Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
The SARS-CoV-2 and mental health: From biological mechanisms to social consequences

Dorota Szczęśniak1, Anna Gladka*,1, Błażej Misiak, Agnieszka Cyran, Joanna Rymaszewska

Department of Psychiatry, Wrocław Medical University, Wybrzeże Ludwika Pasteura 10, 50-367 Wrocław, Poland

A B S T R A C T

In December 2019, the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) infection was reported. In only few weeks it has caused a global pandemic, with mortality reaching 3.4%, mostly due to a severe pneumonia. However, the impact of SARS-CoV-2 virus on the central nervous system (CNS) and mental health outcomes remains unclear. Previous studies have demonstrated the presence of other types of coronaviruses in the brain, especially in the brainstem. There is evidence that the novel coronavirus can penetrate CNS through the olfactory or circulatory route as well as it can have an indirect impact on the brain by causing cytokine storm. There are also first reports of neurological signs in patients infected by the SARS-CoV-2. They show that COVID-19 patients have neurologic manifestations like acute cerebrovascular disease, conscious disturbance, taste and olfactory disturbances. In addition, there are studies showing that certain psychopathological symptoms might appear in infected patients, including those related to mood and psychotic disorders as well as post-traumatic stress disorder. Accumulating evidence also indicates that the pandemic might have a great impact on mental health from the global perspective, with medical workers being particularly vulnerable. In this article, we provide a review of studies investigating the impact of the SARS-CoV-2 on the CNS and mental health outcomes. We describe neurobiology of the virus, highlighting the relevance to mental disorders. Furthermore, this article summarizes the impact of the SARS-CoV-2 from the public health perspective. Finally, we present a critical appraisal of evidence and indicate future directions for studies in this field.

1. Introduction

In December 2019, a first case of pneumonia, later known as novel coronavirus pneumonia was reported in Wuhan, Hubei Province, People’s Republic of China. Experts from the Centers for Disease Control declared that it had been caused by a novel coronavirus (Huang et al., 2020a). The World Health Organization (WHO) named the disease COVID-19, and the International Committee on Taxonomy of Viruses named the virus the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Consequently, the global spread of SARS-CoV-2 contributed to enormous medical and social burden worldwide. The WHO has estimated the SARS-CoV-2 mortality rate at 3.4% (WHO Director-General’s opening remarks at the media briefing on COVID-19 - 3 March 2020 - World Health Organization, 2020).

The SARS-CoV-2 is a novel coronavirus, which has a single-stranded positive sense RNA genome with an organization typical to other coronaviruses (CoVs), such as SARS and MERS (Zhu et al., 2020a). Genomic analyses have revealed that the SARS-CoV-2 also shares structural and biological similarity with other CoVs, such as MERS and SARS (Yu et al., 2020). However, the impact of the SARS-CoV-2 on the central nervous system and mental health remains unclear. Therefore, it may be relevant to refer to biology of other coronaviruses to understand the mechanisms underlying the consequences of SARS-CoV-2 infection. Besides viral structure, most coronaviruses share a similar infection pathway (Hulswit et al., 2016). There is evidence that neurotropism is one of common characteristics of CoVs (Li et al., 2012; Li et al., 2020a; Xu et al., 2005). Their presence has been demonstrated in the central nervous system (CNS) (Netland et al., 2008a) and in the cerebrospinal fluid (Marc et al., 2013). It is also important to note that patients with the SARS-CoV-2 infection can exhibit psychiatric symptoms, like insomnia, depressive mood, aggressive outbursts (Kim et al., 2018; Jeong et al., 2016). During the previous SARS and MERS epidemics, it has been shown that infected individuals commonly presented with symptoms of confusion (27.9%), depression (32.6%), memory impairment (34.1%) insomnia (41.9%) and occasionally steroid-induced mania and psychosis (0.7%). However, the same study indicated the long-term mental health effects, including depression, insomnia, anxiety, irritability, fatigue or even traumatic memories and Post-traumatic stress disorder (PTSD) (Rogers et al., 2020).

Nevertheless, the impact of the current pandemic goes far beyond direct brain damage. Increased panic, public restrictions, mass quarantine and overwhelming pressure on medical professionals might have a great impact on global mental health.

In this article, we provide a narrative review of studies investigating...
the impact of the SARS-CoV-2 on the CNS and mental health outcomes. We describe neurobiology of the virus, highlighting its relevance to mental disorders. Furthermore, this article summarizes the impact of the SARS-CoV-2 on the central nervous system and mental health outcomes.}

**2. Methods**

In order to analyze the existing literature on neurological and psychiatric symptoms associated with the SARS-CoV-2, a review of the following databases was performed: the PubMed, the Scopus, the CINAHL and the Google Scholar. The following keywords were used in the search using the MeSH terminology: “SARS” or “coronavirus” or “COVID” and “brain” or “central nervous system” or “mental health” or “psychiatry”. Search strategy was limited to the publication period covering the years 2019–2020. A total of 1002 records was identified after removing duplicates. Finally, 47 original studies and 2 meta-analyses were included (Table 1, 2, 3). Additionally, this article was based on 22 non-original articles. A narrative review was structured around two main topics: 1) the impact of the SARS-CoV-2 on the CNS and 2) the impact of the SARS-CoV-2 from the public mental health perspective.

### 3. The SARS-CoV-2 impact on the central nervous system

#### 3.1. Central nervous system penetration

There are only few pathways of CNS invasion by CoVs that have been confirmed. It has been shown that CoVs may first invade peripheral nerves, and then enter the CNS via a synapse route (Li et al., 2013; Andries and Pensaert, 1980). Experimental studies have revealed that other CoVs, when given intranasally, could access the brain through the olfactory bulb, and then spread to specific brain regions (Netland et al., 2008a; Netland et al., 2008b). Another well-known pathway of neural invasion is through systemic circulation (Baig et al., 2020). Among the brain areas that should be regarded as involved, the brainstem seems to be the major target for the SARS-CoV (Netland et al., 2008b). There are two crucial nuclei in the brainstem: the nucleus of the solitary tract and the nucleus ambiguus. The former nucleus receives sensory information from receptors in the respiratory tract, and the latter one together with the nucleus of the solitary tract provide innervation to airway glands, smooth muscles, and blood vessels. Such neuroanatomic interconnections indicate that the death of infected patients may be due to the dysfunction of the cardiorespiratory center in the brainstem (Li et al., 2020a).

It has been found that the angiotensin converting enzyme 2 receptor (ACE2) is crucial for penetrating cells by the SARS-CoV and the SARS-CoV-2 (Wrapp et al., 2020; Zhao et al., 2020). It plays a role in cardiovascular disease and is widely present in multiple human organs,
including the nervous system and skeletal muscles (Hamming et al., 2004). The ACE2 is also expressed by the epithelial cells of oral cavity (Xu et al., 2020a), which would support the concept of olfactory route of the CNS invasion by a novel coronavirus (Table 1). Indeed, it has been shown that around one third of patients with COVID-19 report taste or olfactory disorder (Giacomelli et al., 2020). Moreover, based on epidemiological data on COVID-19, the average time from the first symptoms to hospital admission is 7 days, and to the intensive care is 8 days. Therefore, the latency period may be enough for the virus to enter and destroy neurons (Wang et al., 2020a). On the other hand, it has been proposed that the novel coronavirus can reach the ACE2 receptors within CNS also through the systemic circulation (Baig et al., 2020). The aforementioned issue needs to be addressed by future studies (Horn et al., 2020).

Overall, there are several potential mechanisms that may be responsible for the effect of COVID-19 on the CNS. Direct viral invasion of the brain causing encephalitis, neuroinflammation, peripheral organ dysfunction and cerebrovascular changes can separately, or all combined cause neuropsychiatric symptoms (Heneka et al., 2020).

### 3.3. Neuroinflammation

The SARS-CoV-2 can also affect the brain tissue by causing a cytokine storm, which is believed to have an impact on neurological and psychiatric symptoms (Clark and Vissel, 2017). It has been reported that high cytokine release, characterized by increased production of interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemotactant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α, is associated with a severity of COVID-19 (Huang et al., 2020a). In other studies, the authors have found that the release of IL-1b and IL-6 was triggered by the novel coronavirus infection (Conti et al., 2020). Additionally, a retrospective, multicentric study of 150 COVID-19 cases in Wuhan revealed that elevated levels of ferritin and IL-6 might serve as predictors of mortality (Ruan et al., 2020). Authors proposed that chronic low-grade inflammatory response might be crucial in the neuropsychiatric manifestation of the SARS-CoV-2 infection (Debnath et al., 2020). However, it remains questionable whether the SARS-CoV-2 infection has an impact on inflammation and mental health independently (Wang et al., 2020b), or if it is a causal process (Troyer et al., 2020). The aforementioned issue needs to be addressed by future studies.
levels of protein and IgG (14%) (Helms et al., 2020). A large study of 40,469 patients diagnosed with the COVID-19 infection showed that 22.5% of them expressed neuropsychiatric symptoms, including headache (3.7%), insomnia (3.4%), encephalopathy (2.3%), cerebrovascular disease (1%), depression (3.8%) and suicidal ideation (0.2%) (Nalleballe et al., 2020).

3.4. Mental health and SARS-CoV-2 infection

The first studies that have already been carried out, confirm that the novel coronavirus pandemic can also severely affect mental health of infected individuals.

There are case reports of first-episode psychosis in people with SARS-CoV-2 infection (Correa-Palacio et al., 2020; Chandra et al., 2020). However, it is unclear, whether the etiology is related to the virus itself, to the stress related to pandemic, or to treatment with the use of corticosteroids or hydroxychloroquine (Correa-Palacio et al., 2020). Unfavorable mental health outcomes were reported also as one of the first signs of the novel coronavirus infection in a patient with acute manic episode (Mawhinney et al., 2020). Another paper showed 4 cases of delirium in older patients, as the only clinical manifestation of the COVID-19 (Beach et al., 2020).

A meta-analysis of 12 studies considering a combined number of 976 patients with the SARS-CoV-2 infection has shown that depressive symptoms occurred in 35% and anxiety in 28% of them (Kong et al., 2020). One of the studies that have been performed, compared the COVID-19 patients with individuals suffering from other forms of pneumonia (Yang et al., 2020). It has revealed more severe anxiety and depression symptoms in the SARS-CoV-2 patients. Unfavorable outcome due to severe anxiety was reported in one patient, who consequently attempted suicide (Epstein et al., 2020). Four other studies described high prevalence of confusion and consciousness impairment among the COVID-19 patients (2%- 22%) (Chen et al., 2020b; Huang et al., 2020b; Qi et al., 2020a; Leung et al., 2020). Altered consciousness could be associated with more severe progression of the disease, as it had been reported in 21% COVID-19 patients, who subsequently died (Zhang et al., 2020a). A paper elaborated in France, reported agitation in 69% of patients, however it was caused by drugs withdrawal (Helms et al., 2020). As far as 33% of patients from this study had dysexecutive syndrome with attention and movements impairment at the day of discharge. Moreover, a report concerning 730 COVID-19 patients who were in a stable condition, demonstrated that 96.2% of them

| Publication (year) | Tools | Group N | Results |
|--------------------|-------|---------|---------|
| Mo et al. (2020)   | SOS, SAS | 180 | Nurses who fight against COVID-19 are under stress. Being only children, working long hours per week, and anxiety are concerned to be the risk factors. |
| Bo et al. (2020)   | PCL-C  | 730 | As many as 96.2% of the COVID-19 patients in stable condition experience significant posttraumatic stress symptoms. Half of them find the psycho-educational services helpful. |
| Shi et al. (2020)  | 33-item survey questionnaire | 311 | As many as 89.51% of psychiatrists have extensive knowledge of the COVID-19 and 77.17% of them want to treat psychiatric patients with the SARS-CoV-2 virus infection. |
| Pappa et al. (2020) | A metaanalysis | 33,062 | Anxiety was reported by 23.2%, depression by 22.8% and insomnia by 38.9% of medical workers in the analyzed papers. Female professionals and nurses have more prominent affective symptoms. |
| Kang et al. (2020) | PHQ-9, GAD-7, ISI, IES-R | 994 | As many as 22.4% of medical and nursing staff working in Wuhan had moderate, and 6.2% severe disturbances in the wake of the epidemic, especially young women. |
| Lai et al. (2020)  | PHQ-9, GAD-7, ISI, IES-R | 1257 | Depression occurs in 50.4% of health care workers, anxiety in 44.6%, insomnia in 34.0%, and distress concerns 71.5% of them. The risk is higher for women, those with seniority titles and for workers at the center of the epidemic. |
| Lu et al. (2020)   | NRS, HAMA, HAMD | 2299 | Front line medical staff who have close contact with infected patients have higher fear, anxiety and depression scores in comparison to administrative staff. |
| Sun et al. (2020)  | C. S. Psychometric method, interviews conducted face-to-face or by telephone | 20 | Nurses report, that fatigue, discomfort, and helplessness are caused by work, anxiety, and concern for infecting other people. Self-coping styles include: psychological and life adjustment, team support, altruistic acts and rationalization. |
| Xiao et al. (2020) | SAS, GSES, SASR, PSQI, SSRS | 80 | Social support is associated with better self-efficacy and sleep quality, as well as with lower degree of anxiety and stress among medical staff that treated patients with COVID-19 infection. |
| Du et al. (2020)   | BD-II, BAI | 134 | Depression was reported by 12.7% and anxiety by 20.1% of medical workers. |
| Guo et al. (2020)  | SAS, SDS | 11,118 | As many as 31% of healthcare workers reported depression and 17% of them declared anxiety during the pandemic. |
| Liu et al. (2020)  | SAS | 512 | As many as 12.5% of medical stuff working with COVID-19 patients reported anxiety. |
| Qi et al. (2020)   | AIS, PSQI | 1306 | Almost half of all medical workers (45.5%) suffer from insomnia. |
| Tan et al. (2020)  | DASS-21 | 470 | Depressive symptoms were present in 8.9% of healthcare professionals and anxiety in 14.5% of them. |
| Zhang et al. (2020) | GAD-7, ISI, PHQ-9 | 1563 | Half of medical professionals suffers from depression, 45% from anxiety and 36% from insomnia. |
| Zhang et al. (2020) | GAD-2, PHQ-2 | 2182 | Sleep disturbance was reported by 33.9% of healthcare workers. As many as 10% suffered from anxiety and depression. |
| Zhu et al. (2020)  | GAD-7, PHQ-9 | 5062 | As many as 24% of medical stuff experience anxiety, and 13.5% depression symptoms during pandemic. |

PTSD: posttraumatic stress disorder, PCL-5: Checklist for DSM-5, PSQI: Pittsburgh Sleep Quality Index, PTSS: Posttraumatic stress symptoms, GAD-7: Generalized Anxiety Disorder Scale, SAS: Self-Rating Anxiety Scale, SASR: Stanford Acute Stress Reaction questionnaire, SOS: Stress Overload Scale, SAS: Self-Rating Anxiety Scale, PHQ-9: Patient Health Questionnaire, ISI: 7-item Insomnia Severity Index, IES-R: the 22-item Impact of Event Scale-Revised, NRS: a numeric rating scale on fear, HAMA: Hamilton Anxiety Scale, HAMD: Hamilton Depression Scale, GSES: the General Self-Efficacy Scale, SASR: the Stanford Acute Stress Reaction questionnaire, SSRS: the Social Support Rate Scale, BD-II: Beck Depression Inventory, BAI: Beck Anxiety Inventory, AIS: Athens Insomnia Scale, DASS-21: Depression, Anxiety and Stress Scale.
experienced symptoms meeting the criteria of PTSD. Although all the patients were provided with psycho-educational support, only half of them claimed that those interventions were helpful (Bo et al., 2020). On the other hand, different authors suggest much lower percentage of PTSD in this group (8%) (Rohde et al., 2020). Another paper also has shown a high prevalence of PTSD among patients with the COVID-19 (12.2%). Authors highlighted high perceived stigmatization in this group, alongside fatigue (53.9%), anxiety and/or depression (26.8%) (Qi et al., 2020b).

It is also important to mention that psychiatric patients can be more susceptible to the SARS-CoV-2 infection (Yao et al., 2020). Due to their mental health, poor self-control, self-care, and lack of insight, they may be incapable of practicing infection control, therefore being vulnerable to the COVID-19 and its complications (Kim and Su, 2020). On the other hand, patients with obsessive compulsive disorder can be more exposed to stress, which would lead to exacerbation of their symptoms (Fineberg et al., 2020). However, the survey of 311 psychiatrists showed that 89.51% of them obtained extensive knowledge on the COVID-19 and 77.17% of them wanted to treat patients with mental disorders and comorbid SARS-CoV-2 infection (Shi et al., n.d.). Still, it is important to address this point in order to apply new strategies, especially considering a lack of adequate training in internal medicine among psychiatrists in some countries (Xiang et al., 2020a).

4. The impact of the SARS-CoV-2 from the public mental health perspective

4.1. A global perspective

Pandemic should especially be considered in terms of global social phenomena. During the pandemic, public mental health can be affected for multiple reasons (Table 2). Media reporting the escalating numbers of new cases and deaths, public restrictions and mass lockdown are likely to raise anxiety, which may have serious implications for global mental health (Rubin and Wessely, 2020). For instance, it has been estimated that the prevalence of posttraumatic stress symptoms was 7% in most affected areas in China (Liu et al., 2020a). Similar results have been obtained by other authors, who indicated that half of general population feel horrified due to the COVID-19 pandemic, however in general, it had a mild stressful impact (Zhang and Ma, 2020). In contrast, it has been suggested that depression or anxiety symptoms could affect almost 50%. One of the potential risk factors for the occurrence of psychopathological symptoms may be the frequent social media exposure (Junling et al., 2020). For the sake of reference, a recent study in which machine learning techniques have been used, analyzed posts of more than 17 thousand social media users who lived in China, in regions affected by the pandemics. It was found that the level of negative emotions and sensitivity to social risks increased, while the scores of positive emotions and the level of life satisfaction decreased during the pandemic (Li et al., 2020b).

Several regulations that affect daily activities, have been implemented in order to stop the spread of the virus. Most of them are focused on maintaining physical isolation and social distance, which so far are the only effective methods to reduce the possibility of further transmission of coronavirus. However, despite the great need to introduce these restrictions, they can have a negative impact on the mental health of many people. In many countries, non-essential workers have been forced to work at home. It has been estimated that 38% of people had to stop going to their workplace due to the pandemic in China; 25% stopped working at all and experienced high levels of psychological distress. In addition, wellbeing of people who until now have been physically active appeared to be deteriorated (Zhang et al., 2020b). Closing schools and universities was one of first decisions made in many countries facing the coronavirus pandemic, what has also negatively affected most students. In a survey conducted among 7143 college students, it was found that 0.9% of them experienced severe, 2.7% moderate, and 21.3% mild anxiety. Furthermore, the authors found that having relatives or acquaintances with COVID-19, impaired daily life activities. Additionally, delays in academic activities constituted risk factors for experiencing anxiety symptoms (Cao et al., 2020).

However, it should be noted that despite of all these negative emotional consequences, researchers have shown, that public opinion is generally positive with regard to the implemented preventive actions (Zhong et al., 2020). Nevertheless, people still report anxiety, worries about getting infected and sleep problems during the COVID-19 pandemic, which is also reflected by a recent study showing that the increased demand of psychiatric support is reported by 80% of study participants (Roy et al., 2020). Unfortunately, the scenario of global mental health crisis is very likely to occur, which is confirmed in first case reports of psychotic episodes related to pandemic outbreak (Zulkifli et al., 2020).

4.2. Mental health of quarantined people

Restricions that have been taken to decrease the transmission of the SARS-CoV-2 increase the intensity of anxiety, depression, feelings of loneliness and perceived threat in the society (World Health Organization. Mental health and psychosocial considerations during the COVID-19 outbreak, 18 March 2020. No. WHO/2019-nCoV/ MentalHealth/2020.1, 2020). These recommendations and the necessary social isolation can have far-reaching negative consequences and might be associated with limiting the continuation of providing tailored care, support and treatment. Some populations might be particularly vulnerable to such restrictions. These include people suffering from dementia (Armitage and Nellums, 2020), chronic diseases, mental illness and young children who may feel distressed and need parent-child closeness (Jiloha, 2020). The global spread of the SARS-CoV-2 and its disproportionate impact on the aforementioned groups can cause even greater disparities in the access to services they need and their further marginalization. In addition, it is important to emphasize the fact that pandemic is a crisis for everyone. People who have not experienced psychopathological symptoms so far, can react negatively to the new reality by presenting with adjustment disorders in the form of anxiety or depressive symptoms. People who are quarantined loose the possibility to meet face-to-face and access to traditional social help, what is a stressful phenomenon itself (Zhang et al., 2020c). According to the Chinese nationwide study carried out on 52,730 quarantined individuals, almost 35% of them experienced psychological distress. Women, people with higher education and those at older age were much more vulnerable to react with intensive stress and were more prone to develop symptoms meeting the criteria of PTSD, in contrast to young people. However, the distress level was influenced by the availability of local medical resources, efficiency of the regional public health system, as well as by preventive and control measures taken against the epidemic situation (Qiu et al., 2020). In another Chinese study, authors found that low levels of social capital were linked to increased levels of anxiety and stress, and good social situation was positively associated with better quality of sleep (Xiao et al., 2020a).

The most recent review of studies investigating the impact of quarantine reported that negative psychological effects of quarantine could cause adverse mental health outcomes. These included the symptoms of PTSD, depression, anxiety, sleep problems, increased fear, stigmatization, low self-esteem and a lack of self-control (Hossain et al., 2020). The mental health deterioration risk factors which were deemed as significant were: longer quarantine duration, boredom, infection concerns, frustration, inadequate supplies and information, financial loss, and possible stigma. It has been suggested that the pandemic might exert long-lasting adverse psychological effects (Brooks et al., 2020). It is worth noting that not unloaded angry and emotional tension in combination with deficits in individual coping strategies during the social isolation can lead to increased domestic violence (Xiang et al., 2020a).
It has further been indicated that also people working long hours, and those experiencing higher levels of anxiety are at substantial risk of mental health deterioration (Mo et al., 2020).

### 4.3. Medical workers

Health professionals, especially those exposed to the COVID-19, are at high risk of psychopathological symptoms caused by the infection. It is a case because of they have been put in dilemma, in which they had to decide to work combining a real fear of being infected and spreading the virus to their close ones (Xiang et al., 2020b). Moreover, they were faced with an unprecedented situation, being forced to make difficult decisions on how to provide care for all severely unwell patients with constrained resources, and how to work under extreme pressures. This can cause some of them to experience moral injury or mental health problems (Greenberg et al., 2020).

A recent study conducted among Chinese medical staff, demonstrated that 22.4% of them had moderate, and 6.2% experienced severe disturbances in the wake of the epidemic. A considerable number of professionals claimed that they have sought counseling or psychotherapy (Kang et al., 2020) (Table 3). A survey that was carried out among 1257 medical workers in Wuhan (China) found that almost 80% of participants reported distress, half of them declared symptoms of depression, 44.6% experienced anxiety, and one third suffered from insomnia. Especially nurses, women, professionals with more seniority titles, frontline health care workers, and those working in the center of epidemic reported more severe consequences to their mental health. Furthermore, those engaged in a direct care of patients with the COVID-19 were at higher risk of depression, anxiety, insomnia, and distress (Lai et al., 2020). Similar results were obtained by the authors of another Chinese study, which showed that medical staff who had a close contact with infected patients had higher fear, anxiety and depression scores (Lu et al., 2020). Seven other studies indicated the severity of depressive and anxiety symptoms among healthcare professionals working with the COVID-19 patients, with the range of 8.9%–50% and 10%–45%, respectively (Du et al., 2020; Guo et al., 2020; Liu et al., 2020b; Tan et al., 2020; Zhang et al., 2020d; Zhang et al., 2020e; Zhu et al., 2020b). Likewise, the research papers revealed high prevalence of sleep disturbances in this group, ranging from 33.9% to 45.5% (Qi et al., 2020c; Zhang et al., 2020c). Another study conducted among nurses used Colaizzi's phenomenological method, which focuses on the emotions and experience, showing shared patterns. Participants complained on severe fatigue, discomfort, and feeling helplessness caused by working conditions, alongside with fear and anxiety, caused by the concern of infecting other people. Most common self-coping styles incorporated psychological and life adjustment, team support, altruistic acts and rationalization. Despite that, professional caregivers of the COVID-19 patients experienced personal growth, including increased affection and gratefulness, feeling of professional responsibility, and self-reflection (Sun et al., 2020).

A very recent metaanalysis of 13 papers, including 33,062 participants in total has found, that during the COVID-19 pandemic, anxiety, depression and insomnia symptoms were present in 23.2%, 22.8% and 38.9% of healthcare workers respectively (Pappa et al., 2020).

Hopefully, some interventions are proved to be helpful for medical professionals dealing with mental problems. One study found that social support for the medical staff improves self-efficacy and sleep quality, as well as decreases the level of anxiety and stress (Xiao et al., 2020b).

### 5. Conclusions and future perspectives

Although there is still a limited number of studies on the SARS-CoV-2, current evidence strongly suggests its deteriorating impact on the CNS. It is especially important for future studies, as patients, who develop neurological symptoms in the course of the COVID-19, are more likely to have severe progression of the disease. The presence of the novel coronavirus in the brain can also manifest in psychiatric symptoms. It has been documented that the SARS-CoV-2 can pass through the blood-brain barrier, or it can reach the brain via the olfactory bulb. Although it has been shown that the virus can interact with the ACE2 receptors, the exact mechanisms underlying its deleterious effects on the CNS remain unknown. To date, various biological alterations associated with the coronavirus infection have been identified, and some of them, especially those related to the activation of microglia (Li et al., 2004) and cytokine signaling (Qing et al., 2020), might be of relevance to specific mental health outcomes. More and more often, cytokine alterations are being recognized as common findings in mood and psychotic disorders (Misiak et al., 2020; Frydecka et al., 2018; Misiak et al., 2019); however, causal associations are poorly established and their perception as downstream effectors of the underlying pathology cannot be ruled out. Similarly, microgliosis activation has also been demonstrated in severe mental disorders (Enaiche et al., 2019). Apart from the potential contribution of the SARS-CoV-2 to the development of mood and psychotic disorders, the awareness of adverse psychiatric effects of medications used in the treatment of the SARS-CoV-2 infection should be taken into consideration. For instance, it has been reported that psychotic symptoms might be the consequence of the treatment with chloroquine and hydroxychloroquine (Mascolo et al., 2018; Kwak and Kim, 2020).

It is important to note that previously known CoVs have been associated with certain mental disorders. Indeed, significantly higher rates of seropositivity for CoVs has been found in patients with a history of mood disorders (Okusaga et al., 2011). Similarly, Severance et al. (Severance et al., 2011) reported increased seropositivity for CoVs in patients with recent-onset psychosis. The concept of prenatal and perinatal infections as causative factors for various neurodevelopmental disorders has gained particular attention. Although, according to the available reports, pregnant women are at low risk of unfavorable outcomes of the SARS-CoV-2 infection, these conclusions might be premature (Sominsky et al., 2020). At this point, it is of great importance that non-specific maternal immune activation might also be associated with impaired neurodevelopmental trajectories in the offspring (Boulanger-Bertolus et al., 2018).

The outbreak and its media coverage also shape individual attitudes, stress responses and health literacy behaviors. Maintaining appropriate public information might also be of great importance in preventing stress-related mental health outcomes (Depoux et al., 2020). Patients, health professionals, and the general public are under a great psychological stress, which may lead to the development of various psychiatric symptoms and maladaptive responses, such as anxiety, fear, depression, and insomnia. As it has been shown, providing accurate information, professional counseling as well as social support can significantly help in dealing with these issues. Moreover, psychiatric and psychological services also play a pivotal role in the overall disease control (Li et al., 2020c). In times of global lockdown, mental health services should focus on providing help through telemedicine approaches (Zhou et al., 2020). Many psychiatric hospitals and psychological centers have already launched hotlines to provide psychological counseling services for people in need (Bao et al., 2020). However, it is important to stress that this negative impact can last longer than the coronavirus pandemic. In a 3-year follow-up study of the SARS outbreak in 2003, 23% of health care workers still reported moderate or greater depressive symptoms (Liu et al., 2012).

Although our knowledge on biology and long-term clinical outcomes of the SARS-CoV-2 infection is largely limited, approaching the pandemic based on lessons learnt from previous outbreaks of infectious diseases and biology of other CoVs provide the only grounds for developing public mental health strategies. Translation of therapeutic strategies that improve stress coping responses might contribute to alleviate the burden driven by the pandemic. Longitudinal studies will be the basis for further insights into potential consequences of the
outbreak. Animal model studies might also be important to extend early insights into neurobiology of the SARS-CoV-2.

Declaration of Competing Interest

We have no conflict of interest to disclose.

The publication was prepared under the project financed from the funds granted by the Ministry of Science and Higher Education in the „Regional Initiative of Excellence” programme for the years 2019-2022, project number 016/RID/2018/19, the amount of funding 11 998 121.30 PLN.

Acknowledgements

The publication was prepared under the project financed from the funds granted by the Ministry of Science and Higher Education in the „Regional Initiative of Excellence” programme for the years 2019-2022, project number 016/RID/2018/19, the amount of funding 11 998 121.30 PLN.

References

Andries, K., Pensart, M.B., 1980. Immunofluorescence studies on the pathogenesis of hemagglutinating encephalomyelitis virus infection in pigs upon oronasal inoculation. Am. J. Vet. Res. 41 (9), 1372-1378.

Armitage, R., Nellums, L.B., 2020. COVID-19 and the consequences of isolating the elderly [published online ahead of print, 2020 Mar 19]. Lancet Public Health. https://doi.org/10.1016/S2468-2667(20)30061-X. S2468-2667(20)30061-X.

Baig, A.M., Khaleeq, A., Ali, U., Syeda, H., 2020. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem. Neurosci. 11, 995–998. https://doi.org/10.1021/acscchemneuro.0c00122.

Bao, Y., Sun, Y., Meng, S., Shi, J., Lu, L., 2020. 2019-nCoV epidemic: address mental health care to empower society. Lancet. 395 (10244), 1372-1373. https://doi.org/10.1016/S0140-6736(20)30309-3. e37

Beach, R.S., Pruscan, N.C., Hogan, C., Doton, S., Merideth, F., Kontos, N., et al., 2020. Psychiatry in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement. Gen. Hosp. Psychiatry 65, 47–53. https://doi.org/10.1016/j.genhosppsych.2020.05.008.

Bo, H., Li, W., Yang, Y., Wang, Y., Zhang, Q., Cheng, T., et al., 2020. Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China. Psychol. Med. 1–7. https://doi.org/10.1017/S0033291720009999.

Boulanger-Bertolus, J., Pancaro, C., Mashour, G.A., 2018. Increasing role of maternal immune activation in neurodevelopmental disorders. Front. Behav. Neurosci. 12, 230. Published 2018 Oct 5. https://doi.org/10.3389/fnbeh.2018.00220.

Brooks, S.K., Webster, R.K., Smith, L.E., Woodland, L., Wessely, S., Greenberg, N., Rubin, G.J., 2020 Mar 14. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet. 395 (10227), 912–920. https://doi.org/10.1016/S0140-6736(20)30348-5.

Chandra, P.S., Shiva, N., Nagendraappa, S., Ganjeak, S., Thippeswamy, H., 2020. COVID 19 related psychosis as an interface of fears, socio-cultural issues and vulnerability-case report of two women from India. Psychiatry Res. 290, 113115. https://doi.org/10.1016/j.psychres.2020.113115.

Chen, G., Wu, D., Guo, W., et al., 2020. Managing mental health challenges faced by healthcare workers during covid-19 pandemic. BMJ, 368, m1211. https://doi.org/10.1136/bmj.m1211. Mar 26.

Guo, J., Liao, L., Wang, B., 2020. Psychological effects of COVID-19 on hospital staff: a national cross-sectional survey of China mainland. SSRN Electron. J. https://doi.org/10.21238/ssrn.3550050.

Heneka, T., Golenbock, D., Latz, E., Morgan, D., Brown, R., 2020. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res. Ther. 12, 69. https://doi.org/10.1186/s13195-020-00640-3.

Horne, K., Weston, S.J., Fisher, P.A., 2020. Identifying causal role of COVID-19 in immunopsychiatry models [published online ahead of print, 2020 May 29]. Brain Behav. Immun. https://doi.org/10.1016/j.bbi.2020.05.066. S0889-1591(20).

Hossain, M.M., Sultanu, A., Purobit, N., 2020. Mental health outcomes of quarantine and isolation for infection prevention: a systematic umbrella review of the global evidence. PsyArXiv. https://doi.org/10.31234/osf.io/d5c2v.

Huang, C., Wang, Y., Li, X., et al., 2020a. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;]. Lancet. 395 (10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30185-X.

Huang, C., Yang, R., Xu, Y., Gong, F., 2020b. Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China. medRxiv. https://doi.org/10.1101/2020.02.27.20020909. Published online March 5.

Hulsut, R.J., de Haan, C.A., Bosch, B.J., 2016. Coronavirus spike protein and tropism towards different tissues in mammoths. Adv. Virus Res. 94, 215-257. https://doi.org/10.1016/bs.aivir.2016.08.004.

Jeffery, H., Yim, H.W., Song, Y.J., et al., 2016. Mental health status of people isolated due to Middle East respiratory syndrome. Epidemiol Health. 38, e2016048. https://doi.org/10.1177/0266462316648208.

Jokela, R.C., 2020. COVID-19 and Mental Health. Epidemic Int. 5 (1), 7–9. https://doi.org/10.24321/2455.7048.202002.

Junling, G., Pinping, Z., Yingnan, J., Chen, J., Mao, Y., Chen, S., et al., 2020a. Mental health problems and social media exposure during COVID-19 outbreak. PloS One. https://doi.org/10.1371/journal.pone.0231924.

Kang, L., Ma, S., Chen, D., et al., 2020. Impact on mental health and perceptions of psychological care among medical and nursing staff in Wuhan during the 2019 novel coronavirus disease outbreak: A cross-sectional study [published online ahead of print, 2020 Mar 30]. Brain Behav. Immun. https://doi.org/10.1016/j.bbi.2020.03.028. S0889-1591(20)30348-2.

Kim, S.W., Su, K.P., 2020. Using psychoneuroimmunity against COVID-19 [published online ahead of print, 2020 mar 29]. Brain Behav. Immun. 87, 4–5. https://doi.org/10.1016/j.bbi.2020.03.032.

Kim, H.C., Yoo, S.Y., Lee, B.H., Lee, S.H., Shin, H.S., 2018. Psychiatric findings in suspected and confirmed middle east respiratory syndrome patients quarantined in hospital: a retrospective chart analysis. Psychiatry Investig. 15 (4), 355–360. https://doi.org/10.4068/pi.2017.15.4.355.

Kong, X., Zheng, K., Tang, M., et al., 2020. Prevalence and factors associated with depression and anxiety of hospitalized patients with COVID-19. medRxiv. https://doi.org/10.1101/2020.03.23.20040753. Published online April 5.

Kwak, Y., Kim, Y., 2020. Association between mental health and mental illness patterns among elderly Koreans. Geriatr Gerontol Int 18, 161–168. https://doi.org/10.1111/ggi.13106.

Lai, J., Ma, S., Wang, Y., Cai, Z., Hu, J., Wei, N., Wu, J., 2020a. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open 3 (3). https://doi.org/10.1001/jamanetworkopen.2020.3976. e203976. Mar 2.

Leung, K.S.-S., Ng, T.T.-L., Wu, A.K.-L., et al., 2020. A territory-wide study of early
COVID-19 outbreak in Hong Kong community: a clinical, epidemiological and phy- 
logenetic investigation. medRxiv. https://doi.org/10.1101/2020.03.30.20045740. 
published online April 7.

Li, Y., Fu, L., Gonzales, D.M., Lavi, E., 2004. Coronavirus neurovirulence correlates with 
the ability of the virus to induce proinflammatory cytokine signals from astrocytes 
and microglia. J. Virol. 78 (7), 3398–3406. https://doi.org/10.1128/jvi.78.7.3398-
3406.2004.

Li, Y.C., Bai, W.Z., Hirano, N., Sun, C., Zhang, X., Xie, B., Yu, D., 2020b. The influ-
encing factors of immune response in major psychiatric disorders: where are we now and 
what do we want to be? Front. Psychiatry. 10, 5. https://doi.org/10.3389/fpsyt. 
2019.00005.

Qi, R., Chen, W., Li, S., Thompson, P.M., Zhang, L., Xi, F., et al., 2020h. Psychological 
morbidities and fatigue in patients with confirmed COVID-19 during disease out-
break: prevalence and associated biopsychosocial risk factors. medRxiv. https:// 
doi.org/10.1101/2020.05.08.20031666. 05.08.202031666.

Qi, R., Yu, J., Li, R.Z., et al., 2020. Evaluation of psychological symptoms related to 
COVID-19 among medical workers. Psychiatry Res. 288, 112936. https://doi.org/ 
10.1016/j.perspect.2020.112936.

Qi, Y., Bili, W., Jianhua, M., 2020. Cytokine storm in COVID-19 and treatment. J. Inf. 
Secur. https://doi.org/10.1101/2020.04.21.20067744. 04.21.20067744.

Qi, Y., Chen, B., Zhao, M., Wang, X., Xie, B., Yu, X., 2020. A nationwide survey of psy-
chological distress among Chinese people in the COVID-19 epidemic: implications 
and policy recommendations. Gen Psychiatry. 33 (2). https://doi.org/10.1177 
0022184120932313. 2020.04.2022.

Qi, Y., Chen, B., Zhao, M., Wang, X., Xie, B., Yu, X., 2020. A nationwide survey of psy-
chological distress among Chinese people in the COVID-19 epidemic: implications 
and policy recommendations. Gen Psychiatry. 33 (2). https://doi.org/10.1177 
0022184120932313. 2020.04.2022.

Qi, Y., Chen, B., Zhao, M., Wang, X., Xie, B., Yu, X., 2020. A nationwide survey of psy-
chological distress among Chinese people in the COVID-19 epidemic: implications 
and policy recommendations. Gen Psychiatry. 33 (2). https://doi.org/10.1177 
0022184120932313. 2020.04.2022.

Qi, Y., Chen, B., Zhao, M., Wang, X., Xie, B., Yu, X., 2020. A nationwide survey of psy-
chological distress among Chinese people in the COVID-19 epidemic: implications 
and policy recommendations. Gen Psychiatry. 33 (2). https://doi.org/10.1177 
0022184120932313. 2020.04.2022.

Qi, Y., Chen, B., Zhao, M., Wang, X., Xie, B., Yu, X., 2020. A nationwide survey of psy-
chological distress among Chinese people in the COVID-19 epidemic: implications 
and policy recommendations. Gen Psychiatry. 33 (2). https://doi.org/10.1177 
0022184120932313. 2020.04.2022.

Qi, Y., Chen, B., Zhao, M., Wang, X., Xie, B., Yu, X., 2020. A nationwide survey of psy-
chological distress among Chinese people in the COVID-19 epidemic: implications 
and policy recommendations. Gen Psychiatry. 33 (2). https://doi.org/10.1177 
0022184120932313. 2020.04.2022.
Xu, J., Zhong, S., Liu, J., et al., 2005. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. Clin. Infect. Dis. 41, 1089–1096.

Xu, H., Zhong, L., Deng, J., Peng, J., Dan, H., Zeng, X., et al., 2020a. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int. J. Oral Sci. 12 (1). https://doi.org/10.1038/s41368-020-0074-x.

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., et al., 2020 Aprb. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir. Med. 8 (4), 420–422. https://doi.org/10.1016/S2213-2600(20)30076-X.

Yang, L., Wu, W., Hou, Y., et al., 2020. Analysis of psychological state and clinical psychological intervention model of patients with COVID-19. medRxiv. https://doi.org/10.1101/2020.03.22.20040899. published online March 24.

Yao, H., Chen, J.-H., Xu, Y.-F., 2020. Patients with mental health disorders in the COVID-19 epidemic. Lancet Psychiatry 7 (4). https://doi.org/10.1016/S2215-0366(20)30090-0. e21. Apr.

Yu, F., Du, L., Ojcius, D.M., Pan, C., Jiang, S., 2020. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. Microbes Infect. https://doi.org/10.1016/j.micinf.2020.01.003.

Zhang, Y., Ma, Z.F., 2020. Impact of the COVID-19 Pandemic on Mental Health and Quality of Life among Local Residents in Liaoning Province, China: A Cross-Sectional Study. Int. J. Environ. Res. Public Health 17 (7). https://doi.org/10.3390/ijerph17072381. E2381. Mar 31.

Zhang, B., Zhou, X., Qiu, Y., et al., 2020a. Clinical characteristics of 82 death cases with COVID-19. medRxiv. https://doi.org/10.1101/2020.02.26.20028191. published online Feb 27.

Zhang, S., Wang, Y., Rauch, A., Wei, F., 2020b. Unprecedented disruption of lives and work: health, distress and life satisfaction of working adults in China one month into the COVID-19 outbreak. Psychiatry Res. 288. https://doi.org/10.1016/j.psychres.2020.112958.

Zhang, J., Wu, W., Zhao, X., Zhang, W., 2020c. Recommended psychological crisis intervention response to the 2019 novel coronavirus pneumonia outbreak in China: a model of West China Hospital. Precis Clin Med. https://doi.org/10.1093/pcmmed/ pbaa006. Published 2020 Feb 18.

Zhang, C., Yang, L., Liu, S., 2020d. Survey of insomnia and related social psychological factors among medical staff involved in the 2019 novel coronavirus disease outbreak. Front. Psychiatry. 11, 306.

Zhang, W., Wang, K., Yin, L., 2020e. Mental health and psychosocial problems of medical health workers during the COVID-19 epidemic in China. Psychother. Psychosom. 1–9.

Zhang, W., Wang, K., Yin, L., 2020f. Mental health and psychosocial problems of medical health workers during the COVID-19 epidemic in China. Psychother. Psychosom. 1–9.

Zhao, Y., Zhao, Z., Wang, Y., et al., 2020. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. bioRxiv. https://doi.org/10.1101/2020.03.26.919985.

Zhong, B.L., Luo, W., Li, H.M., Zhang, Q.Q., Liu, X.G., Li, W.T., Li, Y., 2020. Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey. Int. J. Biol. Sci. 16 (10), 1745–1752. https://doi.org/10.7150/ijbs.45221.

Zhou, X., Snoswell, C.L., Harding, L.E., Bambling, M., Edirippulige, S., Bai, X., et al., 2020. The role of telehealth in reducing the mental health burden from COVID-19. Telemed. e-Health. https://doi.org/10.1089/tmj.2020.00668.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., et al., 2020a. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733. https://doi.org/10.1056/NEJMoa2001017.

Zhu, Z., Xu, S., Wang, H., 2020b. COVID-19 in Wuhan: immediate psychological impact on 5062 health workers. medRxiv 02 (20), 20025338.

Zulkipli, N.A., Sivapatham, S., Guan, N.C., 2020. Brief psychotic disorder in relation to coronavirus, covid-19 outbreaks: a case report. MJP Online Early. 29, 1.