

## COVID-19: New disease and the largest new human stressor

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**Abstract.** Biological stress is the “nonspecific response of the body to any demand made upon it”. By definition, stress should be caused by different factors (stressors) eliciting similar neuroendocrine changes as well as bodily and behavioural alterations. COVID-19 (coronavirus disease — 2019) caused by the SARS-CoV-2 virus is a new and complex infectious disease. Its sudden and unexpected appearance in late 2019 and early 2020 found most countries unprepared; hence, it is not surprising that the new disease created much confusion, panic and chaos that almost predictably lead to stress. The multifactorial stress etiology is almost a given in a pandemic like this, e. g., anxiety about getting infected, uncertainty about what the future may bring, depression, isolation, family arguments in close quarters, real or perceived food shortages, unemployment, reduced income or its total loss, all culminating in increased domestic violence, suicides and stress-related diseases, such as heart attacks (i. e., myocardial infarction). The first scientific publications documenting these changes, especially in older populations, came from China in early and mid-2020. These results, originating from online surveys and interview-based assessments in various countries showed 20–40% increase in perceived distress, especially anxiety, with a substantial increase in PTSD. Fortunately, both the lay press and scientific publications advocate stress-prevention techniques that range from the “relaxation response” to yoga and specific physical exercises. The long-term health effects and public health consequences of increased distress due to COVID-19 remain to be seen and must be investigated.

**Keywords:** stress, distress, COVID-19, public health, epidemiology, stress-related diseases.

“COVID-19: A stress test for trust in science” is the title of a very recent editorial in the *Lancet* (COVID-19: A stress-test... 2020). The word “stress” in this short overview is not directly related to the biological stress, as Hans Selye first described it almost 85 years ago (Selye 1936; 1937), but nevertheless underlines the popularity and frequent use of not only the word, but also the concept of “stress” during the recent pandemic. The father of biological stress, Hans Selye used to complain during the last decade of his life (he died in 1982) that he had had to fight in the 1940s and 1950s to get the concept of stress or nonspecific adaption syndrome accepted, but in the 1960s and 1970s he had had to fight against its unnecessary use and implications in the scientific literature and the lay press (Szabo et al. 2012). Nevertheless, if he were alive nowadays,

he would enjoy hearing and reading the real and meaningful use of the term “stress” associated with all the travails during the COVID-19 pandemic and especially understanding how much the concept of biological stress has advanced from his early animal experiments to the nonspecific phenomena experienced at individual human and societal level. Thus, it may not be surprising that COVID-19 is the largest human stressor since World War II.

COVID-19 (**coronavirus disease–2019**), caused by the SARS-CoV-2 virus, is a new and complex infectious disease. Its sudden and unexpected appearance in late 2019 and early 2020 found most countries unprepared; thus, it is not surprising that the new disease created much confusion, panic and chaos that almost predictably lead to stress. In a recent review article on this topic written in March

and April 2020, when stress implications were emerging, we summarised new epidemiologic, public health and medical aspects of COVID-19 (Szabo 2020). In this short review, we will focus only on the stress-aspect related to COVID-19.

According to the original definition by Hans Selye, “stress is the nonspecific response of the body to any demand made upon it” (Selye 1974; 1976). Chaos and anxiety are often seen during epidemics, especially when they grow to the pandemic level. As a recent article stated, “crisis response has always been chaotic” (Akst 2020).

By definition, stress should be caused by different factors (stressors) eliciting similar neuroendocrine changes, such as rapidly released catecholamines and sustained, elevated levels of secreted glucocorticoids (Selye 1974; 1976). The multifactorial etiology is almost a given in a pandemic like this, e. g., anxiety about getting infected, uncertainty about what the future may bring, depression, isolation, family arguments in close quarters, real or perceived food shortages, unemployment, reduced income or its total loss, all culminating in increased domestic violence and suicides (Fig. 1). The more psychological, societal and physical stressors hit people, the more serious the resultant distress reaction becomes.

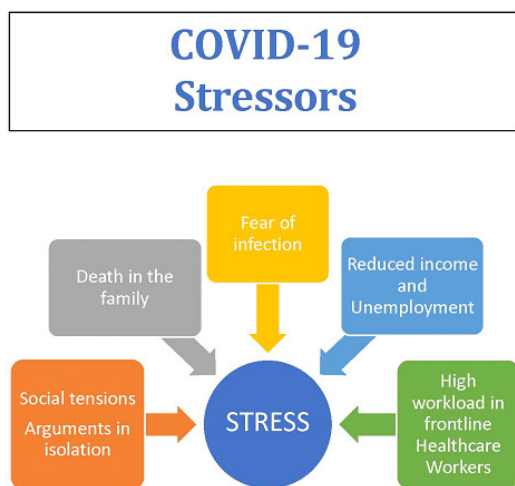


Fig. 1. Multifactorial stressors during the COVID-19 pandemic

### Early descriptive reports on the COVID-associated stress

During the late winter and early spring of 2020, multiple descriptive reports were published in reputable newspapers and media outlets (e. g., *BBC*, *The Guardian*, *Le Monde*, *NPR*, *New York Times*, *Wall Street Journal*, *USA Today*, *Los Angeles Times*) on the perceived distress during the initial chaotic response to COVID-19, often focusing on certain

segments of the population. Some of them are illustrated in a collage of representative newspaper articles (Fig. 2).

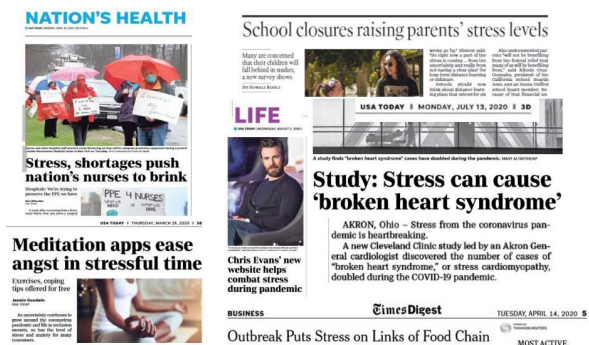


Fig. 2. COVID-19 and stress in public and healthcare workers, as seen in the media. Suggestions for stress-coping and relief (modified from Szabo 2020)

Distress may involve all segments of the population, but the most severely affected ones are healthcare workers (e. g., emergency room and intensive care unit doctors and nurses) and contact tracers. Besides almost all the other factors that hit any segment of the society, additional stress on the healthcare workers includes long hours they have to put in, in part due to the shortages of doctors and nurses, insufficient personal protective equipment, triaging patients who cannot be saved due to the lack of respirators or hospital beds, seeing dying patients, etc. No wonder that healthcare workers in some hospitals demand improvements or refuse to work to protect themselves and their families from potential exposure to the new virus (Fig. 2). All this is compounded by the fact that thousands of doctors and nurses died worldwide, apparently in a much larger percentage than people in any other professional segment.

Some of the early articles offered remedies for the pandemic distress and, fortunately, the social media and the lay press were full of stress-reduction exercises, diets and other measures. The simplest, scientifically proven measures among them are the “relaxation response” (Benson 1975), meditation, yoga and easy seven-minute workouts (Fig. 2). All these measures should be preceded by and associated with a healthy diet (a lot of vegetables, minimal carbohydrates and salt), plenty of hydration, daily exercise (at least 30 min of walking), breathing exercise and (if available) plenty of sunshine. If none of these steps help, it is crucial to obtain professional help from licensed mental health experts to avoid deep depression, alcoholism or domestic violence.

### Understanding stress in the COVID-19 era

Stress is usually perceived as something bad and negative; however, Selye often emphasised that “stress is the salt of life” (Selye 1974; 1976). At the end of his long scientific career, not only did he recognize that stress in small amounts makes us more resilient (he named this “cross resistance”) but also that there is good or positive and bad or negative stress. In his book “Stress without distress” Selye named these “eustress” (like euphoria) and “distress” (Selye 1974). Although the pituitary and adrenal glands cannot differentiate the reasons for increased ACTH and cortisol secretion, some brain areas can (e. g., the prefrontal cortex, the amygdala and the hippocampus). These concepts were further reinforced by subsequent seminal discoveries by Ludmila Filaretova who confirmed that although high levels of glucocorticoids are indeed bad for our body, their small doses are actually protective (Filaretova et al. 1998; 2009).

In this review, due to COVID-19 being a severe disease, we focus on the negative effects of the associated biological stress, i. e., on distress, and we use terms “stress” and “distress” interchangeably.

Life during the COVID-19 pandemic is associated with increased levels of anxiety, distress, mood

disturbances and other mental health disorders in certain population groups (trauma, PTSD, obsessive-compulsive syndrome) (Zvolensky et al. 2020). This section will focus on evidence-based data but also on media-reported information since February 2020. As public health professionals, the authors believe that media advocacy is of utmost importance in developing public health strategies to promote well-being of individuals during the pandemic and unique mental health challenges associated with it. There has never been a comparable chance and urgent need for public health practitioners to take into consideration all emerging data in order to coordinate their efforts in epidemiologic research, to promote public health measures through dissemination of scientifically correct information and to formulate health policies through globally used social media platforms and technologies.

In order to identify population groups at risk of stress and worse general health or mental health outcomes, a certain distinction in the etiology and description of stress is necessary: (a) direct (normal) stress, generated through a full direct cascade of stress responses. This can be expected to include activation of the neuroendocrine HPA stress axis and other systems that maintain homeostasis; (b) stress through indirect mechanisms; e. g., social

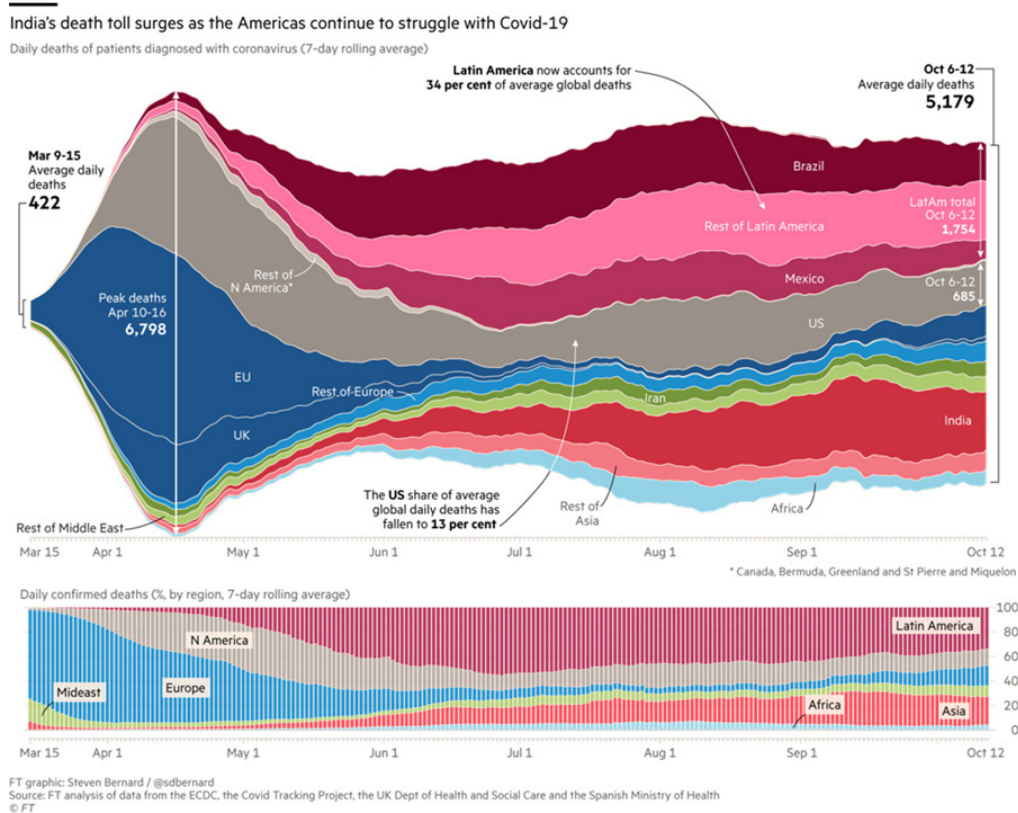


Fig. 3. COVID-19 death rates (as of October 2020). Data from Latin America (separate data from Brazil), Mexico, US, Europe, India and Asia



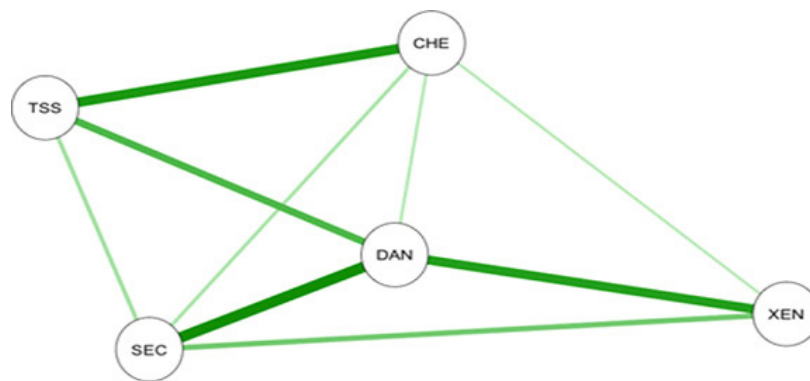


Fig. 4. The COVID stress syndrome is characterised as a network of interconnected symptoms, with the fear caused by COVID-19 and its danger at its centre (DAN), which is interconnected with socioeconomic concerns (SEC), xenophobia (XEN), traumatic stress symptoms (TSS) and compulsive checking and reassurance seeking (CHE). Thicker lines represent stronger connections (modified from Taylor et al. 2020)

distancing and financial hardships likely influence coping/adaptive mechanisms, causing anxiety and stress, and may lead to increased smoking or increased vulnerability and relapse in former users. (Patwardhan 2020; Stubbs et al. 2017). Smoking initiation and severity, in turn, increase the COVID-19 susceptibility and lead to worse disease-related outcomes. It is imperative that healthcare providers assess smoking (including the e-cigarette use) as well as the relapse potential among former users and provide appropriate education and intervention to help mitigate the potential negative effect of this health behaviour on the disease infection and its course.

### Facts and evidence-based data

COVID-19 acts as a broad stressor that increases both normal and pathologic functions in the body, but the resulting distress also leads to mood disturbances and other mental health problems (fear, paranoia, PTSD, obsessive-compulsive syndrome). According to recent research, it may bring about more severe health problems, such as chronic illnesses and drug addiction, especially in people with pre-existing pathologic conditions (Zvolensky et al. 2020). To date, COVID-19 has affected more than 38 million people, with fatal consequences for more than 1 million. The total toll is depicted in Fig. 3.

Recently, the “COVID Stress Syndrome” model (CSS 2020) was developed, which identifies five distinct but also interrelated elements (Taylor et al. 2020):

- 1) Fear of the COVID-19 danger and getting infected by different means, e. g., touching contaminated objects, breathing contaminated air, etc. (DAN).

- 2) Worry about the social and financial impact (socioeconomic costs) of the virus (SEC).
- 3) Marked concern that foreigners spread the disease (XEN).
- 4) Related traumatic stress symptoms (TSS).
- 5) Compulsive checking and seeking reassurance (CHE).

The new “COVID stress syndrome” was described and characterised as a network of interconnected symptoms, with the fear caused by COVID-19 and its danger at its centre, which is interconnected with socioeconomic concerns, xenophobia, traumatic stress symptoms, compulsive checking and reassurance seeking. The network, in turn, is associated with other factors such as excessive avoidance, panic purchasing, high distress levels and maladaptive coping during self-isolation (Fig. 4) (Taylor et al. 2020).

Data from survey studies in China suggest that around 25% of the general population have experienced moderate to severe levels of stress- or anxiety-related symptoms in response to COVID-19 (Qiu et al. 2020; Wang et al. 2020b). Among 1210 respondents in a survey study in China, 8.1% reported moderate to severe stress levels, while 28.8% reported moderate to severe anxiety symptoms (Wang et al. 2020a). A countrywide survey that included 52730 people in China during the COVID-19 epidemic found that about 35% of the participants had psychological distress (Qui et al. 2020). The latter study is in line with the recent Kaiser Family Foundation survey results indicating that 45% of adults in the USA report that their mental health has been negatively impacted due to worry and distress over the coronavirus (Panchal et al. 2020).

Stress is often associated with insomnia, as demonstrated by cross-sectional studies that included medical staff and individuals in self-isolation (Xiao

et al. 2020a; 2020b). In the largest Chinese survey in July 2020, with 56 679 participants across all 34 province-level regions, 31.6% had anxiety symptoms, 29.2% had insomnia and 24.4% had acute distress symptoms during the outbreak (Shi et al. 2020).

Comparison of data from several countries reveals the variability in the perceived distress among the general public, e. g., 32.1% in China (Wang et al. 2020a, an online survey), 35.7% in India (Kazmi et al. 2020, an online survey), 17.5% in Iraq (Othman et al. 2020, an online survey), 37% in Spain (Odriozola-González 2020, social media survey) and 27.2% in Italy (Mazza et al. 2020, an online survey). No difference in depression levels was detected among the COVID-19 patients compared to the general public, nor did the anxiety levels differ between the groups, according to a case-control study in China (Zhang et al. 2020). In an online survey involving infected patients, 96.2% reported PTSD-like symptoms associated with the COVID-19 (Bo et al. 2020).

A survey of 1441 individuals from the US showed that 27.8% had depression symptoms during COVID-19 compared with 8.5% before COVID-19, representing a 3-fold increase in all demographic groups during the pandemic. Furthermore, a higher socioeconomic status was associated with fewer depression symptoms both before and during COVID-19 (Ettman et al. 2020).

Data from most case-control studies originating in China suggest that stress and anxiety levels significantly increased among healthcare professionals (Cai et al. 2020; Lu et al. 2020; Xu et al. 2020; Chen et al. 2020; Xue et al. 2020; Li et al. 2020). However, one case-control study (Liang et al. 2020) showed no differences in anxiety levels when medical health workers in the COVID department were compared to medical staff in other departments (e. g., cardiology). Lastly, in another case-control study, poor sleep quality was detected among healthcare workers with no differences in anxiety levels (Huang, Zhao 2020).

A systematic review and meta-analysis from Greece, which combined data from 12 studies on healthcare workers, showed that the pooled prevalence of anxiety among healthcare workers was 23.2%. Remarkably, when the GAD-7 (Generalised anxiety disorder 7-item scale) was used as the assessment tool, the pooled prevalence of anxiety (from four studies) was as high as 36.9% (Pappa et al. 2020).

Although there is more evidence coming in since the beginning of the pandemic (around 40 studies so far), these results cannot be generalised due to their origin (most studies were conducted in Asia) and the fact that they are not case-control studies

and include various reported outcomes and statistical methods. Lastly, the scientific literature is very limited on psychiatric symptoms among patients with the SARS-CoV-2 infection. The inconsistencies may be due to several factors, such as differences in sampling methods, variations in research participants or screening tools, differences in the time points of the mental health assessment (Peng et al. 2020).

### Prevention and treatment strategies

In the aftermath of the health crisis declared by the WHO as the Public Health Emergency of International Concern, multiple public health measures were implemented at community, regional and national levels in China and most of the countries around the world in an effort to control the disease transmission (Adhikari et al. 2020). The WHO also issued detailed guidelines on the use of face masks in the community, during care at home and in the health care settings during COVID-19 (WHO. Advice on the use of masks in the community, during home care and in health care settings in the context of the novel coronavirus 2019-nCoV outbreak Interim guidance: <https://apps.who.int/iris/handle/10665/330987>).

With the depression prevalence in 23% of the aging population in China, there was an early need to improve mental health services delivery to this population group, as detected by public health professionals (Yang et al. 2020). In this paper, the authors underline the risks caused by an upcoming mental health crisis and the inadequacy of online mental health services due to the restricted technology use by older populations. It was proposed to use online surveys for assessing mental health problems and to provide online counseling and self-help services targeting several age groups (Liu et al. 2020).

Another study highlighted the services that are already provided in China and also listed strategies for the general public to minimize the outbreak-related stress: (a) information accuracy assessment; (b) enhancing social support; (c) reducing the stigma associated with the disease; (d) maintaining as normal a life as possible while adhering to safety measures; (e) using available psychosocial services, particularly online services, when needed (Bao et al. 2020). A recent educational article from the USA underlined mental health issues associated with the COVID-19 pandemic and declared that “under stress, our brain works overtime to regulate our emotions, attention and behaviour” (Bernstein 2020). It called attention to “the one thing you can control now: yourself”.

Psychiatric services have also shifted to telepsychiatry, up to 90% in Europe, especially in Paris, and up to 100% in Italian psychiatric departments. Telemedicine has been embraced by a part of clinicians; however, the majority does not practice. In the US, a consensus guideline exists since 2018 between the American Psychiatric Association and the American Telemedicine Association, and clinicians are encouraged to embrace telemedicine by public health officials (Best practices... 2018). Researchers in China developed intervention models, including AI programs, and suggested that all medical health professionals as well as volunteers should be trained to deliver mental health care in and out of hospitals (Kang et al. 2020).

The “virtual reality” therapy for stress developed by companies involved in Augmented Reality (AR) and Virtual Reality (VR) gained attention during

the pandemic (Fig. 5). Examples include meditative virtual reality games which invoke slow and deep breathing by making players watch virtual worlds using biofeedback mechanics as their control system (DEEP VR, Soundself). In Spain, for instance, the Barcelona-based company Psious has developed an all-in-one virtual reality platform for therapists and mental health professionals to treat anxiety disorders through exposure therapies. In the United States, the Massachusetts-based XR Health is a virtual reality tele-health company with over 500 certified healthcare professionals.

Despite multiple existing stress-coping, preventive and therapeutic programs, the long-term health effects and public health consequences of the increased distress during the COVID-19 pandemic remain to be seen and must be investigated.



Fig. 5. Virtual reality exposure-based therapy (VR) and augmented reality exposure-based therapy (ARET) adopted to combat stress during COVID-19 (a collage based on the Internet resources)



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