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

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Editorial

Why the hypothesis of psychological mechanisms in long COVID is worth considering

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Many patients infected with SARS-CoV-2 report persistent symptoms that may impair their quality of life for months, even after a mild episode of coronavirus disease 2019 (COVID-19), a situation often referred to as 'long COVID'. Figures vary between studies but the proportion of patients affected may be around 20% at 6 months post-infection and 10% at 12 months [1], making this a public health issue and a priority for medical research. Although the potential role of psychological mechanisms in long COVID has long been hypothesized, it has been relatively overlooked so far compared to other potential mechanisms [2]. In line with the principles of psychosomatic medicine, we argue that this hypothesis is worth considering to understand long COVID and to relieve patients who suffer from it.

First, there is already substantial evidence suggesting a role for psychological mechanisms in long COVID. For instance, it is now well-established that psychological distress is not only a symptom but also a risk factor of long COVID. Early in the pandemic, a history of psychiatric disorders was shown to be an independent predictor of 'Post-acute Sequelae of COVID-19' (PASC) [3,4]. Recently, psychological distress measured at the beginning of the pandemic was associated with the risk of persistent symptoms in individuals later infected with SARS-CoV-2, with a dose-response relationship [5]. It is noteworthy that this association was stronger than those observed for other risk factors of long COVID. However, it remains unknown whether this association is only observed in those infected with SARS-CoV-2. For instance, pandemic-related anxiety in the general population has been associated with physical symptoms that may mimic those of long COVID [6]. In contrast to psychological distress, higher levels of personal resilience have been associated with lower severity of PASC [7]. Beyond psychological distress, a recent observational study linked specific beliefs about COVID-19 – such as one's estimated symptom severity if infected and perception of the body's ability to fight diseases – with the experience of symptoms weeks afterwards [8]. Likewise, a cohort study found that symptom expectations associated with COVID-19 and self-reported history of COVID-19 better predicted the worsening of somatic symptom burden during the COVID-19 pandemic than serology test results [9]. Although these findings do not mean than other mechanisms could not be involved, they suggest that at least some persistent symptoms in some patients may be influenced by psychological factors.

Second, theoretical models developed by the *European Research Network to Improve Diagnosis, Treatment and Health Care for Patients with Persistent Somatic Symptoms* (EURONET-SOMA) may account for the role of psychological mechanisms in long COVID. A frequent clinical feature associated with long COVID is the contrast between the severity of symptoms and the normality of the physical examination and daily routine tests [10–14,26]. Such a contrast is common in medicine [15]. While it may stem from subtle or yet unknown structural impairments of the organs pointed by the symptoms (e.g., lung, heart or brain), it may also result from how the information relayed by the body sensors is processed by the brain [16]. While symptoms may arise from both organic and perceptual factors, the balance between these two components may vary between individuals or symptoms and change over time. In certain conditions, genuine symptoms may be experienced without any organic impairment. This may occur when bottom-up input (i.e., information from body sensors) is overweighted by top-down expectation (i.e., information from prior experiences) in shaping perception. This expectation may not be conscious. For instance, just like chemotherapy-induced nausea may persist in some cancer survivors, exposing repeatedly healthy subjects to rebreathing – a physiological cause of breathlessness – in certain circumstances may result in conditioned breathlessness – a core feature of long COVID – when similar circumstances are experienced [17]. In this integrative perceptual framework, physical triggers and psychological processes are not mutually exclusive but rather interact in the genesis of persistent symptoms, in both so-called 'functional disorders' and 'somatic diseases' [15,18]. For instance, it may explain why psychological factors predict the persistence of symptoms months after an infectious episode such as gastro-enteritis [19]. It may also explain why self-reported persistent symptoms poorly correlate with objective long-term organ damage

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associated with COVID-19 [12,14]. It is noteworthy that this framework may also account for the association between psychological distress and the risk of long COVID. In the context of ambiguous perceptive situations, overweighting expectations at the expense of actual sensory inputs may be viewed as an attempt of our brain to reduce uncertainty. Therefore, intolerance of uncertainty, which is a risk factor for psychological distress, may constitute a shared vulnerability factor for psychological distress and persistent symptoms.

Third, we posit that a better understanding of psychological mechanisms of long COVID may help to elucidate purely biological mechanisms. Although identifying biomarkers of long COVID would be a major achievement, searching for such biomarkers will be impeded if patients with heterogenous conditions are pooled or if symptoms of different origins are merged. The World Health Organization defined the 'Post-COVID condition' as the presence of symptoms that occur in the three months from the onset of a SARS-CoV-2 infection, persist for at least two months, impact on everyday functioning, and cannot be explained by another diagnosis. The promulgation of this definition has been important in recognizing the burden of long COVID. However, the lack of specificity of symptoms and their default attribution to SARS-CoV-2 infection inevitably result in a heterogeneous condition. For instance, persistent symptoms may result from sequelae of the COVID-19 episode (e.g., lung damage), from ongoing pathological processes (e.g., dysfunctional immune response), but also from other causes than COVID-19, including another post-infectious syndrome as well as anxiety or depression [20]. Based on the above-mentioned emerging evidence, we posit that psychological features may be critical in subtyping patients and symptoms and thus in identifying relevant biomarkers of long COVID.

Fourth, and perhaps foremost, a better understanding of psychological mechanisms of long COVID may help relieving patients, beyond the discovery of relevant biological targets. Many potential psychological mechanisms of long COVID are modifiable factors that could thus be targeted by already validated therapeutic interventions. Beside the treatment of a comorbid psychiatric condition, which may be associated with fatigue, cognitive impairment or aberrant activation of the autonomous nervous system, therapeutic interventions may build on those used in the treatment of 'functional somatic disorders', defined as the presence of debilitating and persistent symptoms that are not fully explained by damage of the organs they point [21–23]. These disorders are common after an acute medical event, particularly in women, and include psychological risk factors, such as anxiety, depression, and dysfunctional beliefs that can lead to deleterious, yet modifiable health behaviors. Addressing these factors in the management of long COVID may provide an opportunity for patient empowerment.

If psychological mechanisms are so important for understanding long COVID, why have they not been explored further so far? Good question. First, clinicians may have in mind the long and problematic history of ascribing psychological causes to conditions for which the underlying pathology is not yet known. Considering potential psychological mechanisms as exclusive may indeed lead to insufficient workups or inappropriate treatment. Second, as much remains to be learned about the course and mechanisms underlying long COVID, researchers may deem it premature to consider psychological mechanisms. Third, psychological explanations of physical symptoms of uncertain origin are often perceived as stigmatizing [24]. Patient advocacy groups may fear that the stigma associated with mental disorders will reflect on them and harm their interests. As consultation-liaison psychiatrists are well aware, patients considered to be primarily mentally ill often receive poorer quality care for other medical conditions [25]. From a psychosomatic medicine perspective, all these issues originate from the fact that, while psychological mechanisms are ultimately biological (i.e. brain-based), they are often contrasted with biological mechanisms in a dualistic approach. As research in cognitive neuroscience or psychosomatic medicine demonstrates, such an opposition makes no sense. For instance, linking depression to poor outcomes in patients with acute coronary syndrome does not make coronary heart disease purely psychogenic. The threat to public health posed by long COVID deserves a more integrative approach. Psychological mechanisms are real, as are long COVID symptoms and related suffering.

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Access to data and data analysis

N/A.

Authors' contributions

CL wrote the first draft. CG, VP, and BR revised it critically for important intellectual content.

All authors have read and approved the final manuscript.

Declaration of Competing Interest

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