingly, the sleep of health care workers, especially those working in hospitals, has been negatively affected by the pandemic, with many having PTSD symptoms.[24-38,38a,38b] Online cognitive-behavioral therapy for insomnia (CBT-I) programs are being developed for this population.[39]

It appears as though irregular sleeping patterns[40] and shift work,[41] which are both prevalent in the health care occupation, are associated with an increased risk of COVID-19 infection. The long-term outcome of these sleep problems in both the general and health care worker populations is unclear, but a matter of concern.

Sleep Improvements

The increase in disturbed sleep was expected in the context of the abrupt and widespread psychological distress incited by the pandemic. However, sleep improvements were also observed in parallel with social isolation and increased utilization of remote work and learning, which provided greater schedule flexibility for many individuals. For example, in a population of university students, time in bed devoted to sleep on weekdays increased from 7.9 ± 1.0 to 8.4 ± 1.1 hours.[42] Sleep irregularity, as measured by the standard deviation of sleep timing and duration, was also significantly reduced after stay-at-home orders.[42] Additionally, the difference between weekday and weekend sleep times (social jet lag) decreased.[42] These improvements were accompanied by later sleep timing overall, and therefore stay at home orders may have conferred the opportunity to sleep in line with individual circadian preferences.[42] Similar findings have also been observed consistently in nonuniversity populations and were even confirmed with objective, ambulatory monitoring.[43-48,48a] However, despite increased sleep duration and consistency, sleep quality was often reduced.[17c,43,45,46] Regardless, the pandemic revealed changes based on self-selection of sleep times, a phenomena never observed before at such scale.[49]

Prepandemic sleep conditions may play a role in the differential responses to confinement, as individuals with chronic insomnia experienced improvements in sleep quality during lockdown, whereas 20% of prepandemic good sleepers reported a deterioration in sleep quality.[50] Interestingly, individuals who had previously received digital cognitive behavioral therapy for insomnia, appeared relatively resistant to the development of COVID19 lockdown related sleep disturbances.[50a]

Some individuals with specific sleep disorders experienced symptomatic improvements related to changes in day-to-day life during the pandemic. For example, individuals with

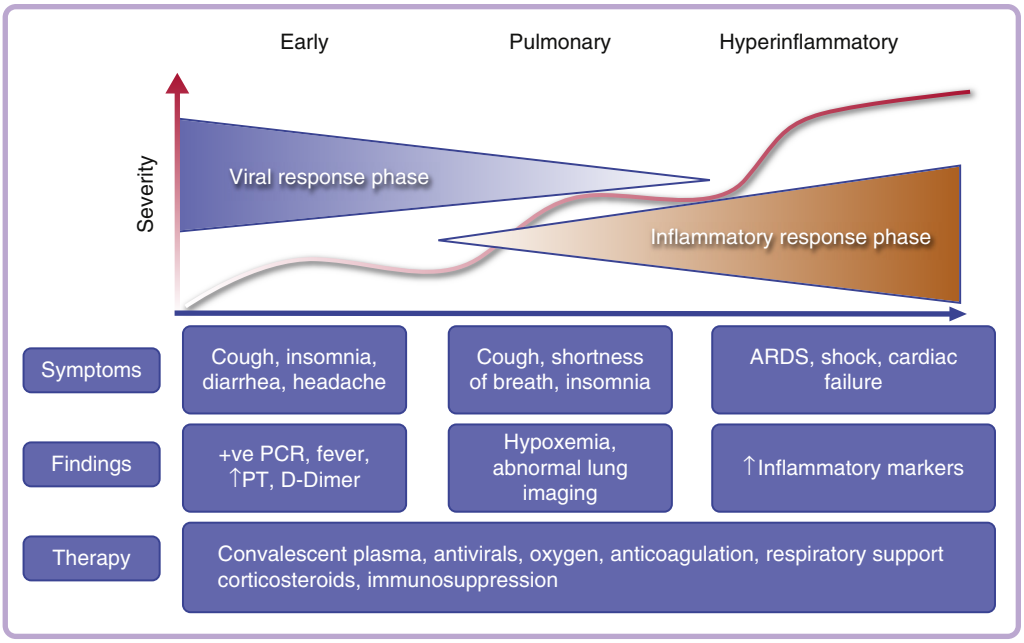

Figure 213.2 The phases of COVID-19 infection. Many patients are infected but are totally asymptomatic. In some patients, the disease progresses in a variable course through several overlapping phases, with changes in symptoms, laboratory findings, and therapy requirements.

central disorders of hypersomnolence attained more sleep and experienced less sleepiness. Even 54% of patients with type 1 narcolepsy reported a decrease in cataplexy.[50b] Additionally, two cases of resolved delayed sleep-wake phase disorder were reported in the context of sleep schedule flexibility conferred by the lockdown.[50c]

Increased sleep consistency during the pandemic could have important relevance, given the finding that COVID-19 risk was 1.2-fold greater per 40-minute increase in variability in sleep timing.[40]

VACCINATION

Starting very early in the pandemic, several vaccines were developed, some based on traditional platforms and some based on new mRNA technology. The following vaccine types were developed (all initially approved for emergency use) or in development by late-2021: inactivated virus, protein subunits, mRNA, and recombinant viral vector.[51] There are significant challenges remaining in supplying vaccines globally.[52] Sleep duration at the time of vaccination may affect efficacy.[53] Side effects of vaccination were generally not life-threatening and were temporary; some people complained of decreased sleep quality.[54,55] Unfortunately, by the time the first vaccines were approved for emergency use, millions of people had been infected. For example, on December 11, 2020, the day that the Pfizer-BioNTech was approved for use in the United States, there were 12,920 deaths and 712,356 new cases of infection worldwide! Vaccine breakthrough infections occurred, especially as more transmissible variants emerged.[55a] Infection by SARS-CoV-2 is associated with devastating effects.

PATHOPHYSIOLOGY OF COVID-19 INFECTION

Respiratory System Infection

After inhalation of droplets or aerosols laden with SARS-CoV-2, pneumonia and acute respiratory distress syndrome (ARDS) may develop via the angiotensin-converting enzyme II (ACE2) receptor.[56] Infection can spread through the ACE2 receptor further to various organs such as the heart, liver, kidney, nervous system, vascular endothelium, immune system, and blood cells. This may be followed by a cytokine storm with the extensive release of proinflammatory cytokines.[56]

The presentation of SARS-Cov-2 (COVID-19) infection ranges from asymptomatic, to atypical pneumonia, to a hyperinflammatory state, to respiratory failure and ARDS (Figure 213.2) with many patients also having venous thromboembolic (VTE) disease and pulmonary embolism (PE).[57] Activation of neutrophils appears to play an important role in the severity of COVID-19 infection and outcome (Figure 213.3).[58]

Those most at risk were older men; individuals of black, Asian, and minority ethnicity; and those with obesity, hypertension, and diabetes.[59-61] Initially, roughly 5% of infected patients required hospital intensive care unit (ICU) admission. The mortality of affected patients gradually decreased during the first year of the pandemic as treatments evolved. Patients in critical care units had the sleep problems associated with severe illness[62] (see Chapter 158), exacerbated by severe anxiety and lack of emotional support of family members who were generally prevented from visiting patients.

Long-Haul Respiratory Outcomes

Long-term sequelae are common in about a third of those who had been hospitalized and nonhospitalized during their acute infection.[63,64] COVID-19 "long-haulers" with respiratory symptoms have impaired lung function that is proportionate to the degree of acute lung injury during the acute infection. Biomarkers of inflammation, fibrosis, and alveolar repair may be the biologic drivers of the respiratory post–COVID-19 syndrome.[65] More than half of hospitalized patients who have recovered from COVID-19 pulmonary infections still have radiologic abnormalities up to 6 months after discharge.[66,67] Reduced lung diffusing capacity and shortness of breath (documented by abnormal Modified Medical Research Council) Dyspnea Scale) are also common 6 months after discharge

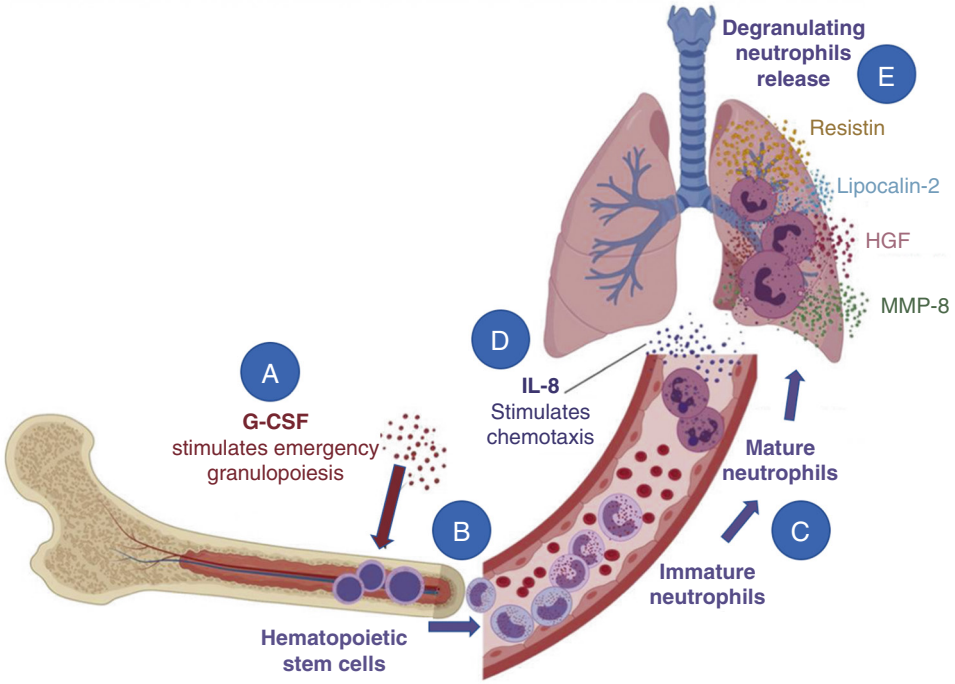

Figure 213.3 After infection with SARS-CoV-2, neutrophil development and activation lead to the development of severe COVID-19. Emergency granulopoiesis in the bone marrow **(A),** driven by granulocyte colony-stimulating factor (G-CSF) stimulate rapid neutrophil development and egress **(B)** into the bloodstream of immature neutrophils, which then differentiate into mature neutrophils **(C),** which are attracted to the lung **(D),** and perhaps the nervous system, by the chemokine IL-8 (CXCL8). When activated, these neutrophils degranulate **(E),** releasing resistin, lipocalin-2, HGF, and MMP-8. Thus the activation of neutrophils leads to the damage that may contribute to severe COVID-19 and clinical decompensation. (Adapted from Meizlish ML, Pine AB, Bishai JD, et al. A neutrophil activation signature predicts critical illness and mortality in COVID-19. *Blood Adv*. 2021;5[5]:1164-1177.)

from hospital and are most abnormal in those who were the most ill in the hospital.[66,68] After one year, many patients continue to have respiratory symptoms.[68a]

Upper airway symptoms are common,[69] and some (e.g., hoarseness and dysphonia[70]) may persist. Post–COVID-19 patients (especially those who were treated in ICUs with tracheal intubation or tracheostomy or high-flow oxygen) may have persistent respiratory symptoms because of persistent anatomic changes in the upper airways or the lungs.[71] A large number of other symptoms (e.g., loss of hair, absent olfactory sense, palpitations) are present in a lower percentage of recovered patients.

Thus follow-up of these patients is important.[72] Patients may have breathlessness at rest and exercise and hypoxemia and disordered breathing during sleep. In one study about a third of post–COVID-19 patients with sleep complaints had OSA.[73] Although oximetry during walking is suggested for these patients to determine whether oxygen therapy is needed,[57] we believe that assessment of oxygenation during sleep will be helpful. In patients with symptoms of sleep-disordered breathing, polysomnography or home sleep testing may be indicated. Some patients may continue to have symptoms and physiologic abnormalities many months after the acute infection.

Neurologic Effects of COVID-19

Neurologic ramifications during and after infection with SARS-CoV-2 are not uncommon and range from mild (e.g., anosmia, dysgeusia, and headaches) to severe (e.g., stroke and encephalopathy).[74] Neurologic and/or psychiatric symptoms are identified in the vast majority of patients with significant COVID-19 infections and often precede respiratory symptoms.[1,75,76] Respiratory abnormalities, when present, have been associated with more frequent neurologic symptoms.[75]

Direct effects of SARS-CoV-2 on the nervous system, immune response to SARS-CoV-2, and the resultant pro-inflammatory and hypercoagulable states, in addition to consequences of critical illness in general, may underlie the neurologic outcomes in patients with COVID-19.[77] The olfactory mucosa may be a possible initial route of entry of SARS-CoV-2 into the central nervous system (CNS) (Figure 213.4).[78] The most compelling evidence was an autopsy study of patients with COVID-19 that identified viral particles and RNA in the olfactory mucosa and CNS areas that receive projections from the olfactory tract, suggesting axonal transfer.[79] Additionally, SARS-CoV-2 was found in areas that are not connected to the olfactory mucosa, and therefore the CNS could be invaded via viral transport across the blood–brain barrier or through the CNS epithelium.[79] In CNS tissue where SARS-CoV-2 RNA was identified, an inflammatory response mediated by microglia was observed.[79] Increased immunoreactivity for SARS-CoV-2 was also noted in the endothelial cells in acute areas of infarction on brain autopsy, which demonstrates the potential of various mechanisms of direct CNS impact of COVID-19.[79] Notably, evidence of SARS-CoV-2 in the brainstem may reveal a centrally mediated contribution to the profound respiratory dysfunction in COVID-19.[79]

Although the ACE2 receptor is the docking receptor for SARS-CoV-2 and there is evidence of ACE2 receptors in

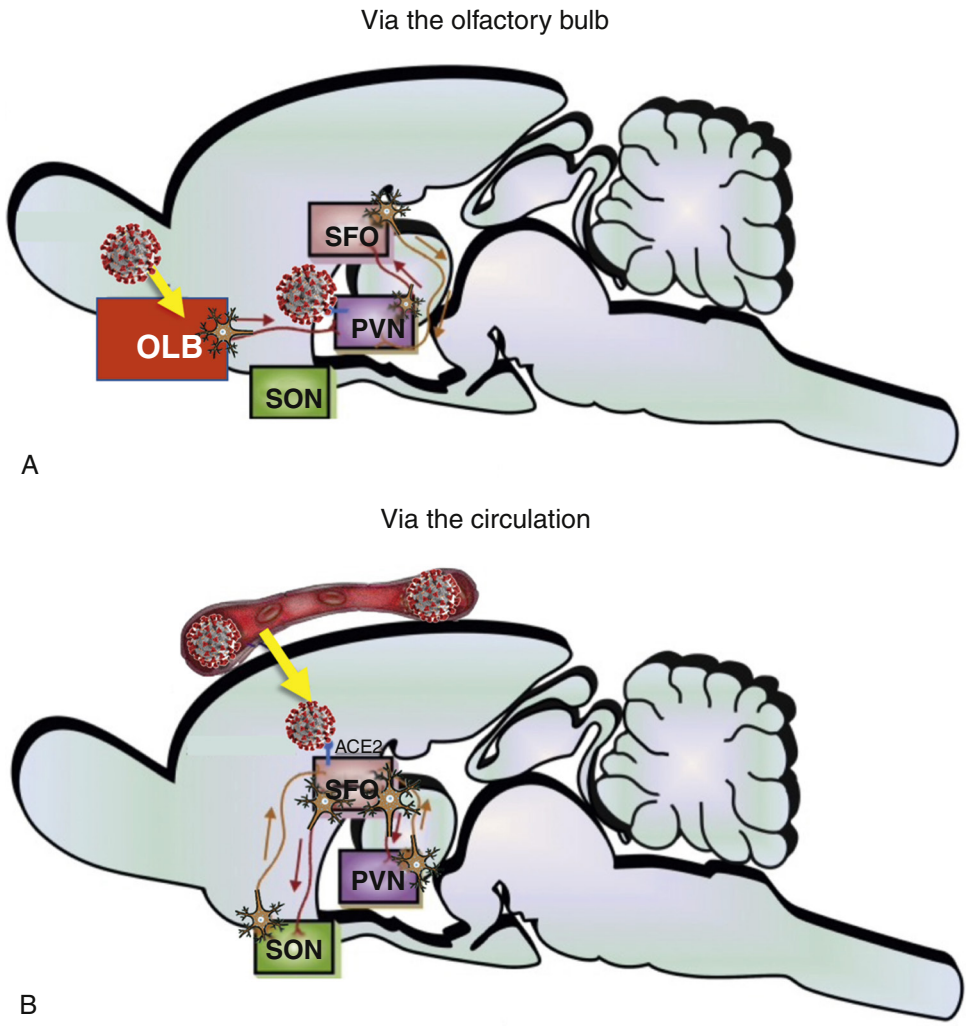

Figure 213.4 Possible SARS-CoV-2 invasion pathways in the brain. SARS-CoV-2 may access the central nervous system *(yellow arrows)* via the olfactory nerve **(A)** or circulation **(B).** In **(A),** the virus is carried by the axons of the olfactory sensory neurons into the OLB toward the PVN. SARS-CoV-2 is transported to the cytoplasm mediated by ACE2 and proteases in PVN. Subsequently, the viral RNA is replicated, transcribed, and translated by viral proteins inside the cell. The viral protein and RNA are assembled to constitute a new virion to be released in the neuronal membrane. **B,** The SARS-CoV-2 moves from blood to extracellular fluid in circumventricular organs. This virus can enter SFO neurons through ACE2. ACE2, Angiotensin-converting enzyme2; OLB, bulb olfactory; PVN, paraventricular hypothalamic nucleus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SFO, subfornical organ; SON, supraoptic hypothalamic nucleus. (Adapted from de Melo IS, Sabino-Silva R, Cunha TM, et al. Hydroelectrolytic disorder in COVID-19 patients: Evidence supporting the involvement of subfornical organ and paraventricular nucleus of the hypothalamus [published online ahead of print, 2021 Feb 10]. *Neurosci Biobehav Rev*. 2021;124:216-223.)

neurons and glial cells of the human CNS, the exact role of ACE2 in mediating the neurologic effects of COVID-19 is unclear.[77] The actual evidence of SARS-CoV-2 invasion into the CNS is based on a small sample of patients and requires replication.

In addition to possible direct infection of the nervous system, the systemic effects of COVID-19 are detrimental to the nervous system. For example, proinflammatory cytokines are thought to play a role specifically in childhood multisystem inflammatory syndrome (MIS-C),[80] and hypercoagulable states may result in thrombotic and cardioembolic strokes.[77] Postinfectious immune-mediated processes may result in neurologic sequela after infection.[77] Conversely, COVID-19 infection can have a deleterious effect on patients who already have a preexisting neurologic disorder (Figure 213.4).[81]

There are diverse neurologic outcomes as a result of acute infection. Mild, nonspecific symptoms such as myalgias, headaches, and dizziness are common,[1] and in some cohorts, anosmia and dysgeusia were present in nearly 90% of patients.[82] Of particular concern are the more severe neurologic manifestations reported in patients with COVID-19. Encephalopathy is frequently observed[83,84] and likely multifactorial in origin, with contributions from critical illness in general, as opposed to COVID-19 specifically. Stroke (primarily ischemic) is a complicating factor in COVID-19 patients[85,86] and associated with increased mortality and more severe disability upon hospital discharge.[86] The hypercoagulable, proinflammatory condition observed in COVID-19 likely contributes to thrombotic or, when combined with cardiac abnormalities, cardioembolic stroke.[87]

Intraparenchymal bleeds are reported less frequently and typically in the context of hemorrhagic transformation of ischemic stroke or use of anticoagulation.[88]

Although Guillain-Barre syndrome (GBS) is often precipitated by infectious agents, and numerous cases of SARS-CoV-2 infection as a potential cause of GBS are reported,[89] larger epidemiologic studies have not revealed the surge of GBS cases that would be expected during a pandemic.[90] Therefore a definitive link cannot yet be established. Other identified peripheral nervous system complications include cases of myopathy and focal and multifocal neuropathies related to COVID-19.[91]

Rare but serious neurologic complications of COVID-19 include meningoencephalitis, both with and without the presence of SARS-CoV-2 identified in the cerebrospinal fluid, although the accuracy of testing in these cases remains in question,[74] and life-threatening acute disseminated encephalomyelitis and acute hemorrhagic necrotizing encephalopathy.[80]

Long-Haul Neurologic Outcomes

Survivors of severe COVID-19 infection must be followed for the possibility of cognitive impairment, psychiatric, and/or physical disability.[81] Complete remission of neurologic symptoms has been reported in about three-quarters of patients[75]; however, residual fatigue, disturbed sleep, and cognitive complaints are common.[66,67] As time elapses, a greater understanding of chronic neurologic sequela related to COVID-19 is expected. Already, cognitive impairment was confirmed with neuropsychological testing in 38% of individuals with persistent symptoms 4 months after hospital admission.[67] Anecdotally, postural orthostatic tachycardia syndrome (POTS) has been observed, and the first published case series confirmed POTS in three individuals 3 months after infection.[92] The pathophysiologic mechanism remains unclear, though chronic inflammatory or autoimmune responses are suspected.

Notably, after recovery from COVID-19, polysomnography performed in a small group of patients revealed stage R sleep without atonia in 36%. Lack of current or premorbid complex behaviors during sleep and no use of medications known to elevate electromyogram tone in stage R at the time of the study suggest the possibility that COVID-19 may affect neurologic pathways that preserve atonia of stage R sleep.[73]

Psychiatric symptoms are often protracted, with more than one-third of patients who recover from acute COVID-19 infection experiencing PTSD, anxiety, or depression 50 days after diagnosis, despite recovery.[93] Abnormal scores on the anxiety subscale of the Hospital Anxiety and Depression scale, Beck depression inventory, and the posttraumatic stress disorder checklist were noted in 31%, 21%, and 14% of patients, respectively, 4 months after discharge.[67] Whether these persistent symptoms represent a direct CNS impact of infection or a response to the acute stressor of illness remains unclear, though some data implicate chronic inflammation.[94]

A large study from the originating location of the pandemic may provide the greatest insight into the prevalence of post-COVID symptoms.[66] In a cohort from Wuhan, the most common symptoms persisting in survivors 6 months after COVID-19 were fatigue or muscle weakness (63%), sleep difficulties (26%), and anxiety or depression (23%).[66] Collectively, the neurologic and psychiatric consequences of COVID-19 may underlie the resultant sleep disruption during and after infection with SARS-CoV-2.

Cardiovascular System

The cardiovascular system can be affected by the entry of COVID-19 through the ACE2 receptors,[56] direct cardiac injury, increased immunothrombotic processes, stress cardiomyopathy, and pulmonary hypertension related to respiratory failure and the COVID-induced cytokine storm.[95,96] Various mechanisms may play a role, including infiltration of inflammatory cells, which could impair cardiac function; proinflammatory cytokines (monocyte chemoattractant protein-1, interleukin-1β; interleukin-6; tumor necrosis factor-α) that could cause necrosis of the myocardium; endothelial injury; severe hypoxia; and pulmonary hypertension from ARDS.[97] Some data are beginning to suggest that the immunothrombotic process (predominantly microvascular) may be the key driving mechanism damaging the heart.[97a]

Thromboembolic complications have been reported, including PE, cerebral venous thrombosis, and stroke.[96] In the Yale COVID-19 Cardiovascular Registry,[98] about 40% of patients hospitalized with COVID-19 had preexisting cardiovascular diseases, such as coronary artery disease, heart failure, and atrial fibrillation. Major adverse cardiovascular events (e.g., myocardial infarction, stroke, acute decompensated heart failure, or cardiogenic shock) occurred in 23% of the admitted patients.[98] New onset of heart failure occurred in a quarter of hospitalized COVID-19 patients, in about one-third of those admitted to the critical care units.[95] There has been high mortality in such patients.[96]

Long-Haul Cardiovascular Outcomes

In survivors of COVID who had not initially had heart failure, there may be the late onset of cardiovascular complications with myocarditis-like changes (revealed by cardiac magnetic resonance imaging) or related to chronic inflammation.[99,100] Persistent myocardial inflammation caused by a postviral autoimmune response may lead to incomplete recovery with residual cardiac dysfunction and remodeling of the left ventricle.[99] Thus COVID-19 survivors may be at risk of developing persistent residual myocardial injury and heart failure. Symptoms such as shortness of breath (at rest and activity), fatigue, and chronic cough are common. Persistent hypertension and persistently elevated heart rates have been reported.[96] Sleep-disordered breathing is an expected outcome in patients with chronic heart failure (Figure 213.5).

PHENOTYPES OF COVID-19–RELATED SLEEP SYMPTOMS AND DISORDERS

In general, disturbed sleep is common in individuals infected with COVID-19, with pooled prevalence estimates from 35% to 75%,[11,101,101a] and chronic sleep problems might emerge, as occurred with previous pandemics.[102] In an investigation of 646 COVID-19 patients, more than one-third had sleep disturbances, with a median total sleep disturbance duration of 7 days (interquartile range [IQR] 4.0–15.0).[75] No statistically significant difference in sleep disturbances was identified between those that did and did not require hospitalization.[75] Although most investigations have evaluated sleep disturbances on a global level, for example, with the Pittsburgh Sleep Quality Index (PSQI),[11,101] specific sleep disorders have also emerged.

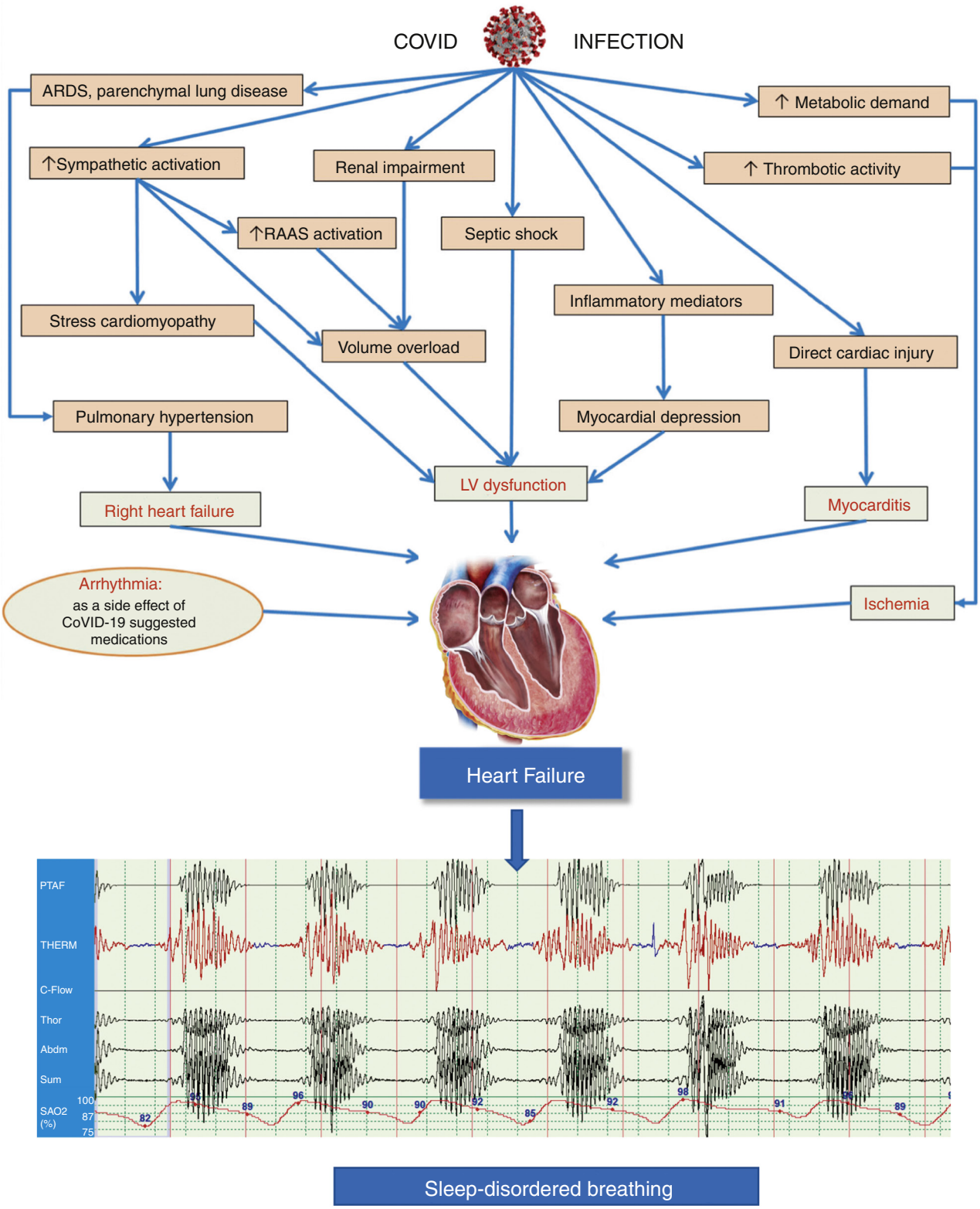

Figure 213.5 SARS-CoV-2 effect on the cardiovascular system. There are many mechanisms whereby COVID-19 can affect the cardiovascular system resulting in acute and chronic heart failure. Chronic heart failure can in turn cause sleep-disordered breathing. (Adapted from Bader F, Manla Y, Atallah B, Starling RC. Heart failure and COVID-19. *Heart Fail Rev*. 2021;26[1]:1-10.)

New-Onset Insomnia

Acute psychological distress that accompanies COVID-19 infection may precipitate insomnia.[103] About a third of patients with severe infections were found to have a neurologic or psychiatric disorder within 6 months after hospital discharge.[104] Different populations of COVID-19 patients have demonstrated a high prevalence of insomnia. Just over half of a large cohort of confirmed COVID-19 patients, both outpatient and hospitalized, reported insomnia and cited anxiety, respiratory symptoms, pain, and fever as disrupting their sleep.[75] When insomnia is defined as an insomnia severity index (ISI) score greater than 7, a meta-analysis of 584 patients across three studies estimated insomnia prevalence of approximately 30%.[101] The evaluation of sleep in patients with COVID-19 has primarily used subjective tools (questionnaires, interview); however, in four hospitalized patients who were recorded with wrist actigraphy, those with the most severe respiratory symptoms and required extended admission to the ICU were found to have lower objective sleep efficiency and higher sleep fragmentation than those with more mild courses.[62]

Because psychological distress and psychiatric morbidity may persist[105] after recovery from COVID,[93] the risk of insomnia may remain, 26% of patients report disturbed sleep at follow-up,[66] and more than 50% of patients were identified with insomnia based on ISI scores 4 months after discharge from hospitalization.[67] Insomnia is more common in patients who had been severely affected at 6 months after discharge compared with patients who have had other respiratory infections.[104]

Other Nonsleep-Disordered Breathing Sleep Disorders

Day-night reversal (12%) and hypersomnia (17%) have also been reported in conjunction with COVID-19, though specific details regarding how these diagnoses were made are unclear.[75] Additionally, a case of restless legs syndrome onset timed with COVID-19 that resolved with recovery was observed.[106]

New-Onset Sleep Breathing Disorders

As mentioned earlier, patients who had been infected with COVID-19 may have residual respiratory pathology, which could lead to chronic V/Q mismatching, resulting in hypoxemia. In one of the author's (MK) experience, those with daytime hypoxemia may have disturbed sleep.

In addition, we have had post–COVID-19 patients who were diagnosed for the first time with OSA (see later) shortly after discharge and 49 of 67 COVID-19 patients who survived ARDS and underwent PSG were found to have moderate to severe OSA 4 to 6 weeks after discharge. Another investigation revealed that OSA diagnosed after discharge was associated with 6-fold greater odds of ARDS while infected with SARS-CoV-2.[106a,106b] We have seen OSA develop in patients who have substantial weight gain, which was common during the pandemic.[107] Hoarseness, which seems common in some post–COVID-19 patients,[69] may represent an upper airway pathology that predisposes to OSA.

Obstructive Sleep Apnea

Comorbidities such as cardiovascular disease, diabetes, hypertension, chronic lung disease, chronic kidney disease, and tobacco use are associated with more severe manifestations of COVID-19 illness and increased mortality.[108-113] Therefore the potential relationship between OSA and COVID-19 has garnered much attention, and OSA patients with COVID-19 appear to have greater morbidity and mortality.[114-125,125a-d]

Potential mechanisms implicated in severe outcomes in patients with COVID-19 and OSA are as follows. Because ACE2 is the entry receptor of SARS-CoV-2, increased expression of ACE and dysregulation of the renin-angiotensin system by OSA could promote SARS-CoV-2 infection.[119,120] Moreover, OSA (and, if present, obesity hypoventilation syndrome) could worsen hypoxemia in pneumonia secondary to COVID-19, and potentially, the proinflammatory states of OSA and obesity might augment the cytokine storm.[121]

Black Americans are particularly at risk of COVID-19 infection because they often have the preexisting metabolic burden (e.g., obesity, hypertension, and diabetes) that is known to be a risk factor for COVID-19, and about half of those with the metabolic burden are at risk of having OSA.[126] In one large series, patients with OSA had an eight fold greater risk for COVID-19 infection controls receiving care in a large, racially, and socioeconomically diverse health care system.[124]

Additionally, OSA has been associated with an increased risk of hospitalization,[123,124,125a,b] and, in large investigations of hospitalized patients with COVID-19, prevalence has been cited at 12%[118] and 20%.[116] Increased risk of critical care requirement, need for mechanical ventilation, and death has been observed in OSA patients infected with SARS-CoV-2.[114,124,125,125e] However, findings have been discrepant[125f] and the contribution of OSA to COVID-19–related outcomes may be attenuated when controlling for body mass index (BMI), hypertension, diabetes, and chronic lung disease.[114,125c]

Paradoxically, in a diabetic population, "treated" OSA was associated with increased mortality at day 7 of admission despite control for age, sex, comorbidities, and medications.[118] However, how individuals with "treated OSA" were identified is not detailed and could refer to treatment ordered, self-reported treatment use, or objectively confirmed treatment of OSA (by assessment of positive airway pressure [PAP]–generated adherence data). Therefore whether the relationship between treated OSA and death reflects a detriment of OSA, treatment of OSA, or an unmeasured confounder remains unclear. In individuals with diagnostic sleep study data, apnea-hypopnea index, minimum oxygen saturation by pulse oximetry (SpO_2), mean SpO_2, and time Spo_2 less than 88% did not appear related to need for mechanical ventilation, vasopressors, or death.[116] The relationship between OSA and COVID-19 outcomes remains an active area of investigation.

Therapeutic Considerations

Ambulatory patients with mild-to-moderate OSA who have contracted COVID-19 should consider not using PAP during the active infectious phase.[127] Coughing, in particular, may interfere with the patient's ability to use PAP. Pulse oximeters were being widely used to monitor SpO_2 levels; however, the validity and accuracy of such devices may be problematic, especially in darkly pigmented people.[128,129] Patients with known OSA and COVID-19 who are not hospitalized might require modification of PAP circuits to minimize viral shedding.[130] In addition, noninvasive ventilation may mask deterioration of clinical status.[131] Known OSA patients 1 month after recovery from COVID-19 infection required an increase

in autoadjusting CPAP pressure. This suggests that COVID-19 affects the upper airways and not just the lungs.[132]

Role of Other Preexisting Sleep Disorders

Additionally, sleep disruption, independent of sleep-disordered breathing, has been proposed as a potential factor in COVID-19 outcomes. Sleep deprivation is associated with increases in the same proinflammatory cytokines (interleukin-6 and tumor necrosis factor-α) associated with severe COVID-19 infection.[133] Sleep deprivation increases viral susceptibility, increases resistance to the antiinflammatory effects of corticosteroids, and increases mortality in the face of septic challenges in experimental animal models and therefore may be associated with worse outcomes after COVID-19 infection.[120,133] Additionally, sleep deprivation in animals induces pulmonary inflammation, which may be of particular relevance to COVID-19 pathogenesis.[133]

Despite the theoretical mechanisms, minimal data are available regarding other sleep disorders and COVID-19 risk or outcomes. Increased odds of COVID-19 infection in association with increased sleep variability (odds ratio [OR], 1.21; 95% confidence interval [CI], 1.08–1.35)[40] and shift work (OR, 1.81; 95% CI, 1.04–3.18), irrespective of occupation,[41] suggests that circadian disruption may be a risk factor. In a group of hospitalized patients with COVID-19, 11% had insomnia and 4% had restless legs syndrome or periodic limb movements disorder, though no significant relationship was apparent between these diagnoses and outcomes.[116]

CHANGES IN THE PRACTICE OF SLEEP MEDICINE

There were dramatic changes in the practice of sleep medicine when the pandemic began to protect patients and staff.[4,134-136,136a,b] Many clinics closed entirely, whereas others continued to operate, but switched entirely to home sleep testing and telemedicine.[136a,b,137] Either telephone or video-based encounters were used. There were difficulties with many patients who were unable to master or could not use computers or smartphones to complete their encounters. As the pandemic eased, clinics increased in-clinic visits and in-lab evaluations, but with enhanced safety measures in place.[138] Often a negative test for COVID-19 was required before a test or a face-to-face encounter in the clinic. It is likely that telemedicine, which was proven effective in many patients during the height of the pandemic, will continue to a degree because it was convenient for many patients.

Many durable medical device companies stopped face-to-face education and mask fitting. Remote monitoring for adherence and efficacy and adjustment of PAP devices with built-in modems became widely used. Even web-based mask fitting systems were introduced.

Some of the telemedicine aspects that were adopted during the height of the pandemic will likely continue once the pandemic is over.[139]

USE OF WEARABLE AND REMOTE SLEEP TECHNOLOGY

The ubiquitous nature of consumer-facing wearable devices, which track activity, cardiac, and sleep metrics, presented an opportunity to identify predictors of COVID-19 in the ambulatory environment at scale.[140-143] Alterations in wearable acquired resting heart rate (RHR), activity, and sleep were identified in 26 of 32 patients with COVID-19 infection, and these abnormalities were seen before or at the start of symptom items in 85% of patients.[144] In 2754 individuals infected by the SARS-CoV-2 virus, a model that incorporated Fitbit-measured RHR, respiratory rate, and heart rate variability (HRV) predicted illness with an area under the curve (AUC) of 0.77 ± 0.018.[145] When investigators added wearable sensor data to self-report symptoms, the ability to distinguish positive from negative COVID-19 cases among symptomatic individuals improved markedly (AUC = 0.71; IQR: 0.63–0.79 versus AUC 0.80; IQR: 0.73–0.86).[146] The DETECT[147] and TemPredict[148] provide further information regarding the role of wearable technologies in public health.

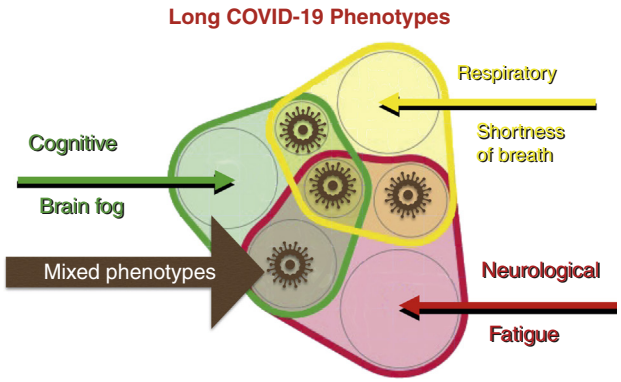

Figure 213.6 Phenotypes of long COVID clinical phenotypes. Some patients present with symptoms with primarily one symptom: brain fog, shortness of breath, or fatigue. Many patients also have mixed phenotypes or overlapping symptoms. The size of each circle is proportional to the number of patients. (Adapted from Writing Committee for the COMEBAC Study Group, Morin L, Savale L, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. *JAMA*. 2021;325[15]:1525-1534.)

THE FUTURE

As mentioned earlier, many patients who have recovered from COVID-19 have chronic symptoms.[67,105] Sleep problems are common in this group.[149] The long-term outcome of these patients is unknown at this time (Figure 213.6). As the pandemic wanes and the world is being vaccinated with the first generation of COVID-19 vaccines, there is and still will be a great deal of uncertainty related to emerging viral variants. Overall there has been a dramatic reduction in the number of cases and deaths worldwide (Figure 213.7).[150,151] Even once the pandemic is over, there will likely be many patients around the world who will have sleep problems related to the pandemic. Sleep medicine reacted quickly during the pandemic to optimize the care of patients. What has been learned will be helpful, and some of the clinical procedures will continue to be used. More important is that the field will be able to pivot quickly when confronted by future pandemics.

SUMMARY

The relationship between sleep and COVID-19 is multifaceted. The pandemic itself and social isolation have been detrimental for some (insomnia related to stress, anxiety, and/or depression) and seemingly beneficial for others (prolonged sleep duration and the ability to sleep within circadian preferences). COVID-19 infection appears to affect sleep directly with resultant acute

and chronic insomnia, sleep-disordered breathing, and dysregulation of motor control in rapid eye movement (REM) and indirectly through the psychological stress of illness. The International COVID–19 Sleep Study (ICOSS) aims to increase our understanding of the impact of COVID-19 on various aspects of sleep and circadian rhythms through harmonized measures and will likely clarify many of the questions that remain in this chapter.[152] The practice of sleep medicine not only survived this worldwide insult but was able to thrive and serve our patients through rapid adoption of telemedicine, remote testing and monitoring, and by leveraging other technological solutions. Lessons learned during this unprecedented time will likely inform and promote innovation in our field for years to come.

CLINICAL PEARL

Many patients hospitalized for COVID-19 infection have long-term medical and/or psychological sequela that may affect their sleep. All such individuals should be followed. Patients who recovered without hospital treatment may still have long-term sequelae. Even patients never infected may have sleep disorders related to the psychological impact of the pandemic and lockdown. Many unknowns remain about patients with long-haul consequences. How this pandemic will ultimately evolve (continue in waves, continue as an endemic or perhaps a seasonal disease, or disappear) is the biggest unknown.

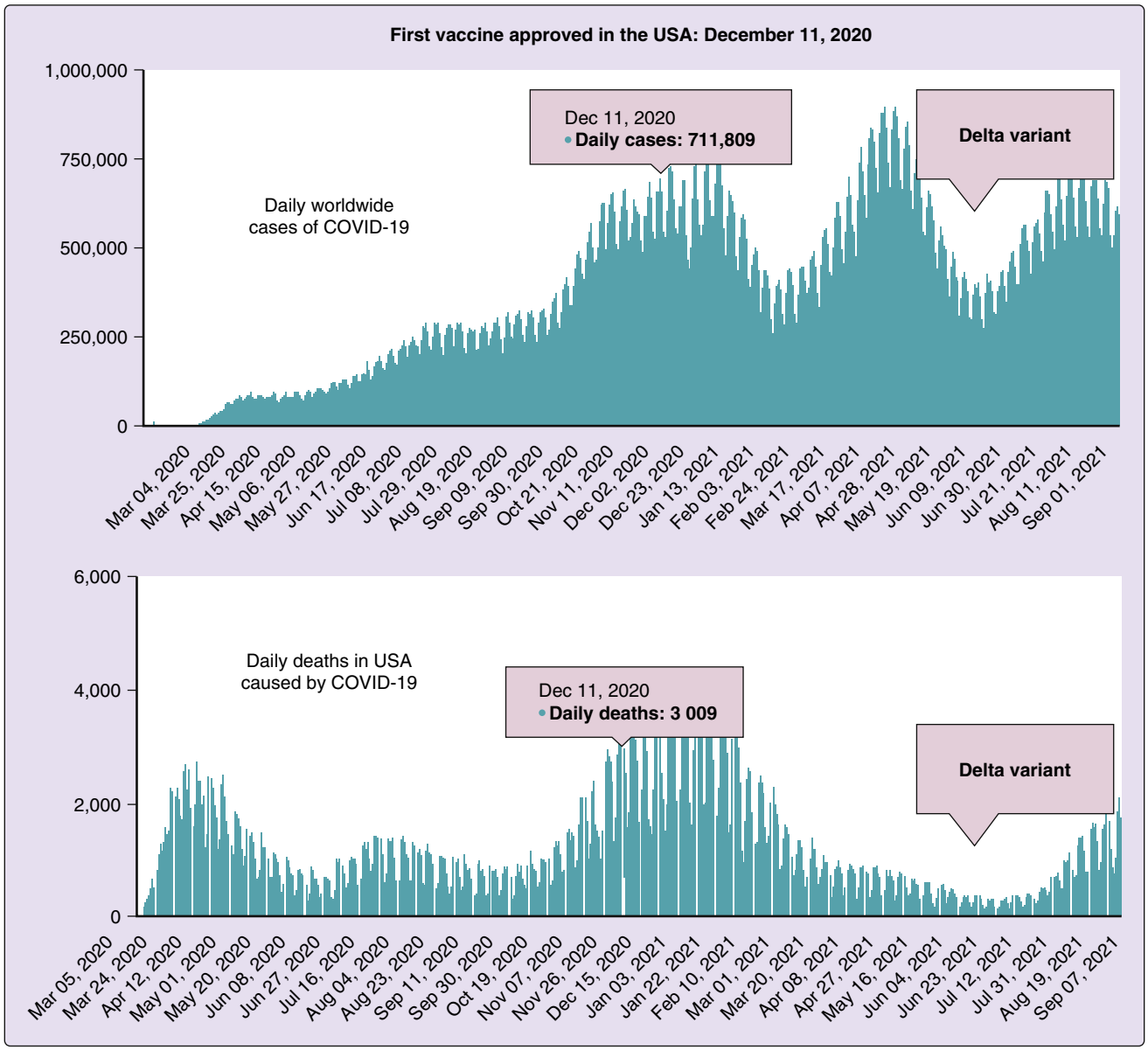

Figure 213.7 Impact of vaccination on the COVID pandemic. The first vaccine was approved in the United States on December 11, 2020. There has been a reduction in the number of cases and deaths worldwide, but in the summer of 2021 infections increased due to the emergence of variants. (https://www.worldometers.info/coronavirus/).

SELECTED READINGS

Altena E, Baglioni C, Espie CA, et al. Dealing with sleep problems during home confinement due to the COVID-19 outbreak: Practical recommendations from a task force of the European CBT-I Academy. *J Sleep Res*. 2020;29(4):e13052.

Crook H, Raza S, Nowell J, Young M, Edison P. Long COVID—mechanisms, risk factors, and management. *BMJ*. 2021;374:n1648.

Grote L, Theorell-Haglöw J, Ulander M, Hedner J. Prolonged effects of the COVID-19 pandemic on sleep medicine services-longitudinal data from the swedish Sleep apnea registry. *Sleep Med Clin*. 2021;16(3):409–416.

Jean-Louis G, Turner AD, Jin P, et al. Increased metabolic burden among blacks: a putative mechanism for disparate COVID-19 outcomes. *Diabetes Metab Syndr Obes*. 2020;13:3471–3479. Published 2020 Oct 2.

Korman M, Tkachev V, Reis C, et al. COVID-19-mandated social restrictions unveil the impact of social time pressure on sleep and body clock. *Sci Rep*. 2020;10:22225. https://doi.org/10.1038/s41598-020-79299-7.

Lin YN, Liu ZR, Li SQ, et al. Burden of sleep disturbance during COVID-19 pandemic: a systematic review. *Nat Sci Sleep*. 2021;13:933–966.

Luks AM, Swenson ER. Pulse oximetry for monitoring patients with COVID-19 at home. potential pitfalls and practical guidance. *Ann Am Thorac Soc*. 2020;17(9):1040–1046.

Mandelkorn U, Genzer S, Choshen-Hillel S, et al. Escalation of sleep disturbances amid the COVID-19 pandemic: a cross-sectional international study. *J Clin Sleep Med*. 2021;17(1):45–53. https://doi.org/10.5664/jcsm.8800.

Mutti C, Azzi N, Soglia M, Pollara I, Alessandrini F, Parrino L. Obstructive sleep apnea, CPAP and COVID-19: a brief review. *Acta Biomed*. 2020;91(4):e2020196. https://doi.org/10.23750/abm.v91i4.10941. Published 2020 Nov 23.

Peker Y, Celik Y, Arbatli S, et al. Effect of high-risk obstructive sleep apnea on clinical outcomes in adults with coronavirus disease 2019: a multicenter, prospective, observational cohort study [published online ahead of print, 2021 Feb 17]. *Ann Am Thorac Soc*. 2021. https://doi.org/10.1513/AnnalsATS.202011-1409OC. 10.1513/AnnalsATS.202011-1409OC.

Semyachkina-Glushkovskaya O, Mamedova A, Vinnik V, et al. Brain mechanisms of COVID-19-sleep disorders. *Int J Mol Sci*. 2021;22(13):6917.

Suen CM, Hui DSC, Memtsoudis SG, Chung F. Obstructive sleep apnea, obesity, and noninvasive ventilation: considerations during the COVID-19 pandemic. *Anesth Analg*. 2020;131(2):318–322.

Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. 2021;8(4):Online First. April 6, 2021.

Voulgaris A, Ferini-Strambi L, Steiropoulos P. Sleep medicine and COVID-19. Has a new era begun? *Sleep Med*. 2020;73:170–176.

Writing Committee for the COMEBAC Study Group, Morin L, Savale L, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. *JAMA*. 2021;325(15):1525–1534.

A complete reference list can be found online at ExpertConsult.com.

This page intentionally left blank

REFERENCES

1. Collantes MEV, Espiritu AI, Sy MCC, Anlacan VMM, Jamora RDG. Neurological manifestations in COVID-19 infection: a systematic review and meta-analysis. *Can J Neurol Sci*. 2021;48(1):66–76.
2. Walitt B, Bartrum E. A clinical primer for the expected and potential post-COVID-19 syndromes. *Pain Rep*. 2021;6(1):e887.
3. Lutchmansingh DD, Knauert MP, Antin-Ozerkis DE, et al. A clinic blueprint for post-coronavirus disease 2019 RECOVERY: learning from the past, looking to the future. *Chest*. 2021;159(3):949–958.
4. Johnson KG, Sullivan SS, Nti A, Rastegar V, Gurubhagavatula I. The impact of the COVID-19 pandemic on sleep medicine practices. *J Clin Sleep Med*. 2021;17(1):79–87.
5. Tsamakis K, Tsiptsios D, Ouranidis A, et al. COVID-19 and its consequences on mental health (Review). *Exp Ther Med*. 2021;21(3):244.
6. Partinen M. Sleep research in 2020: COVID-19-related sleep disorders. *Lancet Neurol*. 2021;20(1):15–17.

6a. Salfi F, Amicucci G, Corigliano D, et al. Changes of evening exposure to electronic devices during the COVID-19 lockdown affect the time course of sleep disturbances. *Sleep*. 2021;44(9):zsab080.

7. Zitting KM, Lammers-van der Holst HM, Yuan RK, Wang W, Quan SF, Duffy JF. Google Trends reveals increases in internet searches for insomnia during the 2019 coronavirus disease (COVID-19) global pandemic. *J Clin Sleep Med*. 2021;17(2):177–184.
8. Mandelkorn U, Genzer S, Choshen-Hillel S, et al. Escalation of sleep disturbances amid the COVID-19 pandemic: a cross-sectional international study. *J Clin Sleep Med*. 2021;17(1):45–53.
9. Goularte JF, Serafim SD, Colombo R, Hogg B, Caldieraro MA, Rosa AR. COVID-19 and mental health in Brazil: psychiatric symptoms in the general population. *J Psychiatr Res*. 2021;132:32–37.
10. Casagrande M, Forte G, Tambelli R, Favieri F. The coronavirus pandemic: a possible model of the direct and indirect impact of the pandemic on sleep quality in Italians. *Nat Sci Sleep*. 2021;13:191–199.
11. Jahrami H, BaHammam AS, Bragazzi NL, Saif Z, Faris M, Vitiello MV. Sleep problems during the COVID-19 pandemic by population: a systematic review and meta-analysis. *J Clin Sleep Med*. 2021;17(2):299–313.
12. Scarpelli S, Alfonsi V, Mangiaruga A, et al. Pandemic nightmares: effects on dream activity of the COVID-19 lockdown in Italy. *J Sleep Res*. 2021:e13300.
13. Agha S. Mental well-being and association of the four factors coping structure model: a perspective of people living in lockdown during COVID-19. *Ethics Med Public Health*. 2021;16:100605.
14. Costi S, Paltrinieri S, Bressi B, Fugazzaro S, Giorgi Rossi P, Mazzini E. Poor sleep during the first peak of the SARS-CoV-2 pandemic: a cross-sectional study. *Int J Environ Res Public Health*. 2021;18(1):306.
15. Martinez-de-Quel O, Suarez-Iglesias D, Lopez-Flores M, Perez CA. Physical activity, dietary habits and sleep quality before and during COVID-19 lockdown: a longitudinal study. *Appetite*. 2021;158:105019.
16. Beck F, Leger D, Fressard L, Peretti-Watel P, Verger P, Coconel G. Covid-19 health crisis and lockdown associated with high level of sleep complaints and hypnotic uptake at the population level. *J Sleep Res*. 2021;30(1):e13119.
17. Salfi F, D'Atri A, Tempesta D, Ferrara M. Sleeping under the waves: a longitudinal study across the contagion peaks of the COVID-19 pandemic in Italy. *J Sleep Res*. 2021:e13313.

17a. Simor P, Polner B, Báthori N, et al. Home confinement during the COVID-19: day-to-day associations of sleep quality with rumination, psychotic-like experiences, and somatic symptoms. *Sleep*. 2021;44(7):zsab029.

17b. Meaklim H, Junge MF, Varma P, Finck WA, Jackson ML. Pre-existing and post-pandemic insomnia symptoms are associated with high levels of stress, anxiety and depression globally during the COVID-19 pandemic [published online ahead of print, 2021 May 14]. *J Clin Sleep Med*. 2021;10.5664/jcsm.9354.

17c. Merikanto I, Kortesoja L, Benedict C, et al. Evening-types show highest increase of sleep and mental health problems during the COVID-19 pandemic-Multinational study on 19,267 adults [published online ahead of print, 2021 Aug 25]. *Sleep*. 2021:zsab216.

18. Bruni O, Malorgio E, Doria M, et al. Changes in sleep patterns and disturbances in children and adolescents in Italy during the Covid-19 outbreak. LID - S1389-9457(21)00094-0 [pii] LID - 10.1016/j.sleep.2021.02.003 [doi]. (1878-5506 (Electronic)).
19. Cellini N, Di Giorgio E, Mioni G, Di Riso D. Sleep and psychological difficulties in Italian school-age children during COVID-19 lockdown. *J Pediatr Psychol*. 2021;46(2):153–167.
20. Tasso AF, Hisli Sahin N, San Roman GJ. COVID-19 disruption on college students: academic and socioemotional implications. *Psychol Trauma*. 2021;13(1):9–15.

20a. Becker SP, Dvorsky MR, Breaux R, Cusick CN, Taylor KP, Langberg JM. Prospective examination of adolescent sleep patterns and behaviors before and during COVID-19 [published online ahead of print, 2021 Feb 25]. *Sleep*. 2021;44(8):zsab054.

20b. Bruni O, Giallonardo M, Sacco R, Ferri R, Melegari MG. The impact of lockdown on sleep patterns of children and adolescents with ADHD [published online ahead of print, 2021 Apr 1]. *J Clin Sleep Med*.

21. Maher JP, Hevel DJ, Reifsteck EJ, Drollette ES. Physical activity is positively associated with college students' positive affect regardless of stressful life events during the COVID-19 pandemic. *Psychol Sport Exerc*. 2021;52:101826.
22. Dai W, Zhou J, Li G, Zhang B, Ma N. Maintaining normal sleep patterns, lifestyles and emotion during the COVID-19 pandemic: the stabilizing effect of daytime napping. *J Sleep Res*. 2021:e13259.
23. Beck F, Leger D, Cortaredona S, Verger P, Peretti-Watel P, group C. Would we recover better sleep at the end of Covid-19? A relative improvement observed at the population level with the end of the lockdown in France. *Sleep Med*. 2021;78:115–119.
24. da Silva FCT, Neto MLR. Psychiatric symptomatology associated with depression, anxiety, distress, and insomnia in health professionals working in patients affected by COVID-19: a systematic review with meta-analysis. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2021;104:110057.
25. da Silva FCT, Neto MLR. Psychological effects caused by the COVID-19 pandemic in health professionals: a systematic review with meta-analysis. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2021;104:110062.
26. Arafa A, Mohammed Z, Mahmoud O, Elshazley M, Ewis A. Depressed, anxious, and stressed: what have healthcare workers on the frontlines in Egypt and Saudi Arabia experienced during the COVID-19 pandemic? *J Affect Disord*. 2021;278:365–371.
27. Aydin Sayilan A, Kulakac N, Uzun S. Burnout levels and sleep quality of COVID-19 heroes. *Perspect Psychiatr Care*. 2020.
28. Conroy DA, Hadler NL, Cho E, et al. The effects of COVID-19 stay-at-home order on sleep, health, and working patterns: a survey study of United States health care workers. *J Clin Sleep Med*. 2020:jcsm. 8808.
29. Chew NWS, Lee GKH, Tan BYQ, et al. A multinational, multicentre study on the psychological outcomes and associated physical symptoms amongst healthcare workers during COVID-19 outbreak. *Brain Behav Immun*. 2020;88:559–565.
30. Demartini B, Nistico V, D'Agostino A, Priori A, Gambini O. Early psychiatric impact of COVID-19 pandemic on the general population and healthcare workers in Italy: a preliminary study. *Front Psychiatry*. 2020;11:561345.
31. Hall H. The effect of the COVID-19 pandemic on healthcare workers' mental health. *JAAPA*. 2020;33(7):45–48.
32. Krishnamoorthy Y, Nagarajan R, Saya GK, Menon V. Prevalence of psychological morbidities among general population, healthcare workers and COVID-19 patients amidst the COVID-19 pandemic: a systematic review and meta-analysis. *Psychiatry Res*. 2020;293:113382.
33. Preti E, Di Mattei V, Perego G, et al. The psychological impact of epidemic and pandemic outbreaks on healthcare workers: rapid review of the evidence. *Curr Psychiatry Rep*. 2020;22(8):43.
34. Sanghera J, Pattani N, Hashmi Y, et al. The impact of SARS-CoV-2 on the mental health of healthcare workers in a hospital setting-A Systematic Review. *J Occup Health*. 2020;62(1):e12175.
35. Serrano-Ripoll MJ, Meneses-Echavez JF, Ricci-Cabello I, et al. Impact of viral epidemic outbreaks on mental health of healthcare workers: a rapid systematic review and meta-analysis. *J Affect Disord*. 2020;277:347–357.
36. Sheraton M, Deo N, Dutt T, Surani S, Hall-Flavin D, Kashyap R. Psychological effects of the COVID 19 pandemic on healthcare workers globally: a systematic review. *Psychiatry Res*. 2020;292:113360.
37. Cenat JM, Blais-Rochette C, Kokou-Kpolou CK, et al. Prevalence of symptoms of depression, anxiety, insomnia, posttraumatic stress disorder, and psychological distress among populations affected by the COVID-19 pandemic: a systematic review and meta-analysis. *Psychiatry Res*. 2021;295:113599.
38. Flateau C, Noel C, Bonnafoux A, Fuentes E, de Pontfarcy A, Diamantis S. Psychological impact of the SARS-CoV-2 outbreak on the staff of a French hospital. *Infect Dis Now*. 2021;51(2):187–193.

38a. Drager LF, Pachito DV, Moreno CRC, et al. Insomnia episodes, new-onset pharmacological treatments and other sleep disturbances during the COVID-19 pandemic: a nationwide cross-sectional study in Brazilian health care professionals. *J Clin Sleep Med*. 2021;10.5664/jcsm.9570.

38b. McCall WV, Mensah-Bonsu D, Withers AE, Gibson RW. Short-term insomnia disorder in health care workers in an academic medical center before and during COVID-19: rates and predictive factors. *J Clin Sleep Med*. 2021;17(4):749–755.
39. Weiner L, Berna F, Nourry N, Severac F, Vidailhet P, Mengin AC. Efficacy of an online cognitive behavioral therapy program developed for healthcare workers during the COVID-19 pandemic: the REduction of STress (REST) study protocol for a randomized controlled trial. *Trials*. 2020;21(1):870.
40. Rowlands AV, Kloecker DE, Chudasama Y, et al. Association of timing and balance of physical activity and rest/sleep with risk of COVID-19: a UK Biobank Study. *Mayo Clin Proc*. 2021;96(1):156–164.
41. Fatima Y, Bucks RS, Mamun AA, et al. Shift work is associated with increased risk of COVID-19: findings from the UK Biobank cohort. *J Sleep Res*. 2021:e13326.
42. Wright Jr KP, Linton SK, Withrow D, et al. Sleep in university students prior to and during COVID-19 Stay-at-Home orders. *Curr Biol*. 2020;30(14):R797–R798.
43. Blume C, Schmidt MH, Cajochen C. Effects of the COVID-19 lockdown on human sleep and rest-activity rhythms. *Curr Biol*. 2020;30(14):R795–R797.
44. Raman S, Coogan AN. Effects of societal-level COVID-19 mitigation measures on the timing and quality of sleep in Ireland. *Sleep Med*. 2021.
45. Barone Gibbs B, Kline CE, Huber KA, Paley JL, Perera S. Covid-19 shelter-at-home and work, lifestyle and well-being in desk workers. *Occup Med (Lond)*. 2021;71(2):86–94.
46. Florea C, Topalidis P, Hauser T, et al. Sleep during COVID-19 lockdown: a cross-cultural study investigating job system relevance. *Biochem Pharmacol*. 2021:114463.
47. Korman M, Tkachev V, Reis C, et al. COVID-19-mandated social restrictions unveil the impact of social time pressure on sleep and body clock. *Sci Rep*. 2020;10(1):22225.
48. Ong JL, Lau T, Massar SAA, et al. COVID-19-related mobility reduction: heterogenous effects on sleep and physical activity rhythms. *Sleep*. 2021;44(2).
48a. Pépin JL, Bailly S, Mordret E, et al. Greatest changes in objective sleep architecture during COVID-19 lockdown in night owls with increased REM sleep. *Sleep*. 2021;44(9):zsab075.
49. Team AR, Milken Research T, Roitblat Y, et al. Owls and larks do not exist: COVID-19 quarantine sleep habits. *Sleep Med*. 2021;77:177–183.
50. Kocevska D, Blanken TF, Van Someren EJW, Rosler L. Sleep quality during the COVID-19 pandemic: not one size fits all. *Sleep Med*. 2020;76:86–88.
50a. Cheng P, Casement MD, Kalmbach DA, Castelan AC, Drake CL. Digital cognitive behavioral therapy for insomnia promotes later health resilience during the coronavirus disease 19 (COVID-19) pandemic. *Sleep*. 2021;44(4):zsaa258.
50b. Nigam M, Hippolyte A, Dodet P, et al. Sleeping through a pandemic: impact of COVID-19 related restrictions on narcolepsy and idiopathic hypersomnia [published online ahead of print, 2021 Jul 27]. *J Clin Sleep Med*. 2021;10.5664/jcsm.9556.
50c. Resolving delayed sleep-wake phase disorder with a pandemic: two case reports. Published online: July 13, 2021.
51. Loo KY, Letchumanan V, Ser HL, et al. COVID-19: insights into potential vaccines. *Microorganisms*. 2021;9(3).
52. Dal-Re R, Bekker LG, Gluud C, et al. Ongoing and future COVID-19 vaccine clinical trials: challenges and opportunities. *Lancet Infect Dis*. 2021.
53. Benedict C, Cedernaes J. Could a good night's sleep improve COVID-19 vaccine efficacy? *Lancet Respir Med*. 2021;9(5):447–448.
54. Kadali RAK, Janagama R, Peruru S, Malayala SV. Side effects of BNT162b2 mRNA COVID-19 vaccine: a randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers. *Int J Infect Dis*. 2021;106:376–381.
55. Kadali RAK, Janagama R, Peruru S, et al. Non-life-threatening adverse effects with COVID-19 mRNA-1273 vaccine: a randomized, cross-sectional study on healthcare workers with detailed self-reported symptoms. *J Med Virol*. 2021;93(7):4420–4429.
55a. Brown CM, Vostok J, Johnson H, et al. Outbreak of SARS-CoV-2 infections, including COVID-19 vaccine breakthrough infections, associated with large public gatherings - Barnstable County, Massachusetts, July 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(31):1059–1062.
56. Loganathan S, Kuppusamy M, Wankhar W, et al. Angiotensin-converting enzyme 2 (ACE2): COVID 19 gate way to multiple organ failure syndromes. *Respir Physiol Neurobiol*. 2021;283:103548.
57. George PM, Barratt SL, Condliffe R, et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*. 2020;75(11):1009–1016.
58. Meizlish ML, Pine AB, Bishai JD, et al. A neutrophil activation signature predicts critical illness and mortality in COVID-19. *Blood Adv*. 2021;5(5):1164–1177.
59. Fathi M, Vakili K, Sayehmiri F, et al. The prognostic value of comorbidity for the severity of COVID-19: a systematic review and meta-analysis study. *PloS One*. 2021;16(2):e0246190.
60. Galanis P, Vraka I, Fragkou D, Bilali A, Kaitelidou D. Seroprevalence of SARS-CoV-2 antibodies and associated factors in healthcare workers: a systematic review and meta-analysis. *J Hosp Infect*. 2021;108:120–134.
61. Abiri B, Guest PC, Vafa M. Obesity and risk of COVID-19 infection and severity: available evidence and mechanisms. *Adv Exp Med Biol*. 2021;1321:97–107.
62. Vitale JA, Perazzo P, Silingardi M, Biffi M, Banfi G, Negrini F. Is disruption of sleep quality a consequence of severe Covid-19 infection? A case-series examination. *Chronobiol Int*. 2020;37(7):1110–1114.
63. Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in adults at 6 Months after COVID-19 infection. *JAMA Netw Open*. 2021;4(2):e210830.
64. Hall J, Myall K, Lam JL, et al. Identifying patients at risk of post-discharge complications related to COVID-19 infection. *Thorax*. 2021.
65. Chun HJ, Coutavas E, Pine A, et al. Immuno-fibrotic drivers of impaired lung function in post-COVID-19 syndrome. *medRxiv*. 2021.
66. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220–232.
67. Writing Committee for the CSG, Morin L, Savale L, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. *J Am Med Assoc*. 2021;325(15):1525–1534.
68. Ekbom E, Frithiof R, Emilsson Ö, et al. Impaired diffusing capacity for carbon monoxide is common in critically ill Covid-19 patients at four months post-discharge. *Respir Med*. 2021;182:106394.
68a. Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet*. 2021;398(10302):747–758.
69. Elibol E. Otolaryngological symptoms in COVID-19. *Eur Arch Oto-Rhino-Laryngol*. 2021;278(4):1233–1236.
70. Lechien JR, Chiesa-Estomba CM, Cabaraux P, et al. Features of mild-to-moderate COVID-19 patients with dysphonia. *J Voice*. 2020.
71. Pandian V, Brodsky MB, Brigham EP, et al. COVID-19 survivorship: how otolaryngologist-head and neck surgeons can restore quality of life after critical illness. *Am J Otolaryngol*. 2021;42(3):102917.
72. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol*. 2021;93(2):1013–1022.
73. Heidbreder A, Sonnweber T, Stefani A, et al. Video-polysomnographic findings after acute COVID-19: REM sleep without atonia as sign of CNS pathology? *Sleep Med*. 2021;80:92–95.
74. McEntire CRS, Song KW, McInnis RP, et al. Neurologic manifestations of the world health organization's list of pandemic and epidemic diseases. *Front Neurol*. 2021;12:634827.
75. Kacem I, Gharbi A, Harizi C, et al. Characteristics, onset, and evolution of neurological symptoms in patients with COVID-19. *Neurol Sci*. 2021;42(1):39–46.
76. de Sousa Moreira JL, Barbosa SMB, Vieira JG, et al. The psychiatric and neuropsychiatric repercussions associated with severe infections of COVID-19 and other coronaviruses. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2021;106:110159.
77. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. *Cell*. 2020;183(1):16–27.e11.
78. Yates DA. CNS gateway for SARS-CoV-2. *Nat Rev Neurosci*. 2021;22(2):74–75.
79. Meinhardt J, Radke J, Dittmayer C, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci*. 2021;24(2):168–175.
80. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020;143(10):3104–3120.
81. von Oertzen TJ, Macerollo A, Leone MA, et al. EAN consensus statement for management of patients with neurological diseases during the COVID-19 pandemic. *Eur J Neurol*. 2021;28(1):7–14.
82. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Oto-Rhino-Laryngol*. 2020;277(8):2251–2261.
83. Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Transl Neurol*. 2020;7(11):2221–2230.

84. Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*. 2021;9(3):239–250.
85. Katsanos AH, Palaiodimou L, Zand R, et al. The impact of SARS-CoV-2 on stroke epidemiology and care: a meta-analysis. *Ann Neurol*. 2021;89(2):380–388.
86. Perry RJ, Smith CJ, Roffe C, et al. Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case-control study. *J Neurol Neurosurg Psychiatry*. 2021;92(3):242–248.
87. Frisullo G, Scala I, Bellavia S, et al. COVID-19 and stroke: from the cases to the causes. *Rev Neurosci*. 2021.
88. Dogra S, Jain R, Cao M, et al. Hemorrhagic stroke and anticoagulation in COVID-19. *J Stroke Cerebrovasc Dis*. 2020;29(8):104984.
89. Lunn MP, Cornblath DR, Jacobs BC, et al. COVID-19 vaccine and Guillain-Barre syndrome: let's not leap to associations. *Brain*. 2021;144(2):357–360.
90. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain*. 2021;144(2):682–693.
91. Andalib S, Biller J, Di Napoli M, et al. Peripheral nervous system manifestations associated with COVID-19. *Curr Neurol Neurosci Rep*. 2021;21(3):9.
92. Johansson M, Stahlberg M, Runold M, et al. Long-haul post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the Swedish experience. *JACC Case Rep*. 2021;3(4):573–580.
93. Poyraz BC, Poyraz CA, Olgun Y, et al. Psychiatric morbidity and protracted symptoms after COVID-19. *Psychiatry Res*. 2021;295:113604.
94. Debnath M, Berk M, Maes M. Changing dynamics of psychoneuroimmunology during the COVID-19 pandemic. *Brain Behav Immun Health*. 2020;5:100096.
95. Bader F, Manla Y, Atallah B, Starling RC. Heart failure and COVID-19. *Heart Fail Rev*. 2021;26(1):1–10.
96. Saeed S, Tadic M, Larsen TH, Grassi G, Mancia G. Coronavirus disease 2019 and cardiovascular complications: focused clinical review. *J Hypertens*. 2021.
97. Adeghate EA, Eid N, Singh J. Mechanisms of COVID-19-induced heart failure: a short review. *Heart Fail Rev*. 2021;26(2):363–369.
97a. Gu SX, Tyagi T, Jain K, et al. Thrombocytopathy and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. *Nat Rev Cardiol*. 2021;18(3):194–209.
98. Pareek M, Singh A, Vadlamani L, et al. Relation of cardiovascular risk factors to mortality and cardiovascular events in hospitalized patients with coronavirus disease 2019 (from the Yale COVID-19 cardiovascular registry). *Am J Cardiol*. 2021;146:99–106.
99. Shchendrygina A, Nagel E, Puntmann VO, Valbuena-Lopez S. COVID-19 myocarditis and prospective heart failure burden. *Expert Rev Cardiovasc Ther*. 2021;19(1):5–14.
100. Abbasi J. Researchers investigate what COVID-19 does to the heart. *J Am Med Assoc*. 2021;325(9):808–811.
101. Deng J, Zhou F, Hou W, et al. The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis. *Ann N Y Acad Sci*. 2021;1486(1):90–111.
101a. Del Brutto OH, Mera RM, Costa AF, Recalde BY, Castillo PR. Sleep quality deterioration in middle-aged and older adults living in a rural Ecuadorian village severely struck by the SARS-CoV-2 pandemic. A population-based longitudinal prospective study. *Sleep*. 2021;44(8):zsab041.
102. Cespuglio R, Strekalova T, Spencer PS, et al. SARS-CoV-2 infection and sleep disturbances: nitric oxide involvement and therapeutic opportunity. *Sleep*. 2021;44(3).
103. Sun N, Wei L, Wang H, et al. Qualitative study of the psychological experience of COVID-19 patients during hospitalization. *J Affect Disord*. 2021;278:15–22.
104. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry*. 2021;8(2):130–140.
105. Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. *JAMA Netw Open*. 2021;4(5):e2111417.
106. Tony AA, Tony EA, Ali SB, Ezzeldin AM, Mahmoud AA. COVID-19-associated sleep disorders: a case report. *Neurobiol Sleep Circadian Rhythms*. 2020;9:100057.
106a. Goyal A, Saxena K, Kar A, et al. Obstructive sleep apnea is highly prevalent in COVID19 related moderate to severe ARDS survivors: findings of level I polysomnography in a tertiary care hospital [published online ahead of print, 2021 Jun 19]. *Sleep Med*. 2021;S1389-9457(21)00350–6.
106b. Labarca G, Henriquez-Beltran M, Llerena F, et al. Undiagnosed sleep disorder breathing as a risk factor for critical COVID-19 and pulmonary consequences at the midterm follow-up [published online ahead of print, 2021 Feb 19]. *Sleep Med*. 2021;S1389-9457(21)00128-3.
107. Flanagan EW, Beyl RA, Fearnbach SN, Altazan AD, Martin CK, Redman LM. The impact of COVID-19 stay-at-home orders on health behaviors in adults. *Obesity (Silver Spring)*. 2021;29(2):438–445.
108. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. *J Am Med Assoc*. 2020;323(13):1239–1242.
109. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 2020;369:m1966.
110. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–1062.
111. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 Years is a risk factor for COVID-19 hospital admission. *Clin Infect Dis*. 2020;71(15):896–897.
112. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430–436.
113. Tartof SY, Qian L, Hong V, et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization. *Ann Intern Med*. 2020;173(10):773–781.
114. Cade BE, Dashti HS, Hassan SM, Redline S, Karlson EW. Sleep apnea and COVID-19 mortality and hospitalization. *Am J Respir Crit Care Med*. 2020;202(10):1462–1464.
115. Zhang S, Xu Y, Li J, et al. Symptomless multi-variable apnea prediction index assesses adverse outcomes in patients with Corona Virus Disease 2019. *Sleep Med*. 2020;75:294–300.
116. Goldstein CA, Rizvydeen M, Conroy DA, et al. The prevalence and impact of pre-existing sleep disorder diagnoses and objective sleep parameters in patients hospitalized for COVID-19. *J Clin Sleep Med*. 2021;17(5):1039–1050.
117. Peker Y, Celik Y, Arbatli S, et al. Effect of high-risk obstructive sleep apnea on clinical outcomes in adults with coronavirus disease 2019: a multicenter, prospective, observational cohort study. *Ann Am Thorac Soc*. 2021.
118. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia*. 2020;63(8):1500–1515.
119. Pazarli AC, Ekiz T, Ilik F. Coronavirus disease 2019 and obstructive sleep apnea syndrome. *Sleep Breath*. 2021;25(1):371.
120. McSharry D, Lam MT, Malhotra A. OSA as a probable risk factor for severe COVID-19. *J Clin Sleep Med*. 2020;16(9):1649.
121. McSharry D, Malhotra A. Potential influences of obstructive sleep apnea and obesity on COVID-19 severity. *J Clin Sleep Med*. 2020;16(9):1645.
122. Miller MA, Cappuccio FP. A systematic review of COVID-19 and obstructive sleep apnoea. *Sleep Med Rev*. 2021;55:101382.
123. Strausz S, Kiiskinen T, Broberg M, et al. Sleep apnoea is a risk factor for severe COVID-19. *BMJ Open Respir Res*. 2021;8(1).
124. Maas MB, Kim M, Malkani RG, Abbott SM, Zee PC. Obstructive sleep apnea and risk of COVID-19 infection, hospitalization and respiratory failure. *Sleep Breath*. 2020:1–3.
125. Lohia P, Sreeram K, Nguyen P, et al. Preexisting respiratory diseases and clinical outcomes in COVID-19: a multihospital cohort study on predominantly African American population. *Respir Res*. 2021;22(1):37.
125a. Kravitz MB, Yakubova E, Yu N, Park SY. Severity of sleep apnea and COVID-19 illness. *OTO Open*. 2021;5(2):2473974X211016283.
125b. Hariyanto TI, Kurniawan A. Obstructive sleep apnea (OSA) and outcomes from coronavirus disease 2019 (COVID-19) pneumonia: a systematic review and meta-analysis. *Sleep Med*. 2021;82:47–53.
125c. Mashaqi S, Lee-Iannotti J, Rangan P, et al. Obstructive sleep apnea and COVID-19 clinical outcomes during hospitalization: a cohort study [published online ahead of print, 2021 May 21]. *J Clin Sleep Med*. 2021;10.5664/jcsm.9424.
125d. Beltramo G, Cottenet J, Mariet AS, et al. Chronic respiratory diseases are predictors of severe outcome in COVID-19 hospitalised patients: a nationwide study [published online ahead of print, 2021 May 20]. *Eur Respir J*. 2021:2004474.

125e. Hariyanto TI, Kurniawan A. Obstructive sleep apnea (OSA) and outcomes from coronavirus disease 2019 (COVID-19) pneumonia: a systematic review and meta-analysis. *Sleep Med*. 2021;82:47–53.
125f. Wang H, Shao G, Rong L, et al. Association between comorbid sleep apnoea-hypopnoea syndrome and prognosis of intensive care patients: a retrospective cohort study. *BMJ Open*. 2021;11(6):e048886.
126. Jean-Louis G, Turner AD, Jin P, et al. Increased metabolic burden among blacks: a putative mechanism for disparate COVID-19 outcomes. *Diabetes Metab Syndr Obes*. 2020;13:3471–3479.
127. Sardesai I, Grover J, Garg M, et al. Short term home oxygen therapy for COVID-19 patients: the COVID-HOT algorithm. *J Family Med Prim Care*. 2020;9(7):3209–3219.
128. Luks AM, Swenson ER. Pulse oximetry for monitoring patients with COVID-19 at home. Potential pitfalls and practical guidance. *Ann Am Thorac Soc*. 2020;17(9):1040–1046.
129. Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. Racial bias in pulse oximetry measurement. *N Engl J Med*. 2020;383(25):2477–2478.
130. Kryger MH, Thomas R. Home PAP devices in patients infected with COVID-19. *J Clin Sleep Med*. 2020;16(7):1217–1219.
131. Suen CM, Hui DSC, Memtsoudis SG, Chung F. Obstructive sleep apnea, obesity, and noninvasive ventilation: considerations during the COVID-19 pandemic. *Anesth Analg*. 2020;131(2):318–322.
132. Fidan V, Koyuncu H, Akin O. Alteration of Auto-CPAP requirements in obstructive sleep apnea patients with COVID-19 history. *Am J Otolaryngol*. 2021;42(3):102919.
133. Salles C, Mascarenhas Barbosa H. COVID-19 and obstructive sleep apnea. *J Clin Sleep Med*. 2020;16(9):1647.
134. Zhang XL, Wang W, Xiao Y. Members of the assembly of sleep disordered breathing of the Chinese Thoracic S. Sleep disordered breathing diagnosis and treatment during the COVID-19 pandemic: a Nationwide survey in China. *Nat Sci Sleep*. 2021;13:21–30.
135. Schiza S, Simonds A, Randerath W, et al. Sleep laboratories reopening and COVID-19: a European perspective. *Eur Respir J*. 2021;57(3).
136. Voulgaris A, Ferini-Strambi L, Steiropoulos P. Sleep medicine and COVID-19. Has a new era begun? *Sleep Med*. 2020;73:170–176.
136a. Kanchan S, Saini LK, Daga R, Arora P, Gupta R. Status of the practice of sleep medicine in India during the COVID-19 pandemic. *J Clin Sleep Med*. 2021;17(6):1229–1235.
136b. Johnson KG, Sullivan SS, Nti A, Rastegar V, Gurubhagavatula I. The impact of the COVID-19 pandemic on sleep medicine practices. *J Clin Sleep Med*. 2021;17(1):79–87.
137. Shamim-Uzzaman QA, Bae CJ, Ehsan Z, et al. The use of telemedicine for the diagnosis and treatment of sleep disorders: an American Academy of Sleep Medicine update. *J Clin Sleep Med*. 2021;17(5):1103–1107.
138. Wilson KC, Kaminsky DA, Michaud G, et al. Restoring pulmonary and sleep services as the COVID-19 pandemic lessens. From an association of pulmonary, critical care, and sleep Division Directors and American Thoracic Society-coordinated Task Force. *Ann Am Thorac Soc*. 2020;17(11):1343–1351.
139. Nicosia FM, Kaul B, Totten AM, et al. Leveraging Telehealth to improve access to care: a qualitative evaluation of Veterans' experience with the VA TeleSleep program. *BMC Health Serv Res*. 2021;21(1):77.
140. Taylor W, Abbasi QH, Dashtipour K, et al. A review of the state of the art in non-contact sensing for COVID-19. *Sensors (Basel)*. 2020;20(19).
141. Islam MM, Mahmud S, Muhammad LJ, Islam MR, Nooruddin S, Ayon SI. Wearable technology to assist the patients infected with novel coronavirus (COVID-19). *SN Comput Sci*. 2020;1(6):320.
142. Massaroni C, Nicolo A, Schena E, Sacchetti M. Remote respiratory monitoring in the time of COVID-19. *Front Physiol*. 2020;11:635.
143. Hernandez N, Castro L, Medina-Quero J, Favela J, Michan L, Mortenson WB. Scoping review of healthcare literature on mobile, wearable, and textile sensing technology for continuous monitoring. *J Healthc Inform Res*. 2021:1–30.
144. Mishra T, Wang M, Metwally AA, et al. Pre-symptomatic detection of COVID-19 from smartwatch data. *Nat Biomed Eng*. 2020;4(12):1208–1220.
145. Natarajan A, Su HW, Heneghan C. Assessment of physiological signs associated with COVID-19 measured using wearable devices. *NPJ Digit Med*. 2020;3(1):156.
146. Quer G, Radin JM, Gadaleta M, et al. Wearable sensor data and self-reported symptoms for COVID-19 detection. *Nat Med*. 2021;27(1):73–77.
147. The Detect Study: Can a Wearable Detect COVID-19 Before Symptoms Appear? Scripps Research. https://detectstudy.org. Published 2021. Accessed 2021.
148. TemPredict. UCSF Osher Center for Integrative Medicine. https://osher.ucsf.edu/research/current-research-studies/tempredict. Published 2021. (Accessed).
149. Frontera JA, Yang D, Lewis A, et al. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. *J Neurol Sci*. 2021;426:117486.
150. Moore JP. Approaches for optimal use of different COVID-19 vaccines: issues of viral variants and vaccine efficacy. *J Am Med Assoc*. 2021;325(13):1251–1252.
151. Moore JP, Offit PA. SARS-CoV-2 vaccines and the growing threat of viral variants. *J Am Med Assoc*. 2021;325(9):821–822.
152. Partinen M, Bjorvatn B, Holzinger B, et al. Sleep and circadian problems during the coronavirus disease 2019 (COVID-19) pandemic: the International COVID-19 Sleep Study (ICOSS). *J Sleep Res*. 2021;30(1):e13206.

REVIEW QUESTIONS

1. Which of the following is a possible mechanism of SARS-CoV-2 entry into the central nervous system?
A. Aquaporin-4 water channel transport
B. Olfactory mucosa followed by axonal transport
C. Ligand-gated ion channel transport
D. Alpha-2-delta ligand agonism

2. What symptom is most likely to persist after COVID-19 infection?
A. Sore throat
B. Myoclonus
C. Diarrhea
D. Fatigue

3. The following sleep patterns have been reported in cohorts of uninfected populations in association with the pandemic:
A. Delay in sleep timing
B. Increased sleep duration
C. Reduced "social jet lag"
D. Nightmares
E. All of the above

4. Which statement best describes the relationship between obstructive sleep apnea (OSA) and COVID-19?
A. OSA appears unrelated to the risk of infection with SARS-CoV-2.
B. OSA is not associated with COVID-19–related outcomes.
C. Patients with OSA appear to have worse COVID-19–related outcomes, including hospitalization and respiratory failure.
D. Positive airway pressure (PAP) setting requirements remain stable after COVID-19.

ANSWERS

1. **B.** The explanation for this answer can be found in the section Neurologic Effects of COVID-19.

2. **D.** The explanation for this answer can be found in the section Long-Haul Neurologic Effects of COVID-19.

3. **E.** The explanation for this answer can be found in the section Sleep in the Uninfected Population.

4. **C.** The explanation for this answer can be found in the section Obstructive Sleep Apnea.