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How COVID-19 shaped mental health: from infection to pandemic effects

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Abstract

The Coronavirus Disease 2019 (COVID-19) pandemic has threatened global mental health, both indirectly via disruptive societal changes and directly via neuropsychiatric sequelae after SARS-CoV-2 infection. Despite a small increase in self-reported mental health problems, this has (so far) not translated into objectively measurable increased rates of mental disorders, self-harm or suicide rates at the population level. This could suggest effective resilience and adaptation, but there is substantial heterogeneity among subgroups, and time-lag effects may also exist. With regard to COVID-19 itself, both acute and post-acute neuropsychiatric sequelae have become apparent, with high prevalence of fatigue, cognitive impairments and anxiety and depressive symptoms, even months after infection. To understand how COVID-19 continues to shape mental health in the longer term, fine-grained, well-controlled longitudinal data at the (neuro)biological, individual and societal levels remain essential. For future pandemics, policymakers and clinicians should prioritize mental health from the outset to identify and protect those at risk and promote long-term resilience.

In 2019, the COVID-19 outbreak was declared a pandemic by the World Health Organization (WHO), with 590 million confirmed cases and 6.4 million deaths worldwide

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as of August 2022 (ref. [1]). To contain the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the globe, many national and local governments implemented often drastic restrictions as preventive health measures. Consequently, the pandemic has not only led to potential SARS-CoV-2 exposure, infection and disease but also to a wide range of policies consisting of mask requirements, quarantines, lockdowns, physical distancing and closure of non-essential services, with unprecedented societal and economic consequences.

As the world is slowly gaining control over COVID-19, it is timely and essential to ask how the pandemic has affected global mental health. Indirect effects include stress-evoking and disruptive societal changes, which may detrimentally affect mental health in the general population. Direct effects include SARS-CoV-2-mediated acute and long-lasting neuropsychiatric sequelae in affected individuals that occur during primary infection or as part of post-acute COVID syndrome (PACS)[2]—defined as symptoms lasting beyond 3–4 weeks that can involve multiple organs, including the brain. Several terminologies exist for characterizing the effects of COVID-19. PACS also includes late sequalae that constitute a clinical diagnosis of ‘long COVID’ where persistent symptoms are still present 12 weeks after initial infection and cannot be attributed to other conditions[3].

Here we review both the direct and indirect effects of COVID-19 on mental health. First, we summarize empirical findings on how the COVID-19 pandemic has impacted population mental health, through mental health symptom reports, mental disorder prevalence and suicide rates. Second, we describe mental health sequalae of SARS-CoV-2 virus infection and COVID-19 disease (for example, cognitive impairment, fatigue and affective symptoms). For this, we use the term PACS for neuropsychiatric consequences beyond the acute period, and will also describe the underlying neurobiological impact on brain structure and function. We conclude with a discussion of the lessons learned and knowledge gaps that need to be further addressed.

Impact of the COVID-19 pandemic on population mental health

Independent of the pandemic, mental disorders are known to be prevalent globally and cause a very high disease burden[4–6]. For most common mental disorders (including major depressive disorder, anxiety disorders and alcohol use disorder), environmental stressors play a major etiological role. Disruptive and unpredictable pandemic circumstances may increase distress levels in many individuals, at least temporarily. However, it should be noted that the pandemic not only resulted in negative stressors but also in positive and potentially buffering changes for some, including a better work–life balance, improved family dynamics and enhanced feelings of closeness[7].

Awareness of the potential mental health impact of the COVID-19 pandemic is reflected in the more than 35,000 papers published on this topic. However, this rapid research output comes with a cost: conclusions from many papers are limited due to small sample sizes, convenience sampling with unclear generalizability implications and lack of a pre-COVID-19 comparison. More reliable estimates of the pandemic mental health impact come from studies with longitudinal or time-series designs that include a pre-pandemic

comparison. In our description of the evidence, we, therefore, explicitly focused on findings from meta-analyses that include longitudinal studies with data before the pandemic, as recently identified through a systematic literature search by the WHO[8].

Self-reported mental health problems

Most studies examining the pandemic impact on mental health used online data collection methods to measure self-reported common indicators, such as mood, anxiety or general psychological distress. Pooled prevalence estimates of clinically relevant high levels of depression and anxiety symptoms during the COVID-19 pandemic range widely—between 20% and 35%[9–12]—but are difficult to interpret due to large methodological and sample heterogeneity. It also is important to note that high levels of self-reported mental health problems identify increased vulnerability and signal an increased risk for mental disorders, but they do not equal clinical caseness levels, which are generally much lower.

Three meta-analyses, pooling data from between 11 and 61 studies and involving ~50,000 individuals or more[13–15], compared levels of self-reported mental health problems during the COVID-19 pandemic with those before the pandemic. Meta-analyses report on pooled effect sizes—that is, weighted averages of study-level effect sizes; these are generally considered small when they are ~0.2, moderate when ~0.5 and large when ~0.8. As shown in Table 1, meta-analyses on mental health impact of the COVID-19 pandemic reach consistent conclusions and indicate that there has been a heterogeneous, statistically significant but small increase in self-reported mental health problems, with pooled effect sizes ranging from 0.07 to 0.27. The largest symptom increase was found when using specific mental health outcome measures assessing depression or anxiety symptoms. In addition, loneliness —a strong correlate of depression and anxiety—showed a small but significant increase during the pandemic (Table 1; effect size = 0.27)[16]. In contrast, self-reported general mental health and well-being indicators did not show significant change, and psychotic symptoms seemed to have decreased slightly[13]. In Europe, alcohol purchase decreased, but high-level drinking patterns solidified among those with pre-pandemic high drinking levels[17]. When compared to pre-COVID levels, no change in self-reported alcohol use (effect size = −0.01) was observed in a recent meta-analysis summarizing 128 studies from 58 (predominantly European and North American) countries[18].

What is the time trajectory of self-reported mental health problems during the pandemic? Although findings are not uniform, various large-scale studies confirmed that the increase in mental health problems was highest during the first peak months of the pandemic and smaller—but not fully gone—in subsequent months when infection rates declined and social restrictions eased[13,19,20]. Psychological distress reports in the United Kingdom increased again during the second lockdown period[15]. Direct associations between anxiety and depression symptom levels and the average number of daily COVID-19 cases were confirmed in the US Centers for Disease Control and Prevention (CDC) data[21]. Studies that examined longer-term trajectories of symptoms during the first or even second year of the COVID-19 pandemic are more sparse but revealed stability of symptoms without clear evidence of recovery[15,22]. The exception appears to be for loneliness, as some studies confirmed further increasing trends throughout the first COVID-19 pandemic year[22,23]. As

most published population-based studies were conducted in the early time period in which absolute numbers of SARS-CoV2-infected individuals were still low, the mental health impacts described in such studies are most likely due to indirect rather than direct effects of SARS-CoV-2 infection. However, it is possible that, in longer-term or later studies, these direct and indirect effects may be more intertwined.

The extent to which governmental policies and communication have impacted on population mental health is a relevant question. In cross-country comparisons, the extent of social restrictions showed a dose–response relationship with mental health problems[24,25]. In a review of 33 studies worldwide, it was concluded that governments that enacted stringent measures to contain the spread of COVID-19 benefited not only the physical but also the mental health of their population during the pandemic[26], even though more stringent policies may lead to more short-term mental distress[25]. It has been suggested that effective communication of risks, choices and policy measures may reduce polarization and conspiracy theories and mitigate the mental health impact of such measures[25,27,28].

In sum, the general pattern of results is that of an increase in mental health symptoms in the population, especially during the first pandemic months, that remained elevated throughout 2020 and early 2021. It should be emphasized that this increase has a small effect size. However, even a small upward shift in mental health problems warrants attention as it has not yet shown to be returned to pre-pandemic levels, and it may have meaningful cumulative consequences at the population level. In addition, even a small effect size may mask a substantial heterogeneity in mental health impact, which may have affected vulnerable groups disproportionally (see below).

Mental disorders, self-harm and suicide

Whether the observed increase in mental health problems during the COVID-19 pandemic has translated into more mental disorders or even suicide mortality is not easy to answer. Mental disorders, characterized by more severe, disabling and persistent symptoms than self-reported mental health problems, are usually diagnosed by a clinician based on the International Classification of Diseases, 10th Revision (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria or with validated semi-structured clinical interviews. However, during the COVID-19 pandemic, research systematically examining the population prevalence of mental disorders has been sparse. Unfortunately, we can also not strongly rely on healthcare use studies as the pandemic impacted on healthcare provision more broadly, thereby making figures of patient admissions difficult to interpret.

On a global scale and based on imputations and modeling from survey data of self-reported mental health problems, the Global Burden of Disease (GBD) study[29] estimated that the COVID-19 pandemic has led to a 28% (95% uncertainty interval (UI): 25–30) increase in major depressive disorders and a 26% (95% UI: 23–28) increase in anxiety disorders. It should be noted that these estimations come with high uncertainty as the assumption that transient pandemic-related increases in mental symptoms extrapolate into incident mental disorders remains disputable. So far, only four longitudinal population-based studies have measured and compared current mental (that is, depressive and anxiety) disorder prevalence

—defined using psychiatric diagnostic criteria—before and during the pandemic. Of these, two found no change[30,31], one found a decrease[32] and one found an increase in prevalence of these disorders[33]. These studies were local, limited to high-income countries, often small-scale and used different modes of assessment (for example, online versus in-person) before and during the pandemic. This renders these observational results uncertain as well, but their contrast to the GBD calculations[29] is striking.

Time-series analysis of monthly suicide trends in 21 middle-income to high-income countries across the globe yielded no evidence for an increase in suicide rates in the first 4 months of the pandemic, and there was evidence of a fall in rates in 12 countries[34]. Also in the United States, there was a significant decrease in suicide mortality in the first pandemic months but a slight increase in mortality due to drug overdose and homicide[35]. A living systematic review[36] also concluded that, throughout 2020, there was no observed increase in suicide rates in 20 studies conducted in North America, Europe and Asia. Analyses of electronic health record data in the primary care setting showed reduced rates of self-harm during the first COVID-19 pandemic year[37]. In contrast, emergency department visits for self-harm behavior were unchanged[38] or increased[39]. Such inconsistent findings across healthcare settings may reflect a reluctance in healthcare-seeking behavior for mental healthcare issues. In the living systematic review, eight of 11 studies that examined service use data found a significant decrease in reported self-harm/suicide attempts after COVID lockdown, which returned to pre-lockdown levels in some studies with longer follow-up (5 months)[36].

In sum, although calculations based on survey data predict a global increase of mental disorder prevalence, objective and consistent evidence for an increased mental disorder, self-harm or suicide prevalence or incidence during the first pandemic year remains absent. This observation, coupled with the only small increase in mental health symptom levels in the overall population, may suggest that most of the general population has demonstrated remarkable resilience and adaptation. However, alternative interpretations are possible. First, there is a large degree of heterogeneity in the mental health impact of COVID-19, and increased mental health in one group (for example, due to better work–family balance and work flexibility) may have masked mental health problems in others. Various societal responses seen in many countries, such as community support activities and bolstering mental health and crisis services, may have had mitigating effects on the mental health burden. Also, the relationship between mental health symptom increases during stressful periods and its subsequent effects on the incidence of mental disorders may be non-linear or could be less visible due to resulting alternative outcomes, such as drug overdose or homicide. Finally, we cannot rule out a lag-time effect, where disorders may take more time to develop or be picked up, especially because some of the personal financial or social consequences of the COVID pandemic may only become apparent later. It should be noted that data from low-income countries and longer-term studies beyond the first pandemic year are largely absent.

Which individuals are most affected by the COVID-19 pandemic?

There is substantial heterogeneity across studies that evaluated how the COVID pandemic impacted on mental health[13–15]. Although our society as a whole may have the ability to adequately bounce back from pandemic effects, there are vulnerable people who have been affected more than others.

First, women have consistently reported larger increases in mental health problems in response to the COVID-19 pandemic than men[13,15,29,40], with meta-analytic effect sizes being 44%[15] to 75%[13] higher. This could reflect both higher stress vulnerability or larger daily life disruptions due to, for example, increased childcare responsibilities, exposure to home violence or greater economic impact due to employment disruptions that all disproportionately fell to women[41], thereby exacerbating the already existing pre-pandemic gender inequalities in depression and anxiety levels. In addition, adolescents and young adults have been disproportionately affected compared to younger children and older adults[12,15,29,40]. This may be the result of unfavorable behavioral and social changes (for example, school closure periods[42]) during a crucial development phase where social interactions outside the family context are pivotal. Alarmingly, even though suicide rates did not seem to increase at the population level, studies in China[43] and Japan[44] indicated significant increases in suicide rates in children and adolescents.

Existing socio-cultural disparities in mental health may have further widened during the COVID pandemic. Whether the impact is larger for individuals with low socio-economic status remains unclear, with contrasting meta-analyses pointing toward this group being protected[15] or at increased risk[40]. Earlier meta-analyses did not find that the mental health impact of COVID-19 differed across Europe, North America, Asia and Oceania[13,14], but data are lacking from Africa and South America. Nevertheless, a large-scale within-country comparison in the United States found that the mental health of Black, Hispanic and Asian respondents worsened relatively more during the pandemic compared to White respondents. Moreover, White respondents were more likely to receive professional mental healthcare during the pandemic, and, conversely, Black, Hispanic, and Asian respondents demonstrated higher levels of unmet mental healthcare needs during this time[45].

People with pre-existing somatic conditions represent another vulnerable group in which the pandemic had a greater impact (pooled effect size of 0.25)[13]. This includes people with conditions such as epilepsy, multiple sclerosis or cardiometabolic disease as well as those with multiple comorbidities. The disproportionate impact may reflect this group's elevated COVID-19 risk and, consequently, more perceived stress and fear of infection, but it could also reflect disruptions of regular healthcare services.

Healthcare workers faced increased workload, rapidly changing and challenging work environments and exposure to infections and death, accompanied by fear of infecting themselves and their families. High prevalences of (subthreshold) depression (13%[46]), depressive symptoms (31%[47]), (subthreshold) anxiety (16%[46]), anxiety symptoms (23%[47]) and post-traumatic stress disorder (~22%[46,47]) have been reported in healthcare workers. However, a meta-analysis did not find a larger mental health impact of the pandemic as compared to the general population[40], and another meta-analysis (of 206 studies) found that

the mental health status of healthcare workers was similar to or even better than that of the general population during the first COVID year[48]. However, it is important to note that these meta-analyses could not differentiate between frontline and non-frontline healthcare workers.

Finally, individuals with pre-existing mental disorders may be at increased risk for exacerbation of mental ill-health during the pandemic, possibly due to disease history–illustrating a higher genetic and/or environmental vulnerability–but also due to discontinuity of mental healthcare. Already before the pandemic, mental health systems were under-resourced and disorganized in most countries[6,49], but a third of all WHO member states reported disruptions to mental and substance use services during the first 18 months of the pandemic[50], with reduced, shortened or postponed appointments and limited capacity for acute inpatient admissions[51,52]. Despite this, there is no clear evidence that individuals with pre-existing mental disorders are disproportionately affected by pandemic-related societal disruptions; the effect size for pandemic impact on self-reported mental health problems was similar in psychiatric patients and the general population[13]. In the United States, emergency visits for ten different mental disorders were generally stable during the pandemic compared to earlier periods[53]. In a large Dutch study[22,54] with multiple pre-pandemic and during-pandemic assessments, there was no difference in symptom increase among patients relative to controls (see Fig. 1 for illustration). In absolute terms, however, it is important to note that psychiatric patients show much higher symptom levels of depression, anxiety, loneliness and COVID-fear than healthy controls. Again, variation in mental health changes during the pandemic is large: next to psychiatric patients who showed symptom decrease due to, for example, experiencing relief from social pressures, there certainly have been many patients with symptom increases and relapses during the pandemic.

Impact of COVID-19 infection and disease on mental health and the brain

Not only the pandemic but also COVID-19 itself can have severe impact on the mental health of affected individuals and, thus, of the population at large. Below we describe acute and post-acute neuropsychiatric sequelae seen in patients with COVID-19 and link these to neurobiological mechanisms.

Neuropsychiatric sequelae in individuals with COVID-19

Common symptoms associated with acute SARS-CoV-2 infection include headache, anosmia (loss of sense of smell) and dysgeusia (loss of sense of taste). The broader neuropsychiatric impact is dependent on infection severity and is very heterogeneous (Table 2). It ranges from no neuropsychiatric symptoms among the large group of asymptomatic COVID-19 cases to milder transient neuropsychiatric symptoms, such as fatigue, sleep disturbance and cognitive impairment, predominantly occurring among symptomatic patients with COVID-19 (ref. [55]). Cognitive impairment consists of sustained memory impairments and executive dysfunction, including short-term memory loss, concentration problems, word-finding problems and impaired daily problem-solving, colloquially termed ‘brain fog’ by patients and clinicians. A small number of infected individuals become severely ill and require hospitalization. During hospital admission, the predominant

neuropsychiatric outcome is delirium[56]. Delirium occurs among one-third of hospitalized patients with COVID-19 and among over half of patients with COVID-19 who require intensive care unit (ICU) treatment. These delirium rates seem similar to those observed among individuals with severe illness hospitalized for other general medical conditions[57]. Delirium is associated with neuropsychiatric sequalae after hospitalization, as part of post-intensive care syndrome[58], in which sepsis and inflammation are associated with cognitive dysfunction and an increased risk of a broad range of psychiatric symptoms, from anxiety to depression and psychotic symptoms with hallucinations[59,60].

A subset of patients with COVID-19 develop PACS[61], which can include neuropsychiatric symptoms. A large meta-analysis summarizes 51 studies involving 18,917 patients with a mean follow-up of 77 days (range, 14–182 days)[62]. The most prevalent neuropsychiatric symptom associated with COVID-19 was sleep disturbance, with a pooled prevalence of 27.4%, followed by fatigue (24.4%), cognitive impairment (20.2%), anxiety symptoms (19.1%), post-traumatic stress symptoms (15.7%) and depression symptoms (12.9%) (Table 2). Another meta-analysis that assessed patients 12 weeks or more after confirmed COVID-19 diagnosis found that 32% experienced fatigue, and 22% experienced cognitive impairment[63]. To what extent neuropsychiatric symptoms are truly unique for patients with COVID remains unclear from these meta-analyses, as hardly any study included well-matched controls with other types of respiratory infections or inflammatory conditions.

Studies based on electronic health records have examined whether higher levels of neuropsychiatric symptoms truly translate into a higher incidence of clinically overt mental disorders[64,65]. In a 1-year follow-up using the US Veterans Affairs database, 153,848 survivors of SARS-CoV-2 infection exhibited an increased incidence of any mental disorder with a relative risk of 1.46 and, specifically, 1.35 for anxiety disorders, 1.39 for depressive disorders and 1.38 for stress and adjustment disorders, compared to a contemporary group and a historical control group (n = 5,859,251)[65]. In absolute numbers, the incident risk difference attributable to SARS-CoV-2 for mental disorders was 64 per 1,000 individuals. Taquet et al.[64] analyzed electronic health records from the US-based TriNetX network with over 81 million patients and 236,379 COVID-19 survivors followed for 6 months. In absolute numbers, 6-month incidence of hospital contacts related to diagnoses of anxiety, affective disorder or psychotic disorder was 7.0%, 4.5% and 0.4%, respectively. Risks of incident neurological or psychiatric diagnoses were directly correlated with COVID-19 severity and increased by 78% when compared to influenza and by 32% when compared to other respiratory tract infections. In contrast, a medical record study involving 8.3 million adults confirmed that neuropsychiatric disorders were significantly elevated among COVID-19 hospitalized individuals but to a similar extent as in hospitalized patients with other severe respiratory disease[66]. In line with this, a study using language processing of clinical notes in electronic health records did not find an increase in fatigue, mood and anxiety symptoms among COVID-19 hospitalized individuals when compared to hospitalized patients for other indications and adjusted for sociodemographic features and hospital course[67]. It is important to note that research based only on hospital records might be influenced by increased health-seeking behavior that could be differential across care settings or by increased follow-up by hospitals of patients with COVID-19 (compared to patients with other conditions).

Consequently, whether PACS symptoms form a unique pattern due to specific infection with SARS-CoV-2 remains debatable. Prospective case–control studies that do not rely on hospital records but measure the incidence of neuropsychiatric symptoms and diagnoses after COVID-19 are still scarce, but they are critical for distinguishing causation and confounding when characterizing PACS and the uniqueness of neuropsychiatric sequalae after COVID-19 (ref. [68]). Recent studies with well-matched control groups illustrate that long-term consequences may not be so unique, as they were similar to those observed in patients with other diseases of similar severity, such as after acute myocardial infarction or in ICU patients[56,66]. A first prospective follow-up study of COVID-19 survivors and control patients matched on disease severity, age, sex and ICU admission found similar neuropsychiatric outcomes, regarding both new-onset psychiatric diagnosis (19% versus 20%) and neuropsychiatric symptoms (81% versus 93%). However, moderate but significantly worse cognitive outcomes 6 months after symptom onset were found among survivors of COVID-19 (ref. [69]). In line with this, a longitudinal study of 785 participants from the UK Biobank showed small but significant cognitive impairment among individuals infected with SARS-CoV-2 compared to matched controls[70].

Numerous psychosocial mechanisms can lead to neuropsychiatric sequalae of COVID-19, including functional impairment; psychological impact due to, for example, fear of dying; stress of being infected with a novel pandemic disease; isolation as part of quarantine and lack of social support; fear/guilt of spreading COVID-19 to family or community; and socioeconomic distress by lost wages[71]. However, there is also ample evidence that neurobiological mechanisms play an important role, which is discussed below.

Neurobiological mechanisms underlying neuropsychiatric sequelae of COVID-19

Acute neuropsychiatric symptoms among patients with severe COVID-19 have been found to correlate with the level of serum inflammatory markers[72] and coincide with neuroimaging findings of immune activation, including leukoencephalopathy, acute disseminated encephalomyelitis, cytotoxic lesions of the corpus callosum or cranial nerve enhancement[73]. Rare presentations, including meningitis, encephalitis, inflammatory demyelination, cerebral infarction and acute hemorrhagic necrotizing encephalopathy, have also been reported[74]. Hospitalized patients with frank encephalopathies display impaired blood-brain barrier (BBB) integrity with leptomeningeal enhancement on brain magnetic resonance images[75]. Studies of postmortem specimens from patients who succumbed to acute COVID-19 reveal significant neuropathology with signs of hypoxic damage and neuroinflammation. These include evidence of BBB permeability with extravasation of fibrinogen, microglial activation, astrogliosis, leukocyte infiltration and microhemorrhages[76,77]. However, it is still unclear to what extent these findings differ from patients with similar illness severity due to acute non-COVID illness, as these brain effects might not be virus-specific effects but rather due to cytokine-mediated neuroinflammation and critical illness.

Post-acute neuroimaging studies in SARS-CoV-2-recovered patients, as compared to control patients without COVID-19, reveal numerous alterations in brain structure on a group level, although effect sizes are generally small. These include minor reduction in gray matter thickness in the various regions of the cortex and within the corpus collosum, diffuse

edema, increases in markers of tissue damage in regions functionally connected to the olfactory cortex and reductions in overall brain size[70,78]. Neuroimaging studies of post-acute COVID-19 patients also report abnormalities consistent with micro-structural and functional alterations, specifically within the hippocampus[79,80], a brain region critical for memory formation and regulating anxiety, mood and stress responses, but also within gray matter areas involving the olfactory system and cingulate cortex[80]. Overall, these findings are in line with ongoing anosmia, tremors, affect problems and cognitive impairment.

Interestingly, despite findings mentioned above, there is little evidence of SARS-CoV-2 neuroinvasion with productive replication, and viral material is rarely found in the central nervous system (CNS) of patients with COVID-19 (refs. [76,77,81]). Thus, neurobiological mechanisms of SARS-CoV-2-mediated neuropsychiatric sequelae remain unclear, especially in patients who initially present with milder forms of COVID-19. Symptomatic SARS-CoV-2 infection is associated with hypoxia, cytokine release syndrome (CRS) and dysregulated innate and adaptive immune responses (reviewed in ref. [82]). All these effects could contribute to neuroinflammation and endothelial cell activation (Fig. 2). Examination of cerebrospinal fluid in patients with neuroimaging findings revealed elevated levels of pro-inflammatory, BBB-destabilizing cytokines, including interleukin-6 (IL-6), IL-1, IL-8 and mononuclear cell chemoattractants[83,84]. Whether these cytokines arise from the periphery, due to COVID-19-mediated CRS, or from within the CNS, is unclear. As studies generally lack control patients with other severe illnesses, the specificity of such findings to SARS-CoV-2 also remains unclear. Systemic inflammatory processes, including cytokine release, have been linked to glial activation with expression of chemoattractants that recruit immune cells, leading to neuroinflammation and injury[85]. Cerebrospinal fluid concentrations of neurofilament light, a biomarker of neuronal damage, were reportedly elevated in patients hospitalized with COVID-19 regardless of whether they exhibited neurologic diseases[86]. Acute thromboembolic events leading to ischemic infarcts are also common in patients with COVID-19 due to a potentially increased pro-coagulant process secondary to CRS[87].

It is also unclear whether hospitalized patients with COVID-19 may develop brain abnormalities due to hypoxia or CRS rather than as a direct effect of SARS-CoV-2 infection. Hypoxia may cause neuronal dysfunction, cerebral edema, increased BBB permeability, cytokine expression and onset of neurodegenerative diseases[88,89]. CRS, with life-threatening levels of serum TNF-α and IL-1 (ref. [90]) could also impact BBB function, as these cytokines destabilize microvasculature endothelial cell junctional proteins critical for BBB integrity[91]. In mild SARS-CoV-2 infection, circulating immune factors combined with mild hypoxia might impact BBB function and lead to neuroinflammation[92], as observed during infection with other non-neuroinvasive respiratory pathogens[93]. However, multiple studies suggest that the SARS-CoV-2 spike protein itself may also induce venous and arterial endothelial cell activation and endotheliitis, disrupt BBB integrity or cross the BBB via adoptive transcytosis[94–96].

Reducing neuropsychiatric sequelae of COVID-19

The increased risk of COVID-19-related neuropsychiatric sequalae was most pronounced during the first pandemic peak but reduced over the subsequent 2 years[64,97]. This may

be due to reduced impact of newer SARS-CoV-2 strains (that is, Omicron) but also protective effects of vaccination, which limit SARS-CoV-2 spread and may, thus, prevent neuropsychiatric sequalae. Fully vaccinated individuals with breakthrough infections exhibit a 50% reduction in PACS[98], even though vaccination does not improve PACS-related neuropsychiatric symptoms in patients with a prior history of COVID-19 (ref. [99]). As patients with pre-existing mental disorders are at increased risk of SARS-CoV-2 infection, they deserve to be among the prioritization groups for vaccination efforts[100].

Adequate treatment strategies for neuropsychiatric sequelae of COVID-19 are needed. As no specific evidence-based intervention yet exists, the best current treatment approach is that for neuropsychiatric sequelae arising after other severe medical conditions[101]. Stepped care —a staged approach of mental health services comprising a hierarchy of interventions, from least to most intensive, matched to the individual's need—is efficacious with monitoring of mental health and cognitive problems. Milder symptoms likely benefit from counseling and holistic care, including physiotherapy, psychotherapy and rehabilitation. Individuals with moderate to severe symptoms fulfilling psychiatric diagnoses should receive guideline-concordant care for these disorders[61]. Patients with pre-existing mental disorders also deserve special attention when affected by COVID-19, as they have shown to have an increased risk of COVID-19-related hospitalization, complications and death[102]. This may involve interventions to address their general health, any unfavorable socioenvironmental factors, substance abuse or treatment adherence issues.

Lessons learned, knowledge gaps and future challenges

Ultimately, it is not only the millions of people who have died from COVID-19 worldwide that we remember but also the distress experienced during an unpredictable period with overstretched healthcare systems, lockdowns, school closures and changing work environments. In a world that is more and more globalized, connectivity puts us at risk for future pandemics. What can be learned from the last 2 years of the COVID-19 pandemic about how to handle future and longstanding challenges related to mental health?

Give mental health equal priority to physical health

The COVID-19 pandemic has demonstrated that our population seems quite resilient and adaptive. Nevertheless, even if society as a whole may bounce back, there is a large group of people whose mental health has been and will be disproportionately affected by this and future crises. Although various groups, such as the WHO[8], the National Health Commission of China[103], the Asia Pacific Disaster Mental Health Network[104] and a National Taskforce in India[105], developed mental health policies early on, many countries were late in realizing that a mental health agenda deserves immediate attention in a rapidly evolving pandemic. Implementation of comprehensive and integrated mental health policies was generally inconsistent and suboptimal[106] and often in the shadow of policies directed at containing and reducing the spread of SARS-CoV-2. Leadership is needed to convey the message that mental health is as important as physical health and that we should focus specific attention and early interventions on those at the highest risk. This includes those vulnerable due to factors such as low socioeconomic status, specific developmental life phase (adolescents and

young adults), pre-existing risk (poor physical or somatic health and early life trauma) or high exposure to pandemic-related (work) changes—for example, women and healthcare personnel. This means that not only should investment in youth and reducing health inequalities remain at the top of any policy agenda but also that mental health should be explicitly addressed from the start in any future global health crisis situation.

Communication and trust is crucial for mental health

Uncertainty and uncontrollability during the pandemic have challenged rational thinking. Negative news travels fast. Communication that is vague, one-sided and dishonest can negatively impact on mental health and amplify existing distress and anxiety[107]. Media reporting should not overemphasize negative mental health impact—for example, putative suicide rate increases or individual negative experiences—which could make situations worse than they actually are. Instead, communication during crises requires concrete and actionable advice that avoids polarization and strengthens vigilance, to foster resilience and help prevent escalation to severe mental health problems[108,109].

Rapid research should be collaborative and high-quality

Within the scientific community, the topic of mental health during the pandemic led to a multitude of rapid studies that generally had limited methodological quality—for example, cross-sectional designs, small or selective sampling or study designs lacking valid comparison groups. These contributed rather little to our understanding of the mental health impact of the emerging crisis. In future events that have global mental health impact, where possible, collaborative and interdisciplinary efforts with well-powered and well-controlled prospective studies using standardized instruments will be crucial. Only with fine-grained determinants and outcomes can data reliably inform mental health policies and identify who is most at risk.

Do not neglect long-term mental health effects

So far, research has mainly focused on the acute and short-term effects of the pandemic on mental health, usually spanning pandemic effects over several months to 1 year. However, longer follow-up of how a pandemic impacts population mental health is essential. Can societal and economic disruptions after the pandemic increase risk of mental disorders at a later stage when the acute pandemic effects have subsided? Do increased self-reported mental health problems return to pre-pandemic levels, and which groups of individuals remain most affected in the long-term? We need to realize that certain pandemic consequences, particularly those affecting income and school/work careers, may become visible only over the course of several years. Consequently, we should maintain focus and continue to monitor and quantify the effects of the pandemic in the years to come—for example, by monitoring mental healthcare use and suicide. This should include specific at-risk populations (for example, adolescents) and understudied populations in low-income and middle-income countries.

Pay attention to mental health consequences of infectious diseases

Even though our knowledge on PACS is rapidly expanding, there are still many unanswered questions related to who is at risk, the long-term course trajectories and the best ways to intervene early. Consequently, we need to be aware of the neuropsychiatric sequelae of COVID-19 and, for that matter, of any infectious disease. Clinical attention and research should be directed toward alleviating potential neuropsychiatric ramifications of COVID-19. Next to clinical studies, studies using human tissues and appropriate animal models are pivotal to determine the CNS region-specific and neural-cell-specific effects of SARS-CoV-2 infection and the induced immune activation. Indeed, absence of SARS-CoV-2 neuroinvasion is an opportunity to learn and discover how peripheral neuroimmune mechanisms can contribute to neuropsychiatric sequelae in susceptible individuals. This emphasizes the importance of an interdisciplinary approach where somatic and mental health efforts are combined but also the need to integrate clinical parameters after infection with biological parameters (for example, serum, cerebrospinal fluid and/or neuroimaging) to predict who is at risk for PACS and deliver more targeted treatments.

Prepare mental healthcare infrastructure for pandemic times

If we take mental health seriously, we should not only monitor it but also develop the resources and infrastructure necessary for rapid early intervention, particularly for specific vulnerable groups. For adequate mental healthcare to be ready for pandemic times, primary care, community mental health and public mental health should be prepared. In many countries, health services were not able to meet the population's mental health needs before the pandemic, which substantially worsened during the pandemic. We should ensure rapid access to mental health services but also address the underlying drivers of poor mental health, such as mitigating risks of unemployment, sexual violence and poverty. Collaboration in early stages across disciplines and expertise is essential. Anticipating disruption to face-to-face services, mental healthcare providers should be more prepared for consultations, therapy and follow-up by telephone, video-conferencing platforms and web applications[51,52]. The pandemic has shown that an inadequate infrastructure, pre-existing inequalities and low levels of technological literacy hindered the use and uptake of e-health, both in healthcare providers and in patients across different care settings. The necessary investments can ensure rapid upscaling of mental health services during future pandemics for those individuals with a high mental health need due to societal changes, government measures, fear of infection or infection itself.

Conclusion

Even though much attention has been paid to the physical health consequences of COVID-19, mental health has unjustly received less attention. There is an urgent need to prepare our research and healthcare infrastructures not only for adequate monitoring of the long-term mental health effects of the COVID-19 pandemic but also for future crises that will shape mental health. This will require collaboration to ensure interdisciplinary and sound research and to provide attention and care at an early stage for those individuals who are most vulnerable—giving mental health equal priority to physical health from the very start.

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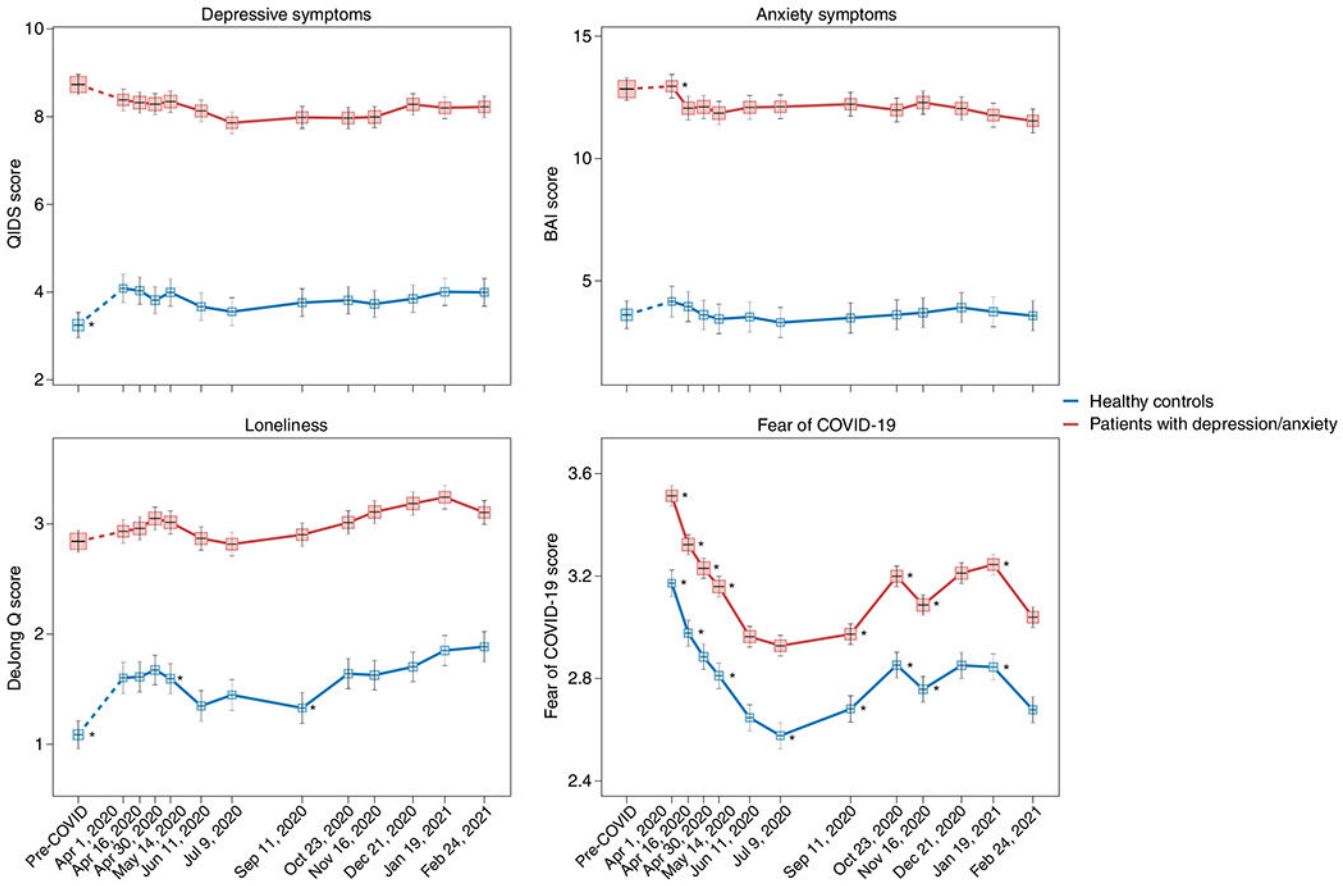

Fig. 1 |. Mental health symptom scores before and during the first COVID-19 pandemic year in Dutch people with or without lifetime depressive and/or anxiety disorders.

Trajectories of mean depressive symptoms (QIDS score), anxiety symptoms (BAI score), loneliness (De Jong questionnaire score) and Fear of COVID-19 score before and during the first year of the COVID-19 pandemic in healthy controls (blue line, $n = 378$) and in patients with depressive and/or anxiety disorders (red line, $n = 908$). The x-axis indicates time with one pre-COVID assessment (averaged over up to five earlier assessments conducted between 2006 and 2019) and 11 online assessments during April 2020 through February 2021. Symbols indicate the mean score during the assessment with 95% CIs. As compared to pre-COVID assessment scores, the figure shows a statistically significant increase of depression and loneliness symptoms during the first pandemic peak (April 2020) in healthy controls but not in patients (for more details, see refs. [22,54]). Asterisks indicate where subsequent wave scores differ from the prior wave scores ($P < 0.05$). The figure also illustrates the stability of depressive and anxiety symptoms during the first COVID year, a significant increase in loneliness during this period and fluctuations of Fear of COVID-19 score that positively correlate with infection rates in the Netherlands. Raw data are from the Netherlands Study of Depression and Anxiety (NESDA), which were re-analyzed for the current plots to illustrate differences between two groups (healthy controls versus patients). BAI, Beck Anxiety Inventory; QIDS, Quick Inventory of Depressive Symptoms.

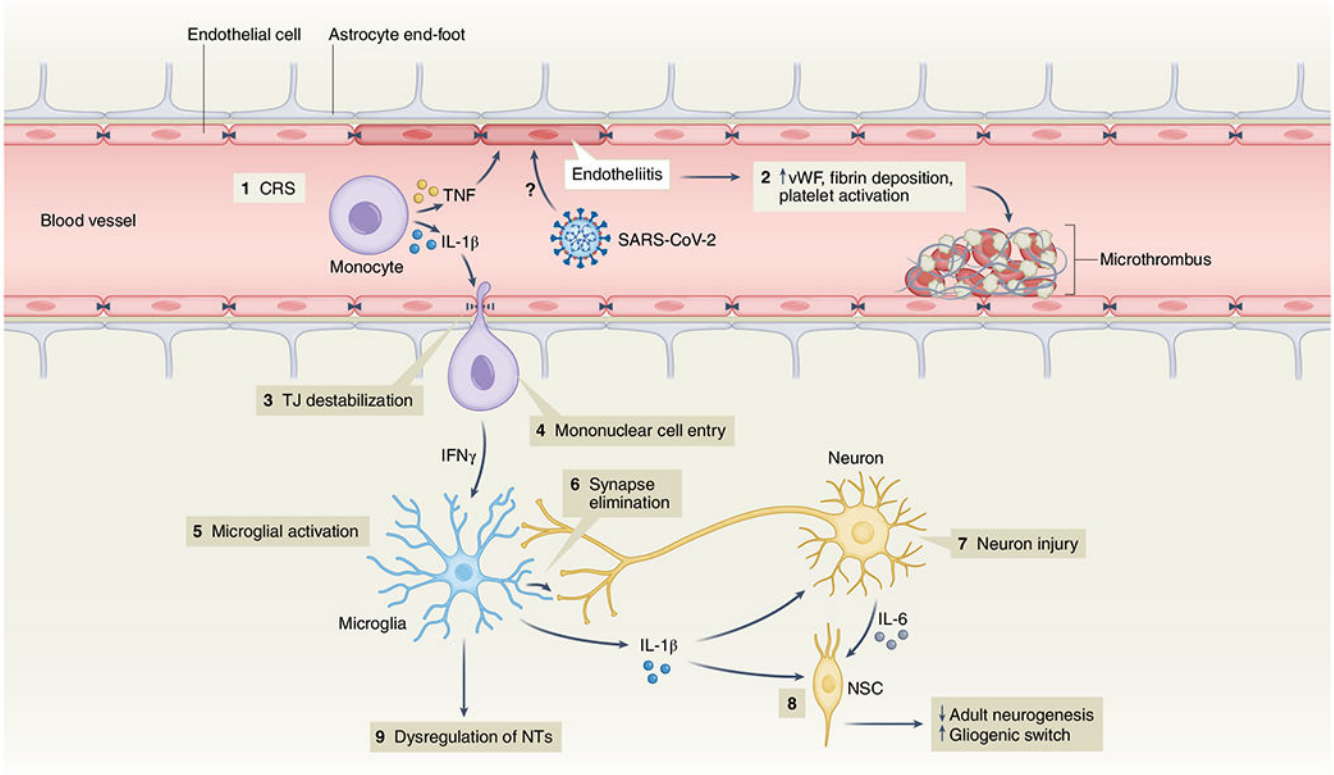

Fig. 2 |. Possible mechanisms of SARS-CoV-2-mediated neuroinflammation.

(1) Elevation of BBB-destabilizing cytokines (IL-1β and TNF) within the serum due to CRS or local interactions of mononuclear and endothelial cells. (2) Virus-induced endotheliitis increases susceptibility to microthrombus formation due to platelet activation, elevation of vWF and fibrin deposition. (3) Cytokine, mononuclear and endothelial cell interactions promote disruption of the BBB, which may allow entry of leukocytes expressing IFNg into the CNS (4), leading to microglial activation (5). (6) Activated microglia may eliminate synapses and/or express cytokines that promote neuronal injury. (7) Injured neurons express IL-6 which, together with IL-1β, promote a ‘gliogenic switch’ in NSCs (8), decreasing adult neurogenesis. (9) The combination of microglial (and possibly astrocyte) activation, neuronal injury and synapse loss may lead to dysregulation of NTs and neuronal circuitry. IFNg, interferon-g; NSC, neural stem cell; NT, neurotransmitter; TJ, tight junction; TNF, tumor necrosis factor; vWF, von Willebrand factor.

Table 1 |

Pooled effect sizes from meta-analyses comparing mental health symptoms before versus during the first year of the COVID-19 pandemic in the general population

	Pooled studies *n* (sample size)	Pooled effect size (95% CI)
Mental health problems (mixed outcomes)		
Robinson et al.[13]	61 (55,015)	0.11 (0.04–0.17)
Mar–Apr 2020		0.10 (0.03–0.19)
May–Jul 2020		0.07 (−0.02–0.16)
Patel et al.[15]	11 (49,993)	
Apr–Jun 2020		0.15 (0.06–0.23)
Jul–Oct 2020		0.18 (0.09–0.27)
Nov–Mar 2021		0.21 (0.10–0.32)
Prati et al.[14]	20 (72,004)	0.17 (0.07–0.26)
Depression symptoms		
Robinson et al.[13]	58	0.22 (0.14–0.30)
Prati et al.[14]	9	0.15 (0.01–0.30)
Anxiety symptoms		
Robinson et al.[13]	52	0.13 (0.02–0.23)
Prati et al.[14]	10	0.17 (0.07–0.27)
Psychotic symptoms		
Robinson et al.[13]	5	−0.21 (−0.38 to −0.05)
Well-being		
Robinson et al.[13]	7	0.07 (−0.12–0.26)
Prati et al.[14]	7	−0.12 (−0.33–0.09)
Loneliness		
Ernst et al.[16]	24 (45,734)	0.27 (0.14–0.40)

Table 2 |

Acute and post-acute neuropsychiatric sequelae of COVID-19 disease as described in empirical studies *

Acute	Post-acute
Very common (>30%)	
Fatigue	
Myalgia	
Hyposmia and dysgeusia **	
Headache	
Delirium (mainly in hospitalized patients)	
Moderately common (20–30%)	
Motor weakness/deficits	Fatigue
Sleep disturbances	Sleep disturbances
Cognitive impairments	Cognitive impairments
Lack of appetite	Irritability and emotional lability
Anxiety and/or depressive symptoms	
Irritability and emotional lability	
Rather common (10–20%)	
Vertigo, nausea	Anxiety and/or depressive symptoms
	Hyposmia and dysgeusia **
	Headache
	Post-traumatic stress symptoms
Less common (1–10%)	
	Vertigo, nausea
	Lack of appetite
	Speech/language difficulties
	Psychotic symptoms

* Estimates are based on the Literature[56,62,63,69,110–113] but vary depending on the population examined. Estimates are mainly from hospitalized patient populations, and neuropsychiatric sequelae are positively correlated to COVID-19 disease severity. Also, sequelae are not per se unique for COVID-19 disease, as similar sequelae are often seen in ICU patients or patients with other severe respiratory infections.

** Including anosmia and ageusia.