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Mental Health Issues During and After COVID-19 Vaccine Era

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ABSTRACT

The COVID-19 pandemic has persisted for more than a year, and post-COVID-19 sequelae of neurological complications, including direct and indirect effects on the central nervous system (CNS), have been recognized. There is a plethora of evidence for neurological, cognitive, and emotional deficits in COVID-19 patients. Acute neurological symptoms like neuroinflammation, cognitive impairment, loss of smell, and brain stroke are common direct effects among SARS-CoV-2 infected individuals. Work-associated stress, lockdowns, social distancing, and quarantine in response to contain SARS-CoV-2 have also affected the mental health of large populations, regardless of age. Public health emergencies have affected individuals and communities, resulting in emotional reactions and unhealthy behaviors. Although vaccines have been widely distributed and administered among large populations, vaccine hesitancy still exists and may be due to apprehension about vaccine efficacy, preliminary trials, and associated side effects. This review highlights the impact of COVID-19 on the CNS by outlining direct and indirect effects and factors contributing to the decline in people's mental health throughout the COVID-19 pandemic both during and after vaccine administration. Furthermore, we also discuss reasons for vaccine hesitancy and why some groups of people are deprived of vaccines. Finally, we touched upon the social determinants of mental health and their impact on disadvantaged populations during times of crisis which may help policymakers set up some action plans to mitigate the COVID-19 mental health turmoil during this ongoing pandemic.

1. Introduction

The recurrent waves of the coronavirus disease 2019 (COVID-19) pandemic have affected the lives of billions of people globally. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated from Asia. It spread worldwide, leading to severe morbidity and mortality, where more than 4.22 million people have succumbed to the disease as of August 1, 2021(Medicine, J.H.U.o., 2021). The critical disease manifestations of COVID-19 include respiratory symptoms that progress to acute respiratory distress syndrome (ARDS), cardiovascular disorders, multiple organ failure, septic shock, and death (Baj et al., 2020; Fanelli et al., 2013; Fu et al., 2020). While the direct effects of SARS-CoV-2 on the central nervous system are under detailed investigation (Desforges et al., 2014; McGavern and Kang, 2011), neurological symptoms like headache, insomnia, impaired cognitive functions, behavioral changes including depression and suicidality, intracranial hemorrhage, and acute cerebral ischemia have been observed in COVID-19 patients (Mao et al., 2020). The mechanism of long-term neurological manifestations of SARS-CoV-2 is still unclear, and researchers are putting extensive efforts into identifying these pathways.

Worldwide, the public is aware of the physical effects of SARS-CoV-2 infection and the preventative steps to take to limit exposure and minimize transmission. Apart from physical medical consequences, including direct brain damage, mental and social values are also disturbed (Kaczorowski and Del Grande, 2021). According to a survey

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by WHO, more than 93% of countries worldwide demand mental health services (Chandra et al., 2020; Correa-Palacio et al., 2020). Studies report that SARS-CoV-2 infected patients experience depression and anxiety (Yang et al., 2020), which are predecessors or risk factors for suicidality. Impaired consciousness, confusion, and post-traumatic stress disorder (PTSD) are highly prevalent in COVID-19 patients (Bo et al., 2020; Chen et al., 2020; Qiu et al., 2020). The possible reasons behind the severe neuropsychiatric symptoms in COVID-19 patients may be poor self-control and the inability to prevent infection. These factors may explain why people with mental disabilities are more prone to infections (Kim and Su, 2020).

To control the rapid human-to-human transmission of SARS-CoV-2, there has been lockdown enforcement, isolation, and closure of public places, educational institutes, and workplaces which have had an overwhelming impact on global mental health. Additionally, mask mandates and strict guidelines for social distancing have been implemented. Anxiety, depression, and other psychopathological symptoms prevail in the areas with severe COVID-19 (Rubin and Wessely, 2020). Even those who are not favorable for SARS-CoV-2 infection had mild to moderate stress levels during the initial wave of COVID-19 due to fear of getting infected. Worry about the duration of the pandemic, job layoffs, and about an individual's future sustainability prevailed. At the same time, information overload, rumors, and misinformation further acted to turmoil the status of mental health among the general population (Verstraelen et al., 2018). Stress, anxiety, fear, sadness, and loneliness have worsened the situation, and people have increased alcohol or drug consumption as coping mechanisms for pandemic-associated stress and anxiety (Grossman et al., 2020; Pollard et al., 2020). Isolation, social distancing, and work from home policies for non-essential workers have negatively impacted people's psychology (Zhang et al., 2020). Closures of schools and universities amongst students have increased fear of academic delays and anxiety symptoms (Cao et al., 2020).

Furthermore, due to enforced social isolation by lockdowns and stay-at-home orders, families show increased domestic abuse and intimate partner violence, negatively impacting physical and mental health. There was a 22% increase in domestic violence arrests on March 16, 2020, in Portland, Oregon, following the closure of public schools. Furthermore, a San Antonio Police Department indicated an 18% increase in calls related to family violence in March 2020 compared to the preceding year (Boserup et al., 2020). Previously, it has been reported that victims of domestic violence are at higher risk for suicidal thoughts and behavior (Kavak et al., 2018; Rahmani et al., 2019). It is also essential to recognize that microaggressions, hate crimes, verbal attacks, and violence towards Asian Americans have increased during the COVID-19 pandemic (Tessler et al., 2020). Currently, the global health crisis has resulted in the stigmatization of people of Asian descent due to exclusionary policies, derogatory rhetoric, and implicit encouragement at federal and institutional levels, which act to perpetuate anti-Asian violence and xenophobia (Gover et al., 2020). Racialized victimization is a strong predictor of poor mental health, and the COVID-19 pandemic has explicitly observed a 22% increase in people utilizing the Mental Health America anxiety screening tool. Within this, Asian American responses have increased by 39% (Berger and Sarnyai, 2015; Gover et al., 2020).

To combat the global COVID-19 pandemic, the Food and Drug Administration (FDA) approved the emergency use authorization (EUA) of mRNA vaccines developed by Pfizer and Moderna (Administration, 2020a,2020b). Janssen, an adenoviral vector-based recombinant vaccine developed by Johnson and Johnson, has also been approved by the FDA for EUA (Administration, 2021). AZD1222, another viral vector-based recombinant vaccine developed by Oxford-AstraZeneca, has not been approved by FDA. However, it is also a vaccine candidate that has been provided to many people worldwide. BBV152, Ad5-nCoV, and Sputnik V are additional vaccines approved in countries outside the United States for use. Although the initial reports from clinical trials seem to be promising, the availability and efficacy of the vaccines in the long term present challenging questions. Premature approval without long-term safety data, potential adverse effects, and confidence about the vaccine efficacy before administration have raised concerns and resulted in occurrences of vaccine hesitancy (Alec Tyson, 2020; Tyson, 2020). Vaccine safety concerns and conspiratorial understanding of newer generation vaccines have introduced anxiety amongst the general public. Side effects from the vaccines, including pain at the injection site, chills, fatigue, headache, fever, and nausea represent significant reasons for the unwillingness of people to get vaccinated. European health regulators have advised that AZD1222 may be responsible for forming blood clots which can be an infrequent and fatal side effect. Supporting this, two groups from Europe have reported possible thrombocytopenia caused by autoantibodies against platelet factor 4-heparin complex and combined life-threatening blood clots in the European population (Greinacher et al., 2021; Scully et al., 2021). The CDC has also released a statement regarding rare reports of myocarditis and pericarditis following administration of mRNA vaccines (Pfizer and Moderna) (CDC, 2021). In addition, several vaccine-related myths exist that have made vaccines appear riskier than they are. Misinformation that these vaccines are related to infertility, poisoning, and other imagined severe effects has caused people to avoid vaccine intake. While rumors about the vaccines are spreading, new vaccines are being developed and undergoing clinical trials.

Thus, mitigating strategies to COVID-19 related mental health should be focused on and consider social determinants, which may play a crucial role in the mental health progression at the individual level. This review describes the direct effects of COVID-19 on physical brain damage and the indirect effects by exploring mental health outcomes. We have also highlighted vaccine insufficiency and vaccine hesitancy as reasons behind pre/post COVID-19-induced mental health. Furthermore, we provide a critical discussion of the relevant topics and indicate future directions.

2. COVID-19 and its direct impact on the central nervous system

SARS-CoV-2 invasion to the central nervous system (CNS) occurs shortly after an infection, followed by an immunological escape. Upon entry to the CNS, the virus spreads in the brain and neurons, causing neurodegenerative dysfunctions (Fig. 1). Very early reports from Wuhan suggested neurological manifestations of COVID-19 were extremely common, occurring in 36.4% of patients (Mao et al., 2020). These symptoms included elevated risk of acute cerebrovascular disease and impaired consciousness among patients with more severe infections. More recently, several meta-analyses have compiled lists of specific neurological symptoms with larger sample sizes, indicating that the most common neurological symptoms are smell and taste dysfunction (anosmia and ageusia, respectively), myalgia, and headaches (Abdullahi et al., 2020; Chen et al., 2021; Collantes et al., 2021). Less common symptoms included dizziness, nausea and vomiting, and impaired consciousness, with some reports additionally indicating occasional, but difficult to quantify, encephalitis and stroke (Fig. 1) (Abdullahi et al., 2020; Collantes et al., 2021). Both encephalitis and stroke can cause hypoxic ischemia, permanently damaging the brain if blood flow does not return. In addition to localized CNS hypoxia, there have been reports of systemic hypoxia primarily due to ARDS (Eketunde et al., 2020). However, some patients instead experience silent hypoxia – also called happy hypoxia – notable for lacking dyspnea, with patients unaware of their dangerously low oxygen levels (Tobin et al., 2020). Silent hypoxia may be due to respiratory center damage in the medulla oblongata, disrupting the "respiratory drive," causing feedforward neurodegeneration. The loss of respiratory drive increases hypoxia, further damaging the respiratory drive (Dhont et al., 2020). Likely exacerbating this feedforward cycle is an increase in ACE2 expression in ischemic brains, which increases CNS infection susceptibility (Choi et al., 2020). In one autopsy study, all 18 COVID-19 patients microscopically examined had an acute hypoxic injury in the cerebrum and cerebellum,

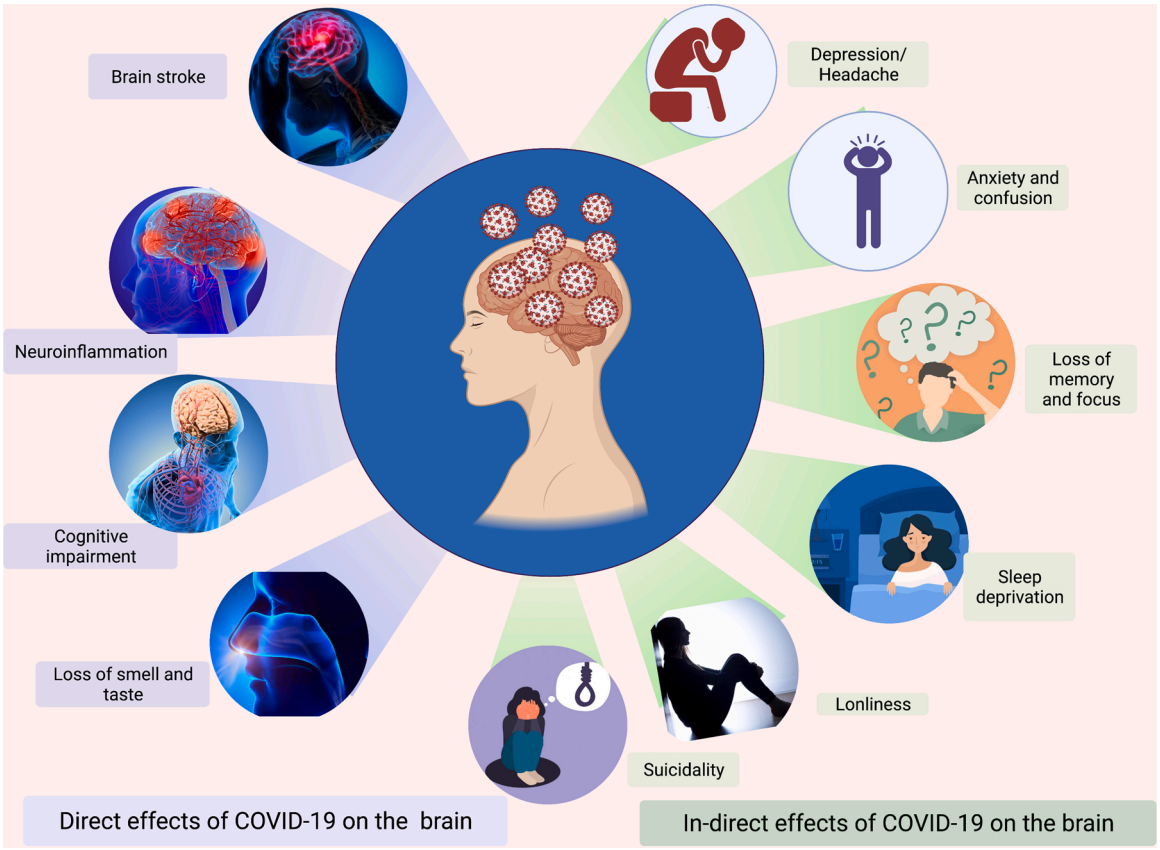

Fig. 1. The direct and indirect effects of COVID-19 on mental health. COVID-19 shows some unique clinical features that affect the brain directly or indirectly. The direct effects include brain stroke and inflammation in CNS, leading to cognitive impairment and loss of smell and taste. Indirectly COVID-19 affects individuals by depression, memory loss, sleep deprivation, feeling lonely, and thought of suicidality.

leading to loss of neurons in the cortex, hippocampus, and cerebellar Purkinje cells (Solomon et al., 2020). It is likely that even if people recover from SARS-CoV-2 infection, a significant number will have similar damage.

Many neurological effects of SARS-CoV-2 may be long-lasting, with an increasing consensus referring to these simply as "Long COVID," which has been characterized by headaches, hyposmia, hypogeusia, and fatigue with more severe conditions including sleep disorders, chronic pain, cognitive impairment, and Guillain-Barré syndrome (Table 1) (The Lancet Neurology, 2021). Some suggest that available SARS-CoV-2 vaccines can reduce or completely alleviate Long COVID symptoms like fatigue, breathlessness, and insomnia, offering further hope for the vaccination era (Arnold et al., 2021). Future studies will need to determine whether neuroinvasion, brain damage from hypoxia, or the neuro-immune response contribute to Long COVID to facilitate effective therapeutics.

In addition to hypoxic conditions, evidence suggests SARS-CoV-2 can also invade the CNS. In a seminal work tracking the spread of SARS-CoV-2 using post-mortem samples, Matscheke et al. (2020) demonstrated viral infiltration to the CNS with a particular focus on the frontal lobe and medulla oblongata, the latter of which had higher viral RNA copies and spike and nucleocapsid protein expression (Matschke et al., 2020). More recently, a study tested the infection capacity of SARS-CoV-2 in CNS tissue using human brain organoids (Song et al., 2021). They

Table 1
Common and non-common long-term neurological symptoms experienced by COVID-19 survivors.

	Common Long-term Neurological experiences of COVID-19 survivors				
		Condition's definition	Symptomatic	Asymptomatic	References
1	Anxiety	Symptoms of phobia, panic attack, or any depression	Yes	Yes	(Ries, 2020)
2	Depression	Disorders in adjustment to condition, sad mood	Yes	Yes	(Reinberg, 2021)
3	Suicide	Intention to self-harm, suicidal thoughts	Yes	Yes	(Pirkis et al., 2021)
4	Eating disorders	Compromise access to 'safe' routine foods	Yes	Yes	(Shah et al., 2020c)
5	Confusion	Also known as "brain fog," it is a mild confusion symptom	Yes	N/A	(Andrew and Budson, 2021)
	Non-common long-term experiences of COVID-19 survivors				
1	Syncope	Faint or pass out due to lack of blood supply to the brain	Yes	Yes	(Ebrille et al., 2020)
2	Brain Pressure	Benign intracranial hypertension, which causes pressure in the brain	Yes	Yes	(Noro et al., 2020)
3	Phantom Smells	Olfactory hallucinations	Yes	Yes	(Islek and Balci, 2021)
4	Feeling Irritable	Irritation and symptoms similar to post-traumatic stress disorder (PTSD)	Yes	Yes	(Kira et al., 2021)
5	Sleeping More Than Normal	Chronic illness causes chronic fatigue due to which trouble shaking off that tiredness	Yes	N/A	(Postiglione et al., 2021)
6	Memory Problems	Cognitive disorders and memory problems	Yes	N/A	(Fotuhi et al., 2020)
7	Difficulty Sleeping	Worries about the virus infection and symptoms	Yes	N/A	(Heidbreder et al., 2021)

demonstrated that SARS-CoV-2 could infect human brain organoids via ACE2 as well as initiate significant neuronal death. Further, they detected anti-viral antibodies in the CSF of a COVID-19 patient who suffered from acute neurological symptoms (Song et al., 2021). Regardless of viral infiltration, astrogliosis was detected in 86% of patients.

Further, microgliosis and cytotoxic T-lymphocyte infiltration were found to be particularly pronounced in the cerebellum and brainstem (medulla oblongata) and mainly concentrated around perivascular regions. Meningeal cytotoxic T lymphocytes were also located in 79% of patients, accompanied by perivascular and meningeal macrophage enrichment. Although these samples were post-mortem, they offer significant insight into SARS-CoV-2 neuropathology. They suggest that neuroinvasion may be particularly effective along the cranial nerves IX and X (glossopharyngeal and vagus nerves) to the medulla oblongata (Matschke et al., 2020). Additional evidence from transgenic mouse models expressing human ACE2 further suggests that the previous SARS-CoV can enter and spread through the CNS via the olfactory bulb (Netland et al., 2008; Song et al., 2021). While intuitive considering anosmia is a frequent symptom during human SARS-CoV-2 infections, there are significant neuroanatomical differences between rodents and humans, particularly at the olfactory bulb, so this finding may not directly translate to humans. In deceased humans infected with SARS-CoV-2, the olfactory mucosa was a site of significant infection. In contrast, the medulla oblongata, not the olfactory bulb, was the primary location of the infection in the CNS (Meinhardt et al., 2021). Interestingly, despite being found in CSF on occasion, SARS-CoV-2 is not found in most patients with neurological complications, further lending credence to neuroinvasion being along cranial nerves via retrograde transport (Pezzini and Padovani, 2020).

3. COVID-19 and its impact on mental health

Many studies have shown that the COVID-19 pandemic is related to physical disturbances and affects people's mental health. For individuals infected with SARS-CoV-2, it remains unclear whether the actual etiology behind the mental disorders is due to the virus itself or antiviral treatment. Regardless, COVID-19 survivors are reportedly experiencing a range of long-term effects, including anxiety, depression, confusion, and less common symptoms like brain pressure, phantom smells, irritability, and sleep disorders (Table 1). However, a range of psychological stressors stemming from the COVID-19 pandemic has been proposed as culprits for the expansive decline in the overall mental health of the general population.

3.1. Psychological stressors and associated mental health conditions

The COVID-19 outbreak was unexpected and resulted in what psychologists are calling a dual pandemic. While frontline healthcare workers and scientists are fighting to keep the disease at bay by treating infected patients, managing the spread of the infection, and developing viable vaccinations and antivirals, the lockdown methods for containment and quarantine also increased risk factors for mental health conditions. Mass tragedies, specifically those associated with infectious diseases, trigger increased anxiety and fear in the general population (Balaratnasingam and Janca, 2006). Boden et al. outlined stressors of the COVID-19 pandemic such as infection, economic hardship, job layoffs, stigma, or quarantine restrictions that may manifest or reinforce adverse mental health outcomes (Boden et al., 2021). In addition to anxiety and fear, these can include depression, stress, complicated grief, suicidality, feelings of loneliness, and triggers for developing eating disorders, obsessive-compulsive disorder, and traumatic stress (Fig. 1) (Banerjee et al., 2021; Fernández-Aranda et al., 2020; Torales et al., 2020). While the psychological stressors of the COVID-19 pandemic act to increase these mental health outcomes, people are dually affected because loneliness, anxiety, and depression further suppress the immune system by reducing resistance to disease and infection (Fig. 1) (Bzdok and Dunbar, 2020). Demographics impacted by the psychological stressors of the COVID-19 pandemic range from individuals with predispositions for mental health conditions to women, parents, the elderly, people of color, children, college students, and the military. People particularly vulnerable to mental health conditions during the setting of the COVID-19 pandemic include those with a history of mental health disorders or a predisposition for feelings of loneliness.

Furthermore, psychiatric disorders and severe mental illness are associated with an increased risk of COVID-19-related morbidity and mortality (Mazereel et al., 2021). As such, several countries declared the COVID-19 pandemic a national emergency, which resulted in lockdowns requiring millions of people to physically and socially isolate and the public experienced disruptions in daily routine, and healthcare and education systems were overwhelmed (Torales et al., 2020). These served as negative reinforcements and caused a decline in overall mental health. Bu and colleagues delineated predictors of loneliness considering settings prior to and following the COVID-19 outbreak; young adults, women, people living alone, the unemployed, and people with lower education or income were shown to be at greater risk for being lonely. This risk was increased in the context of the pandemic (Bu et al., 2020).

Anxiety represents a prominent mental health condition that is elevated during global pandemics. During previous infectious disease outbreaks, people who experienced pandemic-related anxiety often exhibited increased levels of post-traumatic stress, health anxiety, and suicidality (Goodwin et al., 2011). In efforts to manage and quantify anxiety during the current global crisis, a 5-item scale, the Coronavirus Anxiety Scale (CAS), for screening cases of pandemic-associated dysfunctional anxiety was evaluated. CAS offers a promising tool for ongoing clinical research, demonstrated to have robust reliability (90% sensitivity and 85% specificity) in predicting coronavirus diagnosis, impairment, suicidal ideation, alcohol/drug coping, as well as extreme hopelessness (Lee, 2020; Lee et al., 2020). Anxiety is often a predecessor to suicidal behavior or suicidality. There is an association between suicides and pandemics: suicide rates increased during the Great Influenza Epidemic (Spanish Flu) of 1918-19 in the United States and Ebola infection in Africa (Bitanihirwe, 2016; Wasserman, 1992). During the COVID-19 pandemic, the elderly, homeless, frontline workers, migrants, victims of abuse and violence, the unemployed, and stigmatized groups have been identified as vulnerable populations for suicidality (Reviewed in (Banerjee et al., 2021)). Additionally, those affected by the loss of a loved one during the pandemic are at greater risk of declining mental health. Age typifies a severe risk factor for SARS-CoV-2 infection-related mortality. However, natural causes of aging such as cognitive and sensory impairment and abuse, overcrowding, and general neglect of residents in a group or nursing homes contribute to increased feelings of loneliness, depression, and suicidality in the elderly (Armitage and Nellums, 2020).

3.2. Isolation implications for pediatric and family mental health during the vaccination era

COVID-19 pandemic has impacted various age groups for different reasons. Older adults are the highest at-risk group in terms of fatality, and consequently, a vaccine for adults was in greater need than one for pediatrics. Vaccines for pediatrics, considering different age groups, are currently in clinical trials and require different dosages due to variation in immune systems as people age (Zimmermann and Curtis, 2020). The vaccines that have been approved for EUA in the US are approved for individuals 12 and older for Pfizer's mRNA vaccine, and 18 and above for Moderna's mRNA vaccine and Johnson & Johnson's viral vector vaccine (Jenco, 2021). Recently, Pfizer-BioNTech released an official statement on March 31, 2021, announcing the data on their vaccine for 12- to 15-year-olds has demonstrated 100% efficacy for the 1,131 participants who have received the vaccine. Pfizer's vaccine clinical trials for children 6 months to 11 years are underway (Pfizer, 2021). Moderna

announced on March 16, 2021, administering doses to 6,750 healthy participants enrolled in Phase 2/3 for those 12 years old and under (Moderna, 2021). Johnson & Johnson's vaccine for adults received EUA as of February 27, 2021, and clinical trials for pediatrics were mentioned briefly during the company's vaccine data (Kolata, 2021). Although the pediatric population was not as heavily impacted during the pandemic as other age groups, transmission from children to adults could be a potential problem. A pediatric vaccine would ensure safety for the children and educators returning to school in the upcoming year and reduce other COVID-19-associated negative social and psychological impacts.

Children represent a unique factor for considering the repercussions of quarantine. A child's understanding and attitude towards social isolation are dependent on their parent's knowledge of the importance of public health. Many Americans are struggling to see the importance of following the guidelines put in place by the government and CDC. Some areas never required masks, and other regions had a mandatory stay-at-home order (Gramlich, 2020). These conflicting ideations make it difficult for impressionable children to understand the importance of following guidelines set by credible institutions. However, quarantine and social distancing have implications that could be detrimental to a child's atypical mental functions(Vygotsky et al., 1978). Being removed from a classroom mitigates the personalization that students may need to succeed in school. An increase in on-task behavior and decreased disruptive behavior were seen when there was positive, contingent touch from teachers in a classroom (Wheldall et al., 1986). Many educational institutions employed remote learning as the mitigation tactic to reduce the spread of SARS-CoV-2. This led to a reduced or lack of social interactions with friends and participation in extracurricular activities, thus hindering a child's social development (Gifford-Smith and Brownell, 2003; Oberle et al., 2010). Developing friendships or meaningful relationships with people impacts mental health, happiness, and physical health (Staff, 2019). Fear of being infected could potentially influence a child's social interactions. In the following years after the pandemic, social interaction for children would be a valuable resource to study the implications isolation has on social development.

The COVID-19 pandemic has also had implications for the mental health of children and their families. In June of 2020, a survey of U.S. adults showed elevated levels of mental health conditions where 10.7% of responders indicated suicidal ideation in the last 30 days, 13.3% started or increased substance use to cope with pandemic-related stress, 30.9% reported symptoms of anxiety disorder or depressive disorder, and 40.9% had some adverse mental or behavioral health conditions (Czeisler et al., 2020; Stikkelbroek et al., 2016). Parent-child relations are significantly influenced by mental illness and substance abuse, which cause an increase in mental health problems in children (Rasic et al., 2014). Low socioeconomic classes are more vulnerable to mental health effects. During a recession, there is an increase in child abuse encompassing physical, emotional, sexualized violence, and malnutrition associated with a high mortality rate (Huang et al., 2011; Paleologou et al., 2018; Riley et al., 2008; Schneider et al., 2017).

Furthermore, job loss is a significant risk factor for child maltreatment, and there is a significant correlation between parental job loss and psychological abuse during the COVID-19 pandemic (Lawson et al., 2020). Anger, depression, irritability, low mood, insomnia, and emotional exhaustion are other mental health problems that have increased since quarantine(Brooks et al., 2020). Instability negatively impacts child development; these factors include hindering educational attainment, physiological damage caused by stress, and improved problem behaviors. Further, stress-induced physiological damage can impede brain development which affects cognitive and social functioning (Sandstrom and Huerta, 2013). High-risk children, such as children with disabilities, are susceptible to maltreatment that can cause heightened neural responses, increased emotional reactivity, and decreased emotional regulation (Duffy et al., 2018; Hein and Monk, 2017; Seppälä et al., 2020). Interrupted access to mental health facilities adds to the distress and challenges parents and children have associated with the pandemic. Healthy coping mechanisms are essential for managing the stress, anxiety, and fear surrounding the pandemic to prevent aggravating pre-existing disadvantages (Compas et al., 2017; Fegert et al., 2020). Access to mental health resources in the coming months is vital for a healthy transition into a post-pandemic reality.

3.3. Mitigation tactics for psychological stressors

With the global rise in the risk of psychological stressors, coping strategies, and interventions intended to mitigate the mental health symptoms of the COVID-19 pandemic have been proposed (Fig. 2). Within the children's demographic, it is essential to encourage healthy behavior to establish and maintain the structure and well-being of families. The mental status of parents/caregivers can significantly influence a child's mental health and vice versa. These health practices include exercising regularly, eating a balanced diet, avoiding alcohol and drugs, getting adequate sleep quality, and implementing breaks from reading, watching, or listening to news of the pandemic (Fig. 2) (Reviewed in (Shah et al., 2020b)). Additionally, a systematic review outlined some proposed coping measures during the COVID-19 pandemic for all age groups, which include music, indoor play, aerobic exercise, prayer, reading, yoga, or creative activities (Fig. 3)((Kar et al., 2020a,b).

Furthermore, schools and healthcare institutions can adopt psychological first aid (PFA) guidelines to help alleviate acute distress and provide a basis for assessing the further need for more advanced psychiatric care (Shah et al., 2020a). In terms of seeking treatment for mental health, there are often barriers such as stigmatization, access regarding time and convenience, and financial burden. Stigma can be subcategorized to consider racial/ethnic factors, religion, sexual orientation and identity, genetic predispositions, or low mental health literacy. At the collegiate level, there are increasing mental health conditions such as anxiety and depression among students. WHO reported in 2018 that approximately 31% of college students surveyed from 19 colleges in 8 countries screened positive for mental disorders (Auerbach et al., 2018). This statistic calls attention to the reality that while on-campus counseling centers may be adequately positioned to provide mental health care, they are often under-sourced and under-staffed (Xiao et al., 2017). A recent literature review proposed that digital mental health interventions delivered via mobile and web-based platforms may bypass some of these barriers for seeking treatment and offer accessible treatment (Lattie et al., 2019). These interventions included internet-based cognitive behavioral therapy or various forms of coaching, which may be taken from clinical settings into the context of everyday life unrestrained by time and location (Lattie et al., 2019). With the ongoing global COVID-19 pandemic where many people are still working from home or socially isolating, digital mental health interventions may be viable. Digital interventions offer additional benefits, including real-time self-monitoring and self-management in daily journal entries or survey responses within apps. However, there are limitations since digital interventions require a digital device and reliable Internet access, which are not universally available, especially in low-income households. Remarkably, a recent study aimed to understand the intent to use telehealth or digital health interventions within an underserved Hispanic population. The study communicated that 78.9% of participants reported being likely to use the services if offered by a health care provider, though 90.6% had never heard of telehealth previously.

Moreover, ~75% of the participants in the study had an annual household income below $20,000 (Ghaddar et al., 2020). Digital interventions or telehealth offer promising avenues for bridging the gap between accessible and affordable health care, and it is suggested that digital health interventions may represent a more efficient and cost-effective approach. Additionally, another advantage of telehealth is the possibility for patients, particularly refugees and immigrants, to receive psychiatric care in their native language without the need for an

Fig. 2. Proposed coping strategies for COVID-19-induced mental stress. COVID-19 affected individuals can overcome mental anxiety by involving in yoga and exercise, creative activities, calling loved ones, including friends, busy reading and writing exciting books/novels, setting small goals that we can achieve during the lockdowns and finally, be hopeful.

interpreter. This alleviates some stress about seeking care, and the virtual space offered by digital intervention generates a sense of security and anonymity for these individuals. However, efforts should be made to educate people with low-income as well as minority populations on the availability and benefits of telehealth. Digital interventions for mental health have been effective in identifying and treating sleep disorders, anxiety, depression, OCD, schizophrenia, and PTSD (Reviewed in (Di Carlo et al., 2021)), Treatments for these are in the form of computer programs, computer-aided vicarious exposure (CAVE), cognitive behavioral therapy (CBT), behavior-therapy-steps, or telephone-based interventions (Di Carlo et al., 2021).

Interim, it is interesting to know the benefits of human-animal relationships during the COVID-19 pandemic. A study out of the UK surveying 5,926 homes reported that those indicating animal ownership had smaller decreases in mental health and reduced feelings of loneliness than households with no animals (Ratschen et al., 2020). Results from this study suggest that pets may act to alleviate the burden of COVID-19-associated mental health outcomes. Moreover, the elderly population has been primarily affected by lockdown, given that they are disproportionately vulnerable to worse results of SARS-CoV-2 infection. Video calls have been proposed to reduce social isolation and feelings of loneliness in older people, though the effectiveness of this method is still unclear (Noone et al., 2020).

4. COVID-19 vaccine development and mental health factors

With the onset of the COVID-19 pandemic, there have been extensive global efforts to develop various vaccine candidates to prevent infection and spread of SARS-CoV-2. Within the United States, three vaccines have been approved for EUA, including Pfizer-BioNtech's mRNA vaccine BNT162b2, Moderna's mRNA vaccine mRNA-1273, and Johnson and Johnson's viral vector vaccine JNJ-78436735 (Administration, 2021; Administration, 2020a,2020b). Outside the United States, several other vaccines have been approved for use, including AZD1222 from Oxford/AstraZeneca, covaxin from Bharat Biotech, Ad5-nCoV from CanSino, and Sputnik V from Gamaleya (Medicine, U.N.L.o., 2021d,2021e,2021f, 2021j). There are many other candidates in various stages of clinical trials, and these are described in Table 2. The rapid development and approval for EUA of these vaccines have led to vaccine hesitancy, anxiety, and skepticism among the public and left room for the spread of misinformation regarding the safety and efficacy of vaccines.

4.1. Interactions between psychotropic medications and vaccine efficacy

The risk of drug-drug interactions between psychotropic medications and medical treatments for COVID-19 patients is a relevant field of interest (Ostuzzi et al., 2020). Moreover, psychotropic medications have adverse effects in COVID-19 patients. Mainly, the disposition of several psychotropic medications is affected in COVID-related systemic inflammation, which may lead to liver dysfunction. Further, the

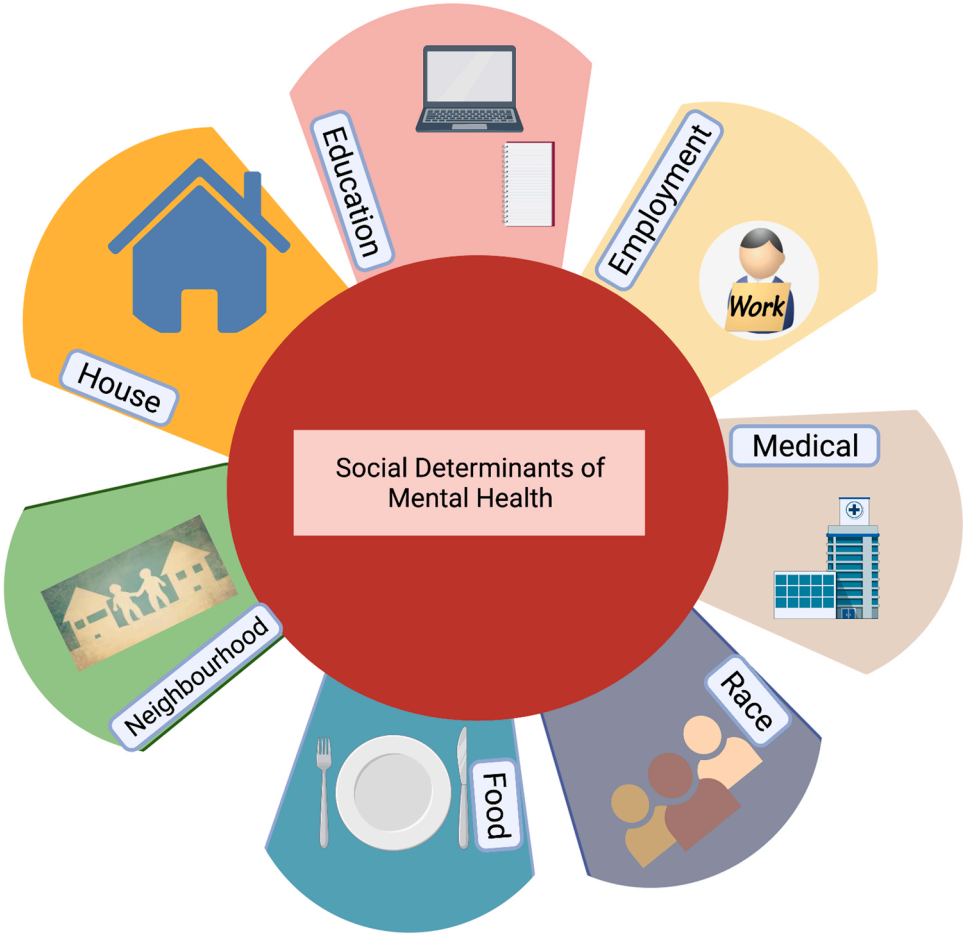

Fig. 3. Social determinants of mental health during COVID-19. Several social determinants and disparities affect mental health pre and post COVID-19, including disproportionate burden in different races, access to quality health care, education, safe housing, social and community context, and a scarcity of balanced diet.

combinations of psychotropic medications with COVID-19 treatment may also influence QTc prolongation, immunity, and coagulation abnormalities commonly observed in COVID-19 patients. As vaccines are made readily available for the public, another factor to consider is possible interactions between the vaccines and prescribed psychotropic medications. To date, there is limited information available about the effects of psychotropic drugs on vaccine response, and current data are often controversial (Reviewed in (Mazereel et al., 2021)). Mood-stabilizing agents, such as carbamazepine, lamotrigine, valproic acid, and lithium, have been shown to have a differential effect on cytokine production. These drugs often exhibit pleiotropic effects demonstrating both inflammatory and anti-inflammatory responses (Himmerich et al., 2013). Some antidepressants can easily cross the blood-brain barrier and have been shown to have anti-inflammatory properties in the brain. Clomipramine, a well-known antidepressant, is under investigation to treat and manage peripheral and central inflammation manifested by SARS-CoV-2 infection (Nobile et al., 2021). However, anti-inflammatory responses are not always advantageous; for example, Clozapine has been associated with a secondary antibody deficiency in individuals with long-term use and has been identified as a possible risk factor for SARS-CoV-2 infection (Govind et al., 2020). Understanding how psychotropic drugs impact vaccination efficacy and response is still underdeveloped, and further research is urgently needed.

4.2. Vaccine hesitancy

According to WHO, vaccine hesitancy refers to a delay or refusal in receiving a vaccine when it is readily available (WHO, 2014). Vaccine hesitancy is a complex and context-specific problem varying across time, place, and type of vaccine (WHO, 2014). It is influenced by factors such as complacency, convenience, and confidence ((SAGE), 2014). Vaccine hesitancy does not apply in situations where vaccine uptake is low because of circumstances beyond a person's control, such as a general lack of vaccines, inaccessible travel, or inadequate vaccination programs available (WHO, 2014). Vaccination hesitancy is a global problem that as of the 2000s, has reached new heights with the invention of the internet, which can serve to propagate the spread of misinformation (Dubé et al., 2015). This was evident in March 2012 when the WHO Strategic Advisory Group of Experts on Immunization (SAGE) established a working group on vaccine hesitancy (WHO, 2014). However, vaccine hesitancy has existed since Edward Jenner's original smallpox vaccine in the 1700s (Dubé et al., 2015). Currently, it is the subject of a multifaceted problem for society since the reasoning for vaccine hesitancy is based on complex historical, political, and sociocultural contexts (WHO, 2014). These contexts include past experiences, risk perception, trust in healthcare systems, societal norms, and religious or moral beliefs regarding healthcare (WHO, 2014).

A decrease in vaccination compliance could lead to lower overall herd immunity (Rashid et al., 2012). Herd immunity is an indirect way of protecting against a specific viral or bacterial disease. It is achieved when a large portion of the population possesses immunity to that particular disease, which can be accomplished through previous infection or mass vaccination (Rashid et al., 2012). Herd immunity is disease-dependent. For instance, poliomyelitis required at least 80% of the population to be immune to establish herd immunity, while measles

Table 2
Potential COVID-19 vaccine candidates at various stages in clinical trials.

Name	Manufacturer/Sponsor	Type	Age group	EUA in the US	Clinical Trials Phase	International Approval	Reported Side Effects	References
BNT162b2	Pfizer-BioNTech	mRNA	>12yrs	Yes	Phase 3	88 countries	*Myocarditis, Pericarditis	(CDC, 2021)
mRNA-1273	ModernaTX, Inc	mRNA	>18yrs	Yes	Phase 3	53 countries	*Myocarditis, Pericarditis	(CDC, 2021)
JNJ-78436735	Johnson & Johnson's Janssen	Viral Vector	>18yrs	Yes	Phase 3	49 countries	*Thrombosis	(Administration, 2021)
AZD1222	Oxford/AstraZeneca	Viral Vector	>18yrs	No	Phase 3	110 countries	*Thrombosis	(Medicine, U.N.L.o., 2021e)
NVX-CoV2373	Novavax	Protein Subunit	>18yrs	No	Phase 3	NA	-	(NIH, 2021)
UB-612	COVAXX	Protein Subunit	NA	No	Phase 1	NA	-	(Medicine, U.N.L.o., 2021d)
bac-TRL-spike	Symvivo	DNA	NA	No	Phase 1	NA	-	(Medicine, U.N.L.o., 2021b)
Covaxin (BBV152)	Bharat Biotech	Inactivated	NA	No	Phase 3	9 countries	*	(Medicine, U.N.L.o., 2021a)
SCB-2019	Clover	Protein Subunit	NA	No	Phase 1	NA	-	(Medicine, U.N.L.o., 2021i)
GX-19	Genexine	DNA	NA	No	Phase 1/2	NA	-	(Medicine, U.N.L.o., 2021h)
Synthetic Minigene	Shenzhen Geno-Immune Medical Institute	Lentiviral vector	NA	No	Phase 2	NA	-	(Medicine, U.N.L.o., 2021c)
Covid-19/aAPC	Shenzhen Geno-Immune Medical Institute	Replicating Viral Vector	NA	No	Phase 1	NA	-	(Medicine, U.N.L.o., 2021g)
Ad5-nCoV	CanSino	Viral Vector	NA	No	Phase 3	5 countries	*	(Medicine, U.N.L.o., 2021f)
Sputnik V	Gamaleya	Viral Vector	NA	No	Phase 3	68 countries	*	(Medicine, U.N.L.o., 2021j)

* For all vaccines currently being administered around the world, reported possible side effects to include headache, pain at the injection site, tiredness, redness, swelling, chills, fever, nausea, or muscle pain.

needed at least 93-95% (2004; Rashid et al., 2012). When 93% of the population is not vaccinated on the schedule against measles, it can lead to outbreaks of preventable diseases (Rashid et al., 2012). This was observed from September 2018 to July 2019 in New York City, New York, when an orthodox Jewish community located in the Williamsburg area of Brooklyn did not reach herd immunity and experienced measles outbreaks where at least 649 people were infected (Zucker et al., 2020). It is not known what proportion of the population must be vaccinated against COVID-19 to establish herd immunity. This statistic likely varies depending on vaccine efficacy and long-term immunity against COVID-19 (Kadkhoda, 2021).

Global COVID-19 vaccination efforts have witnessed an increase in vaccine hesitancy (Chou and Budenz, 2020). To establish long-term control of COVID-19, there will need to be a sizable uptake and acceptance of vaccines by the general population (Chou and Budenz, 2020). However, some of the population may have anxiety or fear directly related to receiving the vaccine because of its safety standards, side effects, and COVID-19's novelty (Chou and Budenz, 2020). Additionally, needle phobia and misinformation provided by social media are other reasons for vaccine hesitancy. These emotional responses could be directly related to the COVID-19 pandemic and the impact it has had on daily life (Chou and Budenz, 2020). For these reasons, to establish strong herd immunity, various programs must constitute vaccine confidence by addressing vaccine hesitancy through targeted interventions (Chou and Budenz, 2020). Programs that involve establishing greater public health outreach and stronger connections with the specific region's healthcare systems could increase trust in vulnerable populations and represent focus areas for reducing vaccine hesitancy (Chou and Budenz, 2020).

Additionally, improving science, technology, engineering, and math (STEM) education could alleviate some concerns regarding COVID-19 vaccination strategies (Chou and Budenz, 2020). However, at-risk populations with anxiety related to the COVID-19 vaccines also need emotional engagement to change health behaviors (Chou and Budenz, 2020). These types of employment have been critical in the past to change at-risk health behaviors, such as texting while driving or associating negative emotions with nicotine usage (Chou and Budenz, 2020). Betsch et al. reported in 2011 that when compared to factual and statistical information, emotions are found to influence vaccine risk perceptions and intentions more strongly (Betsch et al., 2011). Replacing these biased or faulty mental models will be essential for eliminating the COVID-19 pandemic and allow future generations to continue to close the gap between vaccine hesitancy and acceptance (WHO, 2014).

5. Social determinants and disparities on post-COVID-19 mental stress

WHO defines the social determinant of health as the condition where people 'are born, grow, live, work, and age' (Bernardini et al., 2021). From the onset of the COVID-19 pandemic, multiple lines of evidence have established that social determinants of health play a crucial role in the spread of the disease and are a high-risk factor for disease-associated mortality and morbidity (Fig. 3) (Singu et al., 2020). There are several social determinants and disparities that affect mental health pre and post COVID-19-induced mental stress. Some of these social determinants include the disproportionate burden of COVID-19 in different races, access to quality health care, education, safe housing, and social and community context.

5.1. Disproportionate burden of COVID-19 in racial/ethnic minorities and undocumented immigrants

Although the pandemic is far from over, evidenced by the global wax and wane of new cases due to the emergence of super spreader variants of SARS-CoV-2, the preliminary epidemiological data indicate a disproportionate burden of COVID-19 in African Americans in the USA (Fields et al., 2021). Like HIV, initially, the higher risk for COVID-19 among the African American population was underestimated. Due to these racial disparities practiced by policymakers, public health practitioners, and community leaders, in 2018, African Americans represented 42% of new HIV cases and 44% of HIV-related deaths. However, they

represent only 13.4% of the US population (Fields et al., 2021). Although the data are limited, this community has a 1.5 times higher death rate than the white non-Hispanic population due to COVID-19. Most strikingly, the underlying reason for this similarity is not due to the similar disease pathophysiology of the two pathogens. On the contrary, this reflects decades of social inequalities, racial oppression, and civil rights violations experienced by African Americans. It will not be possible to end the pandemic and its associated social and mental stress without resolving the social, economic, and environmental disadvantages of African Americans and other minority populations or increasing their access to advanced health care systems (Millett et al., 2020; Nosyk et al., 2020).

Other groups disproportionately impacted by COVID-19 include the Latinx community and Native Americans (Tai et al., 2021). The Hispanic/Latinx population represents the largest ethnic minority group in the United States. There are approximately 60 million Hispanic people, which constitute 18% of the total U.S. population. However, considering that this group accounts for 28.4% of confirmed COVID-19 cases with identifiable ethnicity reported to the CDC, there is an apparent racial disparity (Macias Gil et al., 2020). Furthermore, as of May 2020 in New York City, a hot spot for COVID-19 related hospitalization, the Hispanic population experienced a 2-fold higher age-adjusted death rate than whites (Health, N.Y.D.o., 2020). The COVID-19 pandemic has disproportionately impacted non-Hispanic American Indians and Alaska Native people; this group comprises 0.7% of the total U.S. population, though they account for 1.3% of COVID-19 cases with confirmed race and ethnicity reported the CDC (Hatcher et al., 2020).

Additionally, undocumented immigrants have experienced economic strain and fear of seeking medical help due to their unauthorized legal status within the country. They had a greater risk of developing a critical illness, which increased their mental stress index several folds (Dyer, 2020). These disproportionate statistics regarding COVID-19 cases and outcomes underscore the desperate, elicit the need for change in the healthcare and education systems, and expose the long-standing structural and societal disparities within the United States.

5.2. Lack of access to quality health care, education, and safe housing

It is now established that most people infected with SARS-CoV-2 remain asymptomatic or mildly symptomatic (Rothan and Byrareddy, 2020). However, the long-term sequelae of COVID-19 among these people remains primarily unknown. Recently, using a systematic review and meta-analysis, Lopez-Leon et al. reported that an estimated 80% of SARS-CoV-2 infected patients develop long-term symptoms that include fatigue, headache, attention disorder, and dyspnea, among others, which warrants the development of long-term rehabilitation and clinical management systems to tackle post-COVID-19 disease management (Lopez-Leon et al., 2021). From the biological perspective, SARS-CoV-2 is similar primarily to SARS-CoV and MERS-CoV in its neurotropism and neuroinvasive capabilities and neurological disease manifestations during the acute phase of infection (Adhikari et al., 2020; Petrosillo et al., 2020). On the other hand, the COVID-19 pandemic added several additional aspects to the long-term mental stress and psychiatric disorders associated with the SARS-CoV-2 outbreak. These include the economic impact and physical isolation of the long-term global lockdown due to the pandemic, shortage of standard medical facilities in different locations at the peak of the outbreak, and mental trauma linked to an extended stay in the ICU (Sommer and Bakker, 2020).

Nevertheless, racial minorities, including African Americans, Native Americans, and the Latinx community, have been impacted the most by these factors. The nature of their job demands physical activity and presence in large groups that cannot be completed from home. Also, their inadequate health insurance availability, crowded living conditions, reduced access to hygienic products and personal protection equipment, and lack of adequate facilities for attending online schools for their children substantially increase their susceptibility to mental stress, which leads to the occurrence of a higher rate of psychiatric disorders (Hamidian Jahromi and Hamidianjahromi, 2020). The Hispanic population in the United States has the lowest rates for medical health insurance coverage. In 2018 the uninsured proportion of Hispanics was 19.8% compared to 5.4% of non-Hispanic whites (Macias Gil et al., 2020). Furthermore, the higher incidence of hypertension, type-2-diabetes, cardiovascular disorders, cerebrovascular disease, and underlying chronic obstructive pulmonary disease also make the African American community a potentially high-risk group for COVID-19 (Clements et al., 2020; Zilbermint et al., 2019). These factors also increase their mental stress many folds.

Access to safe housing is another strong predictor for the spread of SARS-CoV-2. A study considering the living space challenge out of Italy highlights recommendations for healthy, secure, and sustainable housing, denoting them the concept of well-being and public health. The following are some of the outlined points: thermal comfort and indoor air quality, water consumption and wastewater management, urban solid waste management, visualization of green elements, and flexibility of living space (D'Alessandro et al., 2020). According to WHO, a sustainable living space must offer adequate privacy, accessibility, and ergonomic requirements (WHO, 2018). Under this definition, safe housing should provide characteristics enabling a safe space for quarantine or a place to work from home in the current pandemic and avoid instances of overcrowding. In the United States, access to quality and safe housing is lacking for many minority groups and people living below the poverty line. The African American community has experienced housing discrimination such that they have historically been concentrated in denser cities frequently located in environmentally toxic regions. Over time, these regions morphed into unsafe neighborhoods, increasing the prevalence of normalized street crime (Duque, 2020). Furthermore, a study looking at American Indian Reservations in the United States identified access to potable water and complete indoor plumbing as a determinant for increased risk for COVID-19, highlighting that English-only reservation households had reduced risk for COVID-19 (Rodriguez-Lonebear et al., 2020).

5.3. Social and community context

Post-COVID-19, mental stress includes sleep disturbances, depressive symptoms, suicidality, and anxiety-related behaviors (WHO, 2018). As outlined above, social determinants of health dictate the higher prevalence of COVID-19 and associated death. Consequently, the feedback loop makes people from developing countries, conflict prison zones, and refugee camps more vulnerable to post-COVID-19 mental stress and psychiatric disorders. In another aspect, the global lockdown measures disproportionally affected women. The restrictions of freedom and disruption of sexual and reproductive health services estimate millions of unintended pregnancies and thousands of unsafe abortions during the ongoing pandemic (Cousins, 2020). This will also increase the prevalence of sexually transmitted diseases, including HIV/HCV, and subsequent mental stress and illness.

6. Concluding Remarks

Pandemics always come with severe direct and indirect effects on the global population. The COVID-19 pandemic is widespread and never-ending. While scientists battle to dissect mechanisms for how SARS-CoV-2 invades the brain, subsequent mental health issues are emerging. The quality of life (QoL) is an index used to determine how a disease affects various facets of the human lifestyle. The COVID-19 pandemic has not only resulted in massive mortality and morbidity worldwide but has led to disruption of QoL, ranging from access to food, shelter, and health services (Berry et al., 2021; Niles et al., 2020; Smith and Wesselbaum, 2020). There was also an increment in altered mental health as anxiety and panic were shared amongst the public as people were continuously unsure of the future amidst the pandemic's peak

(Algahtani et al., 2021; Altable and de la Serna, 2020; Kar et al., 2020a, b). Multiple reports of sleep disturbance were also noted during the implemented lockdowns (Gupta et al., 2020; Huang and Zhao, 2020; Salles and Mascarenhas Barbosa, 2020). Additionally, financial insecurities, lack of job security, and transition from onsite employment and communal schooling towards working at home and homeschooling have also been linked to worse mental health outcomes during the pandemic (Patel and Rietveld, 2020; Probst et al., 2020; Wilson et al., 2020). Mental health complications have also been reported to persist in COVID-19 survivors. Therefore, it is essential to propose and develop some mitigation or management strategies to sustain mental health. Meditation, yoga, exercises, sharing feelings with loved ones, and engaging in activities of interest could provide some assistance for coping with mental health issues (Fig. 2).

Global organizations involvement is beneficial in the mitigation and management of the disease. Most nations have closed their borders and are operating virtually, causing the world economy to fall out. International agencies and militaries are working to develop and provide aid for their respective countries in these crises. The media plays an essential role in spreading awareness and bringing people together. Along with the help of doctors and healthcare workers, people with mental illness require proper counseling. However, due to lockdowns and hesitations to reach out to psychiatrists, many people do not have access to the appropriate counseling. Therefore, it is essential to reach out to these populations through telephones or the Internet to provide the proper counseling and help people overcome feelings of loneliness and suicidal thoughts. E-learning has already become popular in schools and workplaces, and this strategy can also be incorporated to reach out to people with mental illness.

Social determinants of mental health should be integrated and considered during strategy and policy development for combatting the current pandemic (Fig. 3) (Bernardini et al., 2021). Poor health, lack of a healthy diet, and sanitary practices amongst the neighborhood people are the primary sources of the spread of the disease. Therefore, it is crucial to provide economic aid to low-income people and those below the poverty line. Discrimination towards minority groups is a strong predictor of adverse health outcomes (Nalbandian et al., 2021). Several historical reports have shown that inequalities among people can be the reason for the spread of infectious diseases. Therefore, it is vital to avoid discrimination and respond rapidly to situations of mental illness.

Government and non-governmental agencies like policymakers, state government, health care professionals, public health professionals, psychiatrists, researchers, governments, NIH, CDC, WHO, and others should improve the social determinants of mental health. It is time to correct the actions and measures that went wrong and focus on the physical health of individuals and mental health.

ETHICAL APPROVAL

We declare ethical statement is not applicable.

Declaration of Competing Interest

The authors declared no conflict of interest exists.

Data Availability Statement

All the data to support the findings are within the manuscript.

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