DOI 10.4149/BLL_2024_103

Bratisl Med J 2024; 125 (11):
677–684

PSYCHOSOMATIC APPROACH

COVID-19 pandemic as a huge stressor of the 21st century

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ABSTRACT
The coronavirus disease 2019 (COVID-19) pandemic had a significant impact on the somatic and psychological state of the population worldwide, leading to a wide range of health complications. Most of the studies on the COVID-19 pandemic have focused on the direct psychological and somatic aspects of the disease. However, the negative consequences of the indirect aspect of the pandemic (i.e., stay-at-home orders leading to social isolation) represent a major stressor on psychosomatic health and warrant greater interest. This study examines the COVID-19 pandemic as a significant stressor of the 21st century through the lens of the "allostatic" stress response concept and highlights the stress-related psychosomatic consequences of the COVID-19 pandemic. A better understanding of the pathomechanisms underlying indirect impacts of the pandemic on psychosomatic health can contribute to the implementation of personalized interventions for managing stress responses, thereby reducing the pandemic-linked stress burden and preventing stress-associated disease emergence *(Tab. 1, Fig. 1, Ref. 67)*. Text in PDF www.elis.sk
KEY WORDS: COVID-19 pandemic, social isolation, stress response, allostasis, allostatic load, psychosomatic symptoms.

Introduction

The coronavirus disease 2019 (COVID-19), an infectious disease caused by the SARS-CoV-2 virus, was first reported in December 2019 in Wuhan, the capital of Hubei Province, China. The disease rapidly spread not only within China but also to almost all continents (1). The disease attained a pandemic status in less than three months and was officially declared a pandemic on March 11, 2020 (2). Most state authorities implemented lockdowns and other mitigation efforts to slow down or stop the spread of the virus, including closures of state boundaries, schools, workplaces, and retail stores. Consequently, the COVID-19 pandemic impacted the quality of life worldwide in many aspects (3), including mental and somatic health.

The effects of the COVID-19 pandemic on mental and somatic health can generally be divided into direct and indirect impacts. Direct effects stem from the disease itself, where direct exposure to the virus carries the risk of developing severe illness. Indirect effects arise from pandemic-related restrictions (stay-at-home orders, closure of school, work-places, travel restrictions) which act as significant stressors (4). Regarding the direct impact, the clinical course of the COVID-19 disease is primarily characterized by a respiratory syndrome with varying degrees of severity from mild upper respiratory illness to severe interstitial pneumonia and acute respiratory distress syndrome (5). Importantly, SARS-CoV-2, like other coronaviruses, can infect and replicate in the nervous system cells, leading to direct infection of the central nervous system (CNS). This contributes to various neurological symptoms (e.g., headache, dizziness, smell and taste dysfunctions, impaired consciousness, stroke, seizures, ataxia, encephalopathy, and movement disorders) (6–8) and psychiatric symptoms (e.g., anxiety, depressive symptoms, obsessive-compulsive symptoms, and paranoid ideation (9, 10). The neuro-immune mechanism underlying the development of psychological symptoms in COVID-19 may involve the disruption of the blood-brain barrier, allowing peripheral cells invade CNS, alterations in neurotransmission, and activation of microglia and astrocytes (11–13). Furthermore, SARS-CoV-2 can persist inside CNS cells without being acutely toxic, with effects potentially emerging years later. Consequently, COVID-19 can have both acute and long-term neurological and psychiatric manifestations (13).

Regarding the indirect impact of the COVID-19 pandemic, multiple factors and difficult situations have emerged as significant stressors. Anti-pandemic mitigation efforts led to restriction on free movement and social isolation accompanied by feelings of

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Acknowledgements: This research was funded by the Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic under grant VEGA 1/0048/24.

threat, fear, uncertainty, helplessness, loneliness, and hopelessness (14–16). Moreover, stay-at-home orders increased interpersonal conflicts within families as parents juggled facilitating children's schooling while working from home and spending most of the time in isolation indoors (17). All these pandemic-linked challenging situations and psychosocial stressors profoundly disrupted the quality of life for people worldwide.

The COVID-19 pandemic – a psychosocial stressor of the 21st century in the stress response concept

The organism´s physiological and behavioral reactions to the changes in the internal and external environment (i.e., stressors) constitute the stress response mediated by a complex interplay between the activity of the nervous, endocrine, and immune systems. It is well-known that exposure to long-term and excessive stressors, which an individual is not able to manage, represents a risk factor for developing various mental and somatic disorders (18–20). The COVID-19 pandemic and its related restrictions represent a typical example of an excessive stressor, leading to repetitive and prolonged activation of the stress response.

The present understanding of the stress response is based on the concept of allostasis. The term allostasis refers to the organism´s ability to achieve stability through psychological changes driven by the activities of the autonomic nervous system (ANS), HPA axis, immune system and various endocrine and metabolic processes (21). In other words, the activity of organism's physiologic regulatory systems fluctuates in an integrated fashion in response to environmental demands (21, 22). Additionally, the concept of allostasis includes the ability of feed-forward regulation of physiological and behavioral functions such as anticipatory stress reaction, effect of learning, cognitive modulation of stress response driven by cortical and subcortical neural circuits. In this context, the stress response can be considered useful when understood within the broader framework of allostasis, adaptation to life experiences (both positive and negative), and resultant health behaviors (23–25). On the other hand, the process of inadequately managed allostatic response due to chronic or frequently repeated activation of allostatic mechanisms is termed allostatic load. In more severe cases, this is referred to as allostatic overload. This condition results in maladaptive stress responses and harmful effects of excessive and prolonged release of stress mediators on physiological

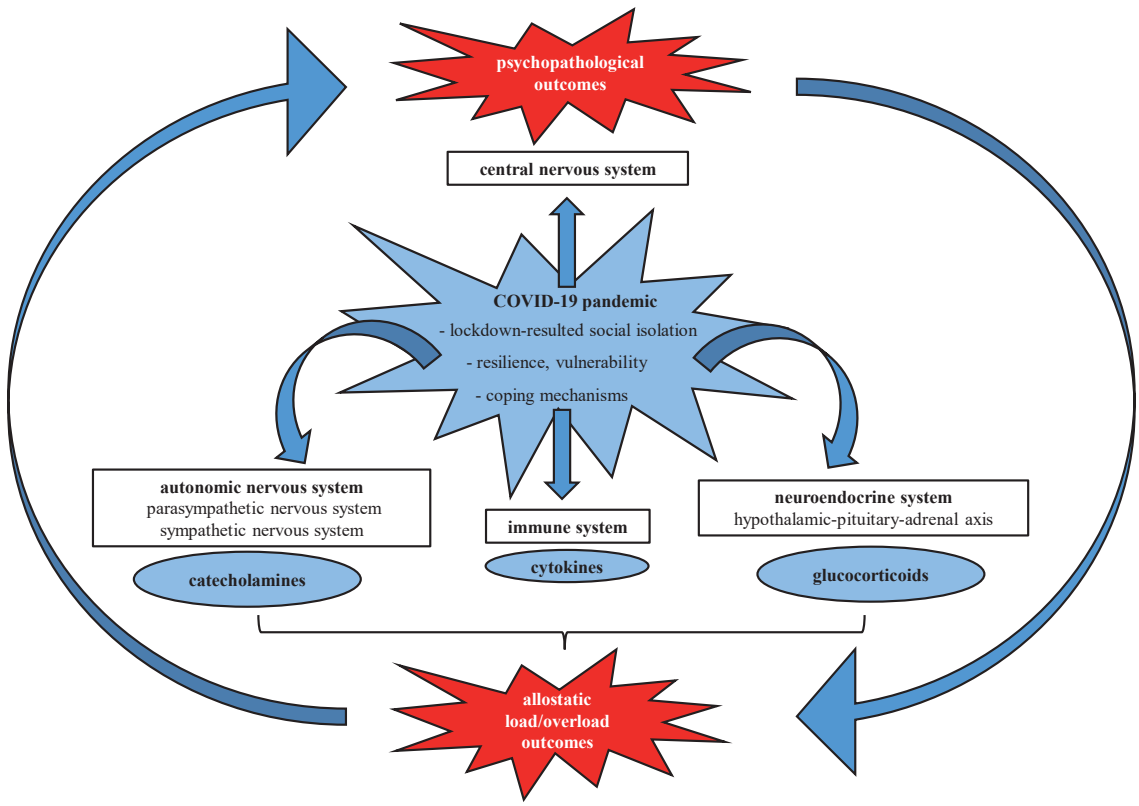

Fig. 1. The COVID-19 pandemic as an enormous psychosocial stressor in the concept of allostasis/allostatic load. The COVID-19 pandemic and its associated lockdown restrictions pose significant psychosocial challenges for the global population, leading to the repeated or chronic over-activation of the body´s allostatic mechanisms. This results in excessive and prolonged release of physiological mediators such as catecholamines, cortisol, and pro-inflammatory cytokines, leading to allostatic load or overload and subsequent psychological and somatic symptoms. Specifically, chronic and repetitive activation of stress response systems driven by COVID-19 pandemic can induce neurobiological dysregulation resulting in dysfunction of the autonomic nervous system, neuroendocrine system , and immune system. This dysfunction contributes to the development of mental health disorder such as depression, anxiety, and post-traumatic stress disorder), as well as somatic pathologies, including gastrointestinal and cardiovascular issues.

systems, health, and well-being (26, 27). However, a proportion of individuals do not necessarily demonstrate maladaptive stress responses even when encountering excessive or repetitive stressors. In this context, it is important to describe the risk of maladaptive stress responses from the aspect of psychological allostasis which is characterized by resilience and vulnerability. Resilience represents the ability to successfully cope with stressful situations through appropriate engagement and effective termination of the allostatic response, thereby maintaining healthy functioning and well-being (28–30). Conversely, vulnerability is a state of increased sensitivity to stressors, where defensive mechanisms function inappropriately or ineffectively, resulting in insufficient or impaired resilience of the organism (28, 30).

Recently, the global population has been exposed to the largest psychosocial stressor of the 21st century driven by the COVID-19 pandemic and its related restrictions leading to social isolation. Physiological adjustment to psychosocial stressors is predominantly mediated via the autonomic nervous system (31). The first mechanism involves the activity of the parasympathetic branch of ANS. According to the polyvagal theory, the myelinated vagal nerve rapidly mobilizes or calms the individual through its rapid inhibitory or disinhibitory effects on the heart. Moreover, the myelinated vagal nerve actively inhibits the effects of the sympathetic nervous system and HPA axis to promote calm behavioral states (32–34). The second mechanism in response to the psychosocial stressor includes the activation of the sympathetic nervous system which occurs when the parasympathetic withdrawal is insufficient to address the stress response (31, 35). The third mechanism is represented by the HPA axis, which is responsible for the long-term response to the stressor through the cortisol effects (31) (Fig. 1).

The neurobiological basis of the stress response to psychosocial stressors involves several key brain structures. The prefrontal cortex (PFC) enables appropriate responses to environmental changes, while limbic structures such as the amygdala (predominantly the basolateral nucleus) are fundamental for detecting potential danger. The hippocampus supports the encoding of stressor-related environmental information and promotes inhibitory control over the HPA axis. The hypothalamus, mainly the paraventricular nucleus, acts as the principal integrator of stress signals. Other structures such as ventral tegmental area and nucleus accumbens also play a role (36). Physiologically, the cortical-subcortical brain structures cooperate in a top-down manner, with PFC exerting predominant inhibitory control. However, prolonged exposure to psychosocial stressors can lead to a more prevalent activity in the amygdala and hippocampus, indicating a shift in stress response control to a bottom-up mechanism. This results in the loss of PFC inhibitory control and consequent amygdala hyperexcitability (36–38). In other words, the orchestration of the brain's response patterns shifts from PFC regulation to the reflexive and rapid emotional responses of the amygdala and related subcortical structures. Chronic exposure to stressors weakens the mechanisms providing negative feedback in the stress response, while strengthening the mechanisms that promote it. Consequently, the disinhibition of the stress-signaling pathways can lead to the development of stress-related pathologies including psychosomatic disorders (36, 39).

Further, the responsivity of the physiological stress response systems to stressful life events can be characterized by various inter-individual differences (40), including psychosocial characteristics, baseline physiological activation, and reactivity to challenges. It is important to note that individual differences in reactivity to psychosocial stress can be described at three levels. Firstly, individuals can differ in cognitive and emotional characteristics, reflecting the interaction of frontal-limbic processes in stress responsivity patterns. Secondly, individuals can differ in ANS and neuroendocrine responses, resulting from differential hypothalamic and brainstem outputs. Lastly, individuals can differ in peripheral responses, reflecting the alterations within the tissues themselves (41). Understanding these individual differences in stress responsivity patterns is crucial for identifying vulnerability to psychosomatic diseases and remains a highly discussed topic in this field.

Psychosomatic aspect of the COVID-19 pandemic

The term "psychosomatic" is derived from the Greek words "psyche", meaning mind and "soma", meaning body. The psychosomatic disorder is thus defined as a disease that involves both the mind and the body, referring to the condition where emotional distress adversely affects physiological (somatic) functioning (42). Generally, the psychosomatic conditions consist of two basic components: the psychological, which predominantly includes negative emotions affecting a person's personality, emotional reactivity, and activation processes during stressful situations; and the somatic which includes a person's physical condition (43).

The emotional distress resulting from COVID-19 pandemic-related mitigation efforts (e.g., stay-at-home orders, school and workplace closures) can play a crucial role in the development of negative mental and somatic outcomes. This distress includes feelings of threat, fear, anger, frustration, uncertainty, helplessness, loneliness, hopelessness, and heightened interpersonal conflicts (44). Specifically, the COVID-19 pandemic and associated lockdown restrictions have been linked to increased levels of anxiety, depressive symptoms, post-traumatic stress disorder symptoms, exhaustion, and sleep disturbances (45–47). Interestingly, approximately 53 million new cases of depressive disorder and 76 million new cases of anxiety disorder were reported in 2020 alone (45). Moreover, excessive attention paid to the mass media in search of information about the pandemic further potentiated individual´s emotional distress, contributing to an increase in various psychological difficulties (48). On the other hand, the most frequently reported somatic complaints resulting from emotional distress during the COVID-19 pandemic included gastrointestinal problems such as stomachache, nausea, regurgitation, vomiting, intestinal problems, and obstipation (46, 49). Other health problems reported during the COVID-19 pandemic include headache, back pain, neck pain, chest pain, unexplained fatigue, eye discomfort, and urological symptoms such as frequent urge to urinate (46, 49, 50). An overview of studies addressing the impact of the COVID-19 pandemic on psychosomatic health is presented in Table 1.

Tab. 1. Summary of the psychosomatic complaints related to the COVID-19 pandemic.

Study (year)	Sample size	Age (mean±SD or age range or median (IQR))	The prevalence of COVID-19 pandemic-linked psychosomatic complaints
Lai et al, 2020 (51)	n=1257	26–40 yrs	Distress (71.5%) Depressive symptoms (50.4%) Anxiety (44.6%) Insomnia (34.0%)
Liu et al, 2020 (52)	n=898	18–30 yrs	Low stress tolerance (74.1%) Low score for resilience (72.0%) High score for feelings of loneliness (61.5%) High level of anxiety (45.4%) High level of depressive symptoms (43.3%) High level of PTSD symptoms (31.8%)
Savarese et al, 2020 (53)	n=266	20–35 yrs	Fatigue (71%) Feeling tired (58%) Psychological and physical discomfort (48%) Anxiety (44%)
Busch et al, 2021 (54) (meta-analysis)	n=75991	Not specified	Concern about transmitting the virus to the family (60.39%) Perceived stress (56.77%) Concerns about own health (45.97%) Sleeping difficulties (39.88%) Burnout (31.81%) Depressive symptoms (25.72%) Anxiety symptoms (25.36%) PTSD symptoms (24.51%) Mental health issues (23.11%) Symptoms of somatization (14.68%)
Hajduk et al, 2021 (55)	n=1786 college students	21.15±3.53 yrs	Depressive symptoms (34.3%) Anxiety (20.1%) Association of depressive and anxiety symptoms with higher perception of stress and loneliness, and lower resilience A two-fold increase in depressive and anxiety symptoms during the second wave of pandemic compared to 2018 y.
Petersen et al, (2021) (56)	n=2190	63 yrs (IQR: 54, 69)	A minor increase in illness worries, emotional distress and physical symptom load Increase in illness worries in men and individuals having physical disease Increase in emotional distress in women and individuals having physical disease Increase in physical symptom load in individuals having physical disease
Wang et al, 2021 (50)	n=600	34±12 yrs	Poor sleep quality (12.17%) Nervousness, anxiety (11.70%) Fatigue (7.33%) Unexplained fatigue (6.67%) Obstipation (6.50%) Depressive symptoms (5.33%) Unreasonable worries (4.67%) Frequent urge to urinate (4.50%) Propensity to agitation and panic (4.17%) Headache, neck pain, chest pain (3.83%)
Zidkova et al, 2021 (46)	n=1431 general population	48.2±16.4 yrs	*Increase in the prevalence of health problems:* Headache (17.3%) Nervousness (17.2%) Irritability (16.6%) Weakness (16.5%) Beck-ache (12.8%) Sleep problems (10.3%) Stomach-ache (7.7%) Intestinal problems (7.7%) Dizziness (3.2%) *Changes in the emotional state:* Threat (33.3%) Fear and anxiety (26.1%) Helpless (24.4%) Loneliness (17.7%) Loss of hope (9.9%)

Tab. 1. (continued)

Study (year)	Sample size	Age (mean±SD or age range or median (IQR))	The prevalence of COVID-19 pandemic-linked psychosomatic complaints
Andhavarapu et al, 2022 (57) (meta-analysis)	n=117143 physicians (28365) nurses (48171) allied health professionals (13903) auxiliary health professionals (10029) "other" (12103)	Not specified	PTSD symptoms (34%) Severe PTSD symptoms (14%)
Barbieri et al, 2022 (58)	n=5159 (parent-report) n=2163 (self-report)	7–19 yrs	Irritability (65%) Feeling nervous (39%) Sleeping problems (35%) Feeling low (34%) Conduct problems (31%) Headache (29%) Stomachache (28%) Generalized anxiety (27%) Emotional problems (24%) Hyperactivity (15%) Depressive symptoms (15%) Backache (14%) Dizziness (10%) Complaints more frequent in girls than boys
Chen et al, 2022 (59)	n=1900 Unexposed to COVID-19 pandemic (1316) COVID-19 exposed (584)	13.5±0.4 yrs (baseline) 15.5±0.4 yrs (2-year follow-up)	Increased levels of psychosomatic symptoms and stress at follow-up compared to baseline Decreased levels of happiness at follow-up compared to baseline
Gundogmus et al, 2022 (60)	n=4031 Healthcare workers 1st peak period – April 2020 (1051) 2nd peak period – December 2020 (1409) 3rd peak period – April 2021 (1571)	33.74±7.95 yrs	Increase in anxiety and depression levels in each peak when compared to the previous peak Increase in stress symptoms in the 2nd peak when compared to the 1st peak with no increase in the 3rd peak compared to the 2nd peak
Zou et al, 2022 (61)	n=525 Frontline medical staff	35.3±7.1 yrs	Anxiety (39.8%) Insomnia (37.9%) Depressive symptoms (29.9%)
Hagquist 2023 (62)	n=3068 Time point 1 – April to June 2020 (3033) Time point 2 – December 2020 to march 2021 (3068)	15–17 yrs	Adolescents who often/always experienced worries either directly or indirectly related to the COVID-19 pandemic more likely reported psychosomatic problems Worry themes were reported to a higher degree in girls than in boys
Jiang et al, 2023 (63)	n=14945 *Healthcare workers* Wave 1 (2704) Wave 2 (634) Wave 3 (1169) Wave 4 (4071) *Non-healthcare workers* Wave 1 (2114) Wave 2 (542) Wave 3 (1431) Wave 4 (2280)	< 18 yrs (168) 18–25 yrs (2414) 26–30 yrs (2614) 31–40 yrs (3933) 41–50 yrs (3465) 51–60 yrs (1856) >60 yrs (495)	Psychosomatic symptoms measured by PSSS *Healthcare workers* Wave 1 (19.3%) Wave 2 (22.9%) Wave 3 (36.4%) Wave 4 (60.7%) *Non-healthcare workers* Wave 1 (24.0%) Wave 2 (35.7%) Wave 3 (34.2%) Wave 4 (50.5%)
Lenger et al, 2023 (64)	n=2655 Screening time 1: April 2020 (160) Screening time 2: Winter 2020/2021 (1361) Screening time 3: Winter 2021/2022 (1134)	18–80 yrs	Higher prevalence of psychosomatic symptoms measured by PHQ-D in frontline compared to non-frontline workers in the health sector at screening times 2 and 3 Higher prevalence of psychosomatic symptoms in females compared to males at screening times 2 and 3

Tab. 1. (continued)

Study (year)	Sample size	Age (mean±SD or age range or median (IQR))	The prevalence of COVID-19 pandemic-linked psychosomatic complaints
Ravens–Sieberer et al, 2023 (65)	n=2471 Prepandemic W1 (May–June 2020) W2 (December 2020–January 2021) W3 (September–October 2021) W4 (February 2022) W5 (September–October 2022)	7–17 yrs	Overall mental health problems from prepandemic 17.6% to 30.4% in W1, 30.9% in W2, 27.0% in W3, 28.5% in W4, and 22.6% in W5 Anxiety symptoms from prepandemic 14.9% to 24.1% in W1 to 30.1% in W2, 26.8% in W3, 27.8% in W4, and 24.8% in W5 Depressive symptoms from prepandemic 15%/10% (CES-DC/PHQ-2) to 18%/11.3% in W1, 24%/15% in W2, 19.7%/11.1% in W3, 21.3%/12.8% in W4, and 14.2%/8.6% in W5 Beck pain from prepandemic 25.9% to 26.4% in W1, 33.0% in W2, 32.8% in W3, 32.1% in W4, and 33.3% in W5 Nervousness from prepandemic 23.6% to 27.9% in W1, 33.3% in W2, 35.3% in W3, 35.5% in W4, and 33.0% in W5 Stomachache from prepandemic 21.3% to 30.5% in W1, 36.4% in W2, 39.2% in W3, 40.9% in W4, and 45.0 in W5 Feeling low from prepandemic 23.0% to 33.8% in W1, 43.4% in W2, 41.2% in W3, 44.5% in W4, 35.5% in W5 Headache from prepandemic 28.3% to 40.5% in W1, 46.4% in W2, 48.7% in W3, 53.7% in W4, and 54.7% in W5 Sleeping problems from prepandemic 39.2% to 43.3% in W1, 47.4% in W2, 46.0% in W3, 50.1% in W4, and 44.3% in W5 Irritability from prepandemic 39.8% to 53.2% in W1, 57.2% in W2, 57.0% in W3, 56.5% in W4, and 51.2% in W5
Wang et al, 2023 (66)	n=288	27–37 yrs	Association of psychosomatic symptoms measured by PSSS with higher perceived stress, more severe anxiety, and depressive mood (35.07%)
Yue et al, 2023 (49)	n=7585 1st wave: n=4317 2nd wave n=1096 3rd wave n=2172	31–40 yrs	The prevalence of psychosomatic problems: 1st wave (22%) 2nd wave (28%) 3rd wave (39%) *Somatic health problems:* fatigue, dizziness, eye discomfort, regurgitation, nausea, vomiting *Psychological health problems:* depressive mood, lack of interest
Zolotareva et al, 2023 (67)	n=10205	36.1±14.1 yrs	Being somatised (37%) Low somatic burden (23.9%) Medium somatic burden (22.2%) High somatic burden (17.4%) Very high somatic burden (19.7%)

CES-DC – Center for Epidemiological Studies Depression Scale for Children, PHQ-2 – Patient Health Questionnaire 2, PHQ-D – Patient Health Questionnaire, PSSS – Psychosomatic Symptom Scale, PTSD – post-traumatic stress disorder

Conclusion

The anti-pandemic restrictions associated with the COVID-19 pandemic have undoubtedly caused an excessive increase in emotional distress, leading to adverse impacts on the overall health of the global population. Therefore, understanding the pathomechanisms underlying the chronic stress response activation during COVID-19 pandemic can illuminate pathways for implementing personalized interventions. These interventions for stress management and resilience enhancement can help prevent the emergence of pandemic-linked psychosomatic disease.

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Received March 6, 2024.
Accepted May 11, 2024.