Received: 8 September 2020 | Revised: 3 November 2020 | Accepted: 9 December 2020

DOI: 10.1002/smi.3017

COMMENTARY

WILEY

Does inflammation link stress to poor COVID-19 outcome?

Steven J. Lamontagne[1,2] | Diego A. Pizzagalli[2] | Mary C. Olmstead[1,3]

[1]Department of Psychology, Queen's University, Kingston, Ontario, Canada

[2]Center for Depression, Anxiety and Stress Research, McLean Hospital/Harvard Medical School, Belmont, Massachusetts, USA

[3]Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada

Correspondence

Steven J. Lamontagne Center for Depression, Anxiety, & Stress Research 115 Mill Street McLean Hospital Belmont, MA, USA.
Email: slamontagne@mclean.harvard.edu

Funding information

National Institute of Mental Health (NIMH), Grant/Award Numbers: R01 MH095809, R37 MH068376; Alexander Graham Bell Graduate Scholarship from the Natural Sciences and Engineering Research Council (NSERC) of Canada; Discovery Grant from the Natural Sciences and Engineering Research Council (NSERC) of Canada, Grant/Award Number: 203707

Abstract

Coronavirus disease 2019 (COVID-19) continues to ravage communities across the world. Despite its primary effect on the respiratory system, the virus does not solely impact those with underlying lung conditions as initially predicted. Indeed, prognosis is worsened (often fatal) in patients with pre-existing hyperinflammatory responses (e.g., hypertension, obesity and diabetes), yet the mechanisms by which this occurs are unknown. A number of psychological conditions are associated with inflammation, suggesting that these may also be significant risk factors for negative outcomes of COVID-19. In this review, we evaluate preclinical and clinical literature suggesting that chronic stress-induced hyperinflammation interacts synergistically with COVID-19-related inflammation, contributing to a potentially fatal cytokine storm syndrome. In particular, we hypothesize that both chronic stress and COVID-19-related hyperinflammation are a product of glucocorticoid insufficiency. We discuss the devastating effects of SARS-CoV-2 on structural and functional aspects of the biological stress response and how these induce exaggerated inflammatory responses, particularly interleukin (IL)-6 hypersecretion. We postulate that chronic stress should be considered a significant risk factor for adverse COVID-19-related health outcomes, given overlapping peripheral and central immune dysregulation in both conditions. We conclude by discussing how people with a history of chronic stress could mitigate their risk for COVID-19 complications, identifying specific strategies that can be implemented during self-isolation.

KEYWORDS

chronic stress, COVID-19, inflammation, interleukin (IL)-6, risk factors

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is 'the defining global health crisis of our time' (World Health Organization (WHO), 2020). As of 27 October 2020, the number of cases exceeded 42 million with 1.1 million deaths worldwide, carrying a mortality rate several times higher than influenza (WHO, 2020a). Whereas most cases are asymptomatic or mild to moderate (80%), others are severe and require intensive care (20%; WHO, 2020b), suggesting predisposing mechanisms influence susceptibility to a worse prognosis. Indeed, certain populations are more vulnerable to poorer outcomes: hypertension is the most common comorbidity in COVID-19 patients (27%–30% of patients), followed by diabetes and cardiovascular disease (Wu et al., 2020; Zhou et al., 2020b). These comorbidities, linked to increased COVID-19-related complications and fatality (Wu et al., 2020), are independently associated with stress-induced inflammatory responses (Black & Garbutt, 2002; Brydon & Steptoe, 2005; Joseph & Golden, 2017). In this review, we integrate preclinical and clinical literature suggesting that pre-existing psychological stress and inflammation interact with immune responses to SARS-CoV-2 infection, worsening its prognosis. Whereas

several recent articles discuss the stressful nature of contracting COVID-19 (e.g., Bo et al., 2020), social isolation during stay-at-home orders (e.g., Usher, Bhullar, & Jackson, 2020), as well as SARS-CoV-2-induced stress reactivity (e.g., Steenblock et al., 2020), our aim is to describe how pre-existing exposure to chronic stress interacts synergistically with SARS-CoV-2 pathogenesis, producing potentially fatal outcomes. In doing so, we propose a novel framework that implicates prolonged stress as a significant risk factor for COVID-19-related morbidity and fatality, which has yet to be thoroughly discussed in the scientific or medical community. We conclude by discussing how people with a history of prolonged stress could mitigate their risk for COVID-19-related complications.

To ensure we reviewed the most recent literature on COVID-19, we conducted daily literature searches (PubMed, MEDLINE and Google Scholar) and monitored international public health agency databases, namely the World Health Organization (WHO), throughout manuscript preparation. Relevant articles were retrieved using search terms that included 'COVID-19', 'SARS-CoV-2', 'inflammation', 'IL-6', 'stress', 'HPA axis' and 'cortisol'. These searches were also combined with terms related to randomized controlled trials, epidemiology, prevalence, risk factors and predisposition. We reviewed articles published between database inception and September 2020.

2 | STRESS AND INFLAMMATION

Psychological stress is a reaction to any stimulus that alters homoeostatic responses across stress mediators (Lee & Choi, 2015). The hypothalamic-pituitary-adrenal (HPA) axis regulates some aspects of the relationship between stress and biological responses that maintain homoeostasis, including glucocorticoid and proinflammatory cytokine release. Following stress exposure, the HPA axis triggers adrenal cortical release of glucocorticoid hormones (i.e., corticosterone in rodents and cortisol in humans; CORT), which are significant regulators of the 'fight or flight' response (Pariante & Lightman, 2008). HPA activation also engages the sympathetic nervous system (SNS), which triggers the release of proinflammatory cytokines, including interleukin (IL)-6, through α_2-adrenoreceptor activation on immune cells (Raison, Capuron, & Miller, 2006). Notably, this relationship is bidirectional in that IL-6 potently activates the HPA axis, initiating a feed-forward activation cycle that increases SNS activity (Mastorakos, Weber, Magiakou, Gunn, & Chrousos, 1994). Once a stressor is removed, further release of glucocorticoids and cytokines is attenuated through feedback inhibition as a result of CORT binding to glucocorticoid receptors (GR) in the hippocampus, as well as the hypothalamus (Pariante & Lightman, 2008).

Under acute (i.e., short term) stress, this biological cascade promotes immediate survival by mobilizing and allocating bodily resources (McEwen & Seeman, 1999). Indeed, glucocorticoids are critical for stabilizing proinflammatory cytokine action, thereby restoring homoeostasis following stress (Ruzek, Pearce, Miller, & Biron, 1999). Persistent activation of the HPA axis (e.g., as a result of chronic stress), however, causes GR downregulation (Paskitti, McCreary, & Herman, 2000) and blunted GR-mediated signal transduction (Mizoguchi et al., 2001) in the hippocampus, both of which characterize glucocorticoid insufficiency (Raison & Miller, 2003). Consequently, under conditions of persistent stress, the HPA axis operates with reduced hippocampal-mediated regulation, contributing to CORT dysregulation and unrestrained cytokine release (Raison & Miller, 2003). Additionally, stress-induced cytokine release may interact directly with GRs, leading to reduced GR sensitivity (Pace, Hu, & Miller, 2007). Various inflammatory and immunoregulatory signalling pathways, like nuclear factor-κB (NF-κB), contribute to GR resistance (for comprehensive review, see Pace et al., 2007). This effect has been observed in various animal models of stress, including social defeat paradigms, whereby glucocorticoid resistance correlates with the number of wounds received during defeat (Avitsur, Stark, & Sheridan, 2001). In this scenario, glucocorticoid resistance is an adaptive response to elevated CORT levels, which would typically suppress inflammatory responses, thereby interfering with the proper healing of physical injury (Avitsur, Stark, Dhabhar, Padgett, & Sheridan, 2002). This phenomenon explains how increases in circulating CORT can coincide with elevations in proinflammatory markers, as seen in many preclinical models of chronic stress (e.g., Savignac, Hyland, Dinan, & Cryan, 2011) as well as mental health disorders, like major depressive disorder (MDD) (Karlović, Serretti, Vrkić, Martinac, & Marčinko, 2012).

Given the important role of CORT in mediating cytokine transmission, HPA dysregulation perturbs normal immune responses. When CORT is elevated (e.g., during periods of acute stress) (see Figure 1a, b), helper T cell type-2 (TH2)-mediated immune responses, which activate the production of anti-inflammatory cytokines, are predominant (Assaf, Al-Abbassi, & Al-Binni, 2017). Though evolutionarily adaptive, this response can be detrimental when recruited repeatedly (i.e., during chronic stress; Morey, Boggero, Scott, & Segerstrom, 2015) as it invokes the suppression of TH1 cytokines, proinflammatory cytokines that are needed for immunity. Thus, elevated CORT results in immediate immunosuppressive consequences that could increase susceptibility to negative health outcomes, including infectious disease. Critically, prolonged stress exposure causes leukocytes to downregulate GRs (see Figure 1c, d), reducing the immune system's ability to respond to anti-inflammatory actions of CORT (Miller, Cohen, & Ritchey, 2002). As a result, proinflammatory processes, such as IL-6 release, become dominant (see Figure 1e). Relatedly, during periods of hypocortisolemia (i.e., following the removal of a chronic stressor), proinflammatory cytokine levels spike as TH1-mediated immune responses prevail. Adults with adverse early life experiences (particularly those with post-traumatic stress disorder [PTSD]) most commonly show hypocortisolism, which is likely due to a compensatory state of self-preservation as well as a counteraction to prolonged hypercortisolism that occurs throughout stress exposure ('adrenal fatigue'; Gunnar & Vazquez, 2001). Notably, these individuals are particularly vulnerable to IL-6 hypersecretion following acute stress (Carpenter et al., 2010).

Individuals with a history of chronic stress or trauma are at increased risk for poor disease prognoses due to the activation of a conserved transcriptional response to adversity (CTRA). This is

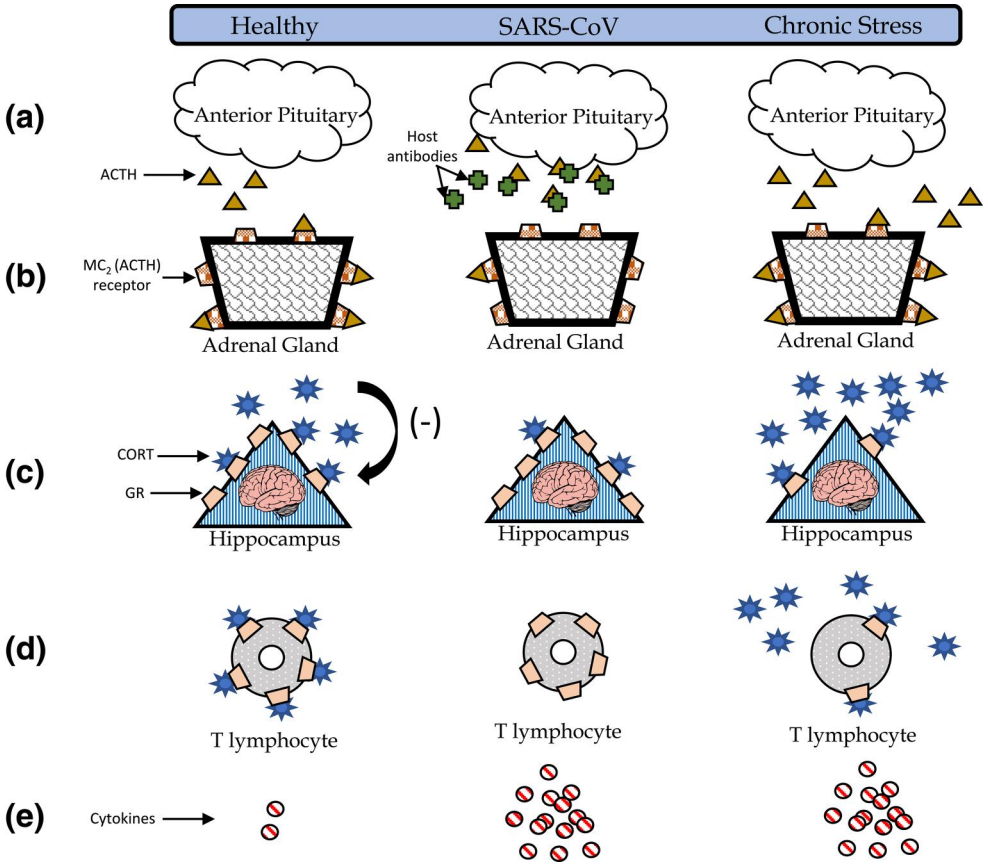

FIGURE 1 Differential processes contribute to hypercytokinemia in severe acute respiratory syndrome coronavirus (SARS-CoV) patients and chronic stress-exposed individuals. At baseline in both conditions and in healthy individuals, the paraventricular nucleus (PVN) of the hypothalamus secretes corticotropin-releasing hormone (CRH), which activates (a) anterior pituitary gland release of adrenocorticotropic hormone (ACTH). In SARS-CoV patients, the virus mimics ACTH, causing host antibodies to destroy endogenous ACTH (b) ACTH binds to its receptors (melanocortin receptor type 2; MC_2) in the adrenal cortex, stimulating the production of glucocorticoids, namely, cortisol (CORT). Due to insufficient bioavailability of ACTH, SARS-CoV leads to less adrenal CORT production (c) In a negative feedback system, CORT binds to glucocorticoid receptors (GR) in the hippocampus, which suppresses further release of glucocorticoids from the adrenal glands. Chronic stress causes GR downregulation, impairing the ability of the hippocampus to regulate CORT secretion. Associated decreases in GR-mediated signal transduction lead to hypercortisolism (d) In SARS-CoV patients, insufficient CORT is available to bind to GRs whereas in chronic stress, there is an abundance of CORT with few receptors available to bind. Under normal conditions, CORT inhibits immune cells, like T lymphocytes, thereby leading to (e) suppression of inflammatory responses, namely proinflammatory cytokine release. In SARS-CoV patients, decreased CORT bioavailability promotes unrestrained cytokine release. Similarly, in individuals experiencing chronic stress, GR downregulation in immune cells prevents CORT from suppressing the inflammatory response, leading to hypercytokinemia

predominantly characterized by (1) increased NF-κB signalling, which regulates proinflammatory cytokine production and (2) decreased interferon response factors (IRFs) signalling, which mediates innate antiviral gene expression (Cole, 2014) (see Figure 2). The CTRA is especially salient in the context of social-environment conditions, whereby social threats (e.g., interpersonal conflict or social isolation) may upregulate genes that are critical in initiating an inflammatory response (e.g., IL-1β) and downregulate those that promote antiviral responses (e.g., interferon-stimulated genes) (Murray, Haselton, Fales, & Cole, 2019). These gene expression profiles are evoked by SNS activation, which indirectly activates proinflammatory transcription factors while inhibiting antiviral responses (Murray et al., 2019). In Section 6, we discuss the importance of maintaining social integration during COVID-19 stay-at-home orders and how this can be achieved safely.

Critically, the deleterious effects of chronic stress are not uniform across all individuals and stress resistance factors are implicated in a subset of stress-exposed humans (Bonanno, 2004) and rats (Bergström, Jayatissa, Thykjaer, & Wiborg, 2007). Adrenal gland enlargement, which is a marker for adrenal hypertrophy and hyperplasia (Ulrich-Lai et al., 2006), is commonly observed following chronic stress exposure, but only in some cases. In this context, preclinical research shows increased adrenal weight following chronic stress in some rats (Hueston et al., 2011), which is also seen in some stress-exposed humans (Hayashi, Bunai, Ago, Ago, & Ogata, 2011) and those with depression (Nemeroff et al., 1992). Individual variability in stress reactivity might also influence inflammatory responses. For instance, in a social defeat paradigm, subordinate mice that are exposed to daily social interaction with a dominant mouse show elevated proinflammatory cytokine profiles (e.

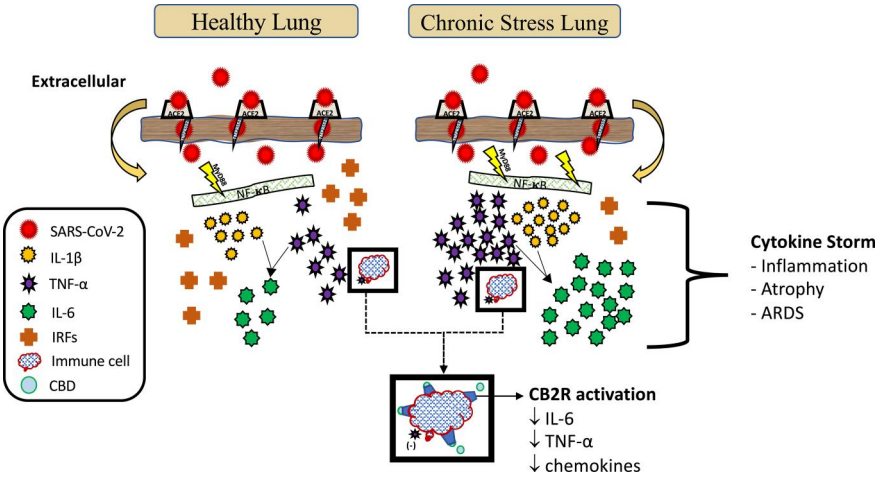

FIGURE 2 Coronavirus disease 2019 (COVID-19) activates similar inflammatory responses as chronic stress, leading to a cytokine storm. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) penetrates cells through the angiotensin-converting enzyme 2 (ACE2) receptor after its spike glycoprotein is cleaved by transmembrane protease serine 2 (TMPRSS2) and Furin. Subsequently, the MyD88 pathway activates nuclear factor kappa B (NF-κB), initiating a proinflammatory response marked by hypersecretion of interleukin (IL)-1β, tumour necrosis factor-alpha (TNF-α) and IL-6. Each of these cytokines are significantly elevated in severe COVID-19 patients, but IL-6 is uniquely associated with acute respiratory distress syndrome (ARDS)-related mortality. Critically, chronic stress similarly activates NF-κB signalling pathways, upregulating genes that are critical for initiating intense inflammatory responses, namely increases in IL-1β, TNF-α and IL-6. In particular, chronic stress-induced TNF-α and IL-1β transmission is associated with hyperinflammatory pulmonary responses, which is particularly relevant to its role in lung atrophy and the development of ARDS in COVID-19 patients. Furthermore, chronic stress also decreases interferon response factors (IRFs) signalling, which has an important role in mediating innate antiviral gene expression and immune responses. Stimulation of cannabinoid type 2 receptors (CB2R), which are abundantly expressed on cytokine-releasing immune cells (i.e., macrophages, T-helper cells), restrains proinflammatory cytokine release. Non-psychotropic cannabidiol (CBD), which activates CB2 receptors, is a promising therapeutic that could modulate immune function and cytokine production in COVID-19 patients with a history of chronic stress

g., IL-6, IL-7, IL-15; Stewart et al., 2015). In contrast, dominant mice show increases in IL-10, an anti-inflammatory cytokine (Stewart et al., 2015). In a similar resident-intruder paradigm, passive stress-coping rats (i.e., those with a shorter latency to assume defeat) show elevations in IL-1β, which initiates a proinflammatory response, whereas active coping rats (i.e., those with a longer latency to assume defeat) show a suppression of proinflammatory responses (Wood et al., 2015). Similar patterns are observed in humans, such that high stress perception is associated with substantially higher production of various cytokines, including IL-6, tumour necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ), each of which are critical for initiating an immune response (Maes et al., 1998). Thus, the apparent heterogeneity in individual physiological responses to identical stressors is important when considering chronic stress as a risk factor for various morbidities, including COVID-19.

3 | HPA DYSREGULATION IN COVID-19 PATIENTS: INSIGHTS FROM SARS-CoV

Although little is currently known about the pathogenesis of SARS-CoV-2, 79% of its genetic sequence is shared with SARS-CoV (SARS) (Coronaviridae Study Group, 2020) (for a more comprehensive comparison, see Xu et al., 2020). Like SARS, the virus penetrates cells through the angiotensin-converting enzyme 2 (ACE2) receptor of the host (Li, Geng, Peng, Meng, & Lu, 2020a). In order to do so, its spike glycoprotein (S) is cleaved at two sites by host cell proteases, namely transmembrane protease serine 2 (TMPRSS2) and Furin (Bestle et al., 2020). Indeed, replication of SARS-CoV-2 is substantially reduced using either TMPRSS2 or Furin inhibitors (Bestle et al., 2020), suggesting that inhibition of these proteases may be critical in preventing and/or treating this virus. Furthermore, emerging research shows an important role for nicotinic receptors (nAChRs) in regulating ACE2 receptor expression, pointing to nAChR agonism as a potential treatment for COVID-19 (Farsalinos et al., 2020). ACE2 is markedly expressed on pneumocytes in the lung, but also on endothelial cells of the adrenal glands in humans (Harmer, Gilbert, Borman, & Clark, 2002) and rats (Riviere et al., 2005). Unlike cells of most other organs (e.g., kidneys, liver, thyroid), lung macrophages and adrenal gland stromal cells show marked co-expression of the ACE2 gene with TMPRSS2 and Furin, implicating these organs as primary targets for SARS-CoV-2 infection (Zhou et al., 2020b). Some have suggested that adrenal necrosis and vasculitis in COVID-19 patients is likely caused by viral entry through the adrenal glands (Somasundaram et al., 2020). In support of this claim, autopsies of SARS patients identified the virus in the adrenal glands and revealed degeneration and necrosis of adrenal cortical cells (Ding et al., 2004), which are responsible for regulating secretion

of adrenal hormones. Relatedly, a recent case study shows bilateral adrenal hemorrhaging in a COVID-19 patient, marked by increased size and blurring of both adrenal glands (Álvarez-Troncoso et al., 2020). These findings implicate a direct cytopathic effect of the virus on adrenal cells, potentially altering CORT transmission in these patients. In line with these findings, a recent study found marked elevations in CORT responses in COVID-19 patients within 48 h of hospital admission, which positively correlated with mortality (Tan et al., 2020). Either adrenal atrophy or hypercortisolism would be particularly detrimental to those with a history of chronic stress, given pre-existing adrenal gland damage (Rygula et al., 2005) and HPA dysregulation (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001). Notably, pre-existing health conditions that are most associated with COVID-19 mortality (e.g., advancing age, obesity, cardiovascular disease) are also associated with hypercortisolism (Black & Garbutt, 2002; Brydon & Steptoe, 2005; Joseph & Golden, 2017).

In addition to its direct effect on adrenal structure, SARS-CoV expressed specific amino acid sequences that mimic adrenocorticotropic hormone (ACTH), causing the host antibodies to unintentionally destroy endogenous ACTH (Wheatland, 2004). Whether SARS-CoV-2 similarly downregulates ACTH remains elusive; however, the majority of its proteins (≥95%) are homologous with those of SARS-CoV (Xu et al., 2020), suggesting similar amino acid sequences could be present. Indeed, a prospective study (ChiCTR20000301150) is evaluating whether SARS-CoV-2 similarly mimics ACTH molecules, which could be likely given that multi-organ damage in COVID-19 patients is associated with its molecular mimicry of several proteins related to vascular function, anosmia and leukopenia (Angileri et al., 2020). Owing to the fact that ACTH stimulates adrenal secretion of CORT, downregulation of this hormone leads to sustained CORT deficiency (see Figure 1). Although this appears to contradict the recent study linking hypercortisolism to COVID-19 mortality (Tan et al., 2020), the paradox may be explained by temporal changes in HPA reactivity following SARS-CoV-2 infection. Thus, circulating CORT levels could initially be elevated due to reduced metabolism and clearance of the molecule, which is commonly observed in critically ill patients (Boonen et al., 2013). In the later disease course, it is possible that patients show adrenal insufficiency as a consequence of ACTH mimicry. Indeed, ~40% of SARS patients showed hypocortisolism three months after SARS recovery, which persisted for up to a year (Leow et al., 2005). Notably, these individuals did not have pre-existing endocrine deficiencies that are common in people with a history of chronic stress. Some adults with past childhood trauma show unusually low plasma CORT (e.g., Edwards, Heyman, & Swidan, 2011) and elevated IL-6 (Carpenter et al., 2010) concentrations. This is concerning given that mild CORT deficiency is associated with increased morbidity and mortality in critically ill patients (Ledingham & Watt, 1983). Specifically, CORT suppresses cellular immunity (namely, the release of cytokines) to prevent excessive inflammatory responses (Ruzek et al., 1999). Thus, CORT deficiency (i.e., hypocortisolism) facilitates proinflammatory cytokine release (Raison & Miller, 2003), producing a variety of immune-related syndromes. This 'serum sickness response', mediated by proinflammatory cytokines, can manifest as a range of symptoms that resemble physiological and behavioural changes observed during infection (e.g., rash, fever, appetite suppression and anhedonia; Yorulmaz et al., 2018). These symptoms are observed in animal models of maternal separation and can be reversed by proinflammatory blockade (Deak, Kudinova, Lovelock, Gibb, & Hennessy, 2017; Hennessy, Deak, & Schiml-Webb, 2001). Hence, pre-existing hypocortisolism could interact with elevated cytokine levels from the natural immune response to the virus, creating a 'cytokine storm', which is defined by a state of intense hyperinflammation. Indeed, this syndrome, which is characterized by hypercytokinemia, is found in a subset of COVID-19 patients (Mehta et al., 2020) and is commonly associated with sepsis or septic shock (Li et al., 2020a). Given potential interactions with HPA reactivity in vulnerable populations, it is imperative for future research to elucidate circulating ACTH and CORT levels, as well as adrenal morphology, in COVID-19 patients. This is particularly important given that hypercortisolism, which is observed following prolonged stress, causes glucocorticoid insufficiency, preventing CORT from effectively exerting its anti-inflammatory effect (thereby resulting in hypercytokinemia) (see Figure 1). In the following section, we examine specific inflammatory processes that contribute to a cytokine storm syndrome in COVID-19 patients and discuss how this relates to chronic stress-induced hypercytokinemia.

4 | STRESS-LIKE INFLAMMATORY RESPONSES IN COVID-19 PATIENTS

4.1 | Th1/Th2-mediated immune responses

Hyperinflammatory responses are consistently observed in COVID-19 patients (Qin et al., 2020) and proinflammatory cytokine levels are associated with pulmonary inflammation and lung damage (Huang et al., 2020). In addition, the effects of SARS-CoV-2 on immune dysregulation are more complex than those associated with previous coronaviruses. As expected, TH1-mediated immune responses appear to be activated in these patients (marked by substantial increases in proinflammatory cytokines; 'cytokine storm' syndrome) and cytokine levels are correlated with disease severity (Huang et al., 2020). Paradoxically, TH2-mediated responses are also activated in COVID-19 patients (marked by increases in anti-inflammatory cytokines, like IL-4 and IL-10, which typically suppress proinflammatory cytokine release) (Huang et al., 2020). Relatedly, type 1 interferons (IFN), which have anti-inflammatory properties that are critical in restraining viral replication, are deficient in the blood and lungs of COVID-19 patients (Hadjadj et al., 2020), contributing to COVID-19 pathogenesis.

This unusual contrast is akin to the cytokine shift seen with chronic stress, whereby immune responses are simultaneously enhanced or suppressed by differential production of cytokines (Marshall et al., 1998; Segerstrom & Miller, 2004), a process that is

regulated by CORT (Chiappelli, Manfrini, Franceschi, Cossarizza, & Black, 1994). This is particularly salient in the context of age-related susceptibility to poor COVID-19 outcome, given that elderly individuals are at higher risk for complications and fatality (Liu, Chen, Lin, & Han, 2020). Among the elderly, both TH1 and TH2-mediated immune responses contribute to vulnerability to viral infection and poor health outcomes. For instance, chronic stress in older adults impairs antibody responses to influenza virus vaccine and decreases proinflammatory IL-2 and IL-1β (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996), which are critical for initiating an immune response. Indeed, chronic stress-induced immune dysregulation in the elderly persists for years after the stressor has abated (Gouin, Hantsoo, & Kiecolt-Glaser, 2008), which appears to be mediated by elevated glucocorticoid secretion (Vedhara et al., 1999). Additionally, ageing is associated with a state of low-grade inflammation ('inflammaging'), contributing to chronic proinflammatory responses (e.g., IL-6 and IL-8 hypersecretion; Franceschi & Campisi, 2014). Consequently, elderly individuals may not only be more prone to contracting COVID-19 but are more susceptible to a hyperinflammatory reaction to the virus, increasing their risk for health complications.

4.2 | T-lymphopenia

The contrasting immune responses in COVID-19 patients could be driven by downregulated production of T cells (Qin et al., 2020), which are critical in orchestrating immune responses and for producing pro- and anti-inflammatory cytokines. Indeed, T-lymphopenia, a deficiency in lymphocyte counts in the blood, is more pronounced in severe, compared to mild, cases (Qin et al., 2020). Effector memory T (T_{EM}) cells, which are a subset of memory $CD8^+$ T cells, rapidly respond to re-infecting pathogens. Notably, recent immunophenotyping studies reveal that $CD8^+$ T_{EM} cells are significantly depleted in COVID-19 patients, which correlate with the severity of disease progression (Laing et al., 2020; Mathew et al., 2020). The authors suggest that T_{EM} cell depletion is particularly worrisome for the elderly who rely on memory T cells, given a reduced ability to generate naïve T cell repertoires with age (Laing et al., 2020). Such subset-specific T cell depletion in COVID-19 patients is likely attributable to increased apoptosis and may help elucidate age-related differences in susceptibility to poor outcomes (Laing et al., 2020). Importantly, distinct heterogeneity of the immune response is observed in hospitalized COVID-19 patients, with certain subgroups showing robust $CD8^+$ T cell activation and proliferation whereas others show no detectable responses (Mathew et al., 2020).

Fluctuations in lymphocyte levels typically coincide with those of plasma CORT, such that elevated CORT levels are associated with low lymphocyte counts (Krüger et al., 2011). This is commonly observed in people with depression, whereby hypercortisolism occurs in conjunction with lymphopenia (Toben & Baune, 2015). In rodents, chronic stress is associated with involution of the thymus gland (a vital producer of T lymphocytes), which is a product of CORT-induced apoptosis (Tarcic, Ovadia, Weiss, & Weidenfeld, 1998). In line with this research, chronic stress has well-documented effects on lymphocyte redistribution, such that plasma T cells, B cells, natural killer cells and monocytes are significantly decreased during and after stress exposure (Dhabhar & McEwen, 1997). This is an immune cell trafficking process that is mediated by adrenal hormones (Dhabhar, Miller, McEwen, & Spencer, 1996). Tan et al. (2020) found significantly elevated CORT levels in COVID-19 patients within 48 h of hospitalization, but it is unclear how this might affect T cell depletion, particularly that of $CD8^+$ T_{EM} cells. Importantly, $CD8^+$ T_{EM} cell counts negatively correlate with CORT rhythms (Dimitrov et al., 2009), further highlighting the role of CORT in redistributing these cells away from peripheral blood circulation. Research from SARS-CoV shows that elevated CORT was associated with general lymphopenia (Panesar, 2008), suggesting that similar biological mechanisms could be involved with SARS-CoV-2. Given that lymphopenia is a sequela of COVID-19, stress might predispose patients to a greater risk of complications due to abnormal cytokine transmission (Di Lorenzo, 2020).

4.3 | Proinflammatory cytokines

COVID-19 severity is strongly predicted by neutrophil and Nod-like receptor levels, which are inflammatory markers (Qin et al., 2020). These inflammatory parameters likely reflect hypercytokinemia, particularly elevated IL-6 release, which is very common in severe cases (Zhang et al., 2020b). Indeed, relative to COVID-19 patients who recovered, IL-6 levels in non-survivors are significantly elevated (Zhou et al., 2020b). Other work confirmed a role of elevated IL-6 levels in critically ill COVID-19 patients (Wu et al., 2020), with levels being 10-fold higher than levels in mild or moderate cases (Chen et al., 2020). Though several factors, including lymphopenia, are associated with the development of acute respiratory distress syndrome (ARDS) in COVID-19 patients, IL-6 is uniquely associated with death (Wu et al., 2020). Notably, chronic stress is similarly associated with elevated IL-6 secretion in humans (Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012) and rodents (Himmerich et al., 2013), which appears to be modulated by CORT. In chronic stress-exposed adults, administration of a synthetic glucocorticoid (dexamethasone) does not suppress IL-6 production as it does in non-stressed people (Miller et al., 2002). Thus, given that it potentiates cytokine responses to infection, chronic stress is likely to be a significant risk factor for poorer COVID-19 prognosis. Furthermore, elevated IL-6 levels are found in most COVID-19 comorbidities that are associated with severe outcomes, namely hypertension (Brydon & Steptoe, 2005), diabetes (Joseph & Golden, 2017), heart disease (De Mello et al., 2009) and obesity (Park et al., 2010). These levels are pronounced in the elderly population (Cohen, Pieper, Harris, Rao, & Currie, 1997), which is most vulnerable to a fatal COVID-19 outcome (Liu et al., 2020). Collectively, these findings suggest that predisposition to elevated IL-6 levels could promote severe adverse outcomes to SARS-CoV-2 infection.

As previously mentioned, NF-κB signalling pathways contribute to GR resistance and are critical mediators of inflammatory responses. In COVID-19 patients, hyperactivation of the NF-κB pathway initiates a cytokine storm, which is a catalyst for ARDS-mediated fatality (Hirano & Murakami, 2020). Specifically, the MyD88 pathway activates NF-κB through pattern recognition receptors (PRRs), thereby leading to proinflammatory cytokine release, namely IL-6, TNF-α and chemokines (Hirano & Murakami, 2020) (see Figure 2). Notably, chronic unpredictable stress in rodents similarly activates NF-κB signalling pathways, leading to depressive- and anhedonic-like phenotypes (Koo, Russo, Ferguson, Nestler, & Duman, 2010), which map onto similar patterns observed in people with MDD (Pace et al., 2006). Moreover, stress-induced suppression of hippocampal neurogenesis is blocked using NF-κB inhibitors (Koo et al., 2010). Given the critical role of hippocampal negative feedback in regulating HPA reactivity, these findings suggest that NF-κB hyperactivation may contribute to HPA dysregulation. In the context of SARS-CoV-2 infection, chronic stress potentiates lipopolysaccharide (LPS)-induced activation of NF-κB (Munhoz et al., 2006), suggesting that viral inflammatory reactions could be compounded by similar responses following chronic stress. Importantly, this potentiated effect is abolished by pretreatment of a GR antagonist, implicating glucocorticoid transmission in mediating NF-κB hyperactivation following chronic stress exposure.

NF-κB hyperactivation initiates an intense proinflammatory cytokine cascade, leading to deleterious consequences. TNF-α and IL-1β each play a key role in inducing these hyperinflammatory responses and (among several other cytokines) are elevated in COVID-19 patients (Tufan, Guler, & Matucci-Cerinic, 2020). Comparably, mice exposed to five weeks of chronic mild stress show substantial elevations in plasma TNF-α, IL-1β, IL-6 and CORT (Li et al., 2008), suggesting once again that stress and SARS-CoV-2 pathogenesis could synergize to produce detrimental health outcomes. Among severe COVID-19 cases, plasma concentration of TNF-α is significantly greater than that of mild to moderate cases (Qin et al., 2020), and this effect is more pronounced in patients requiring intensive care (Huang et al., 2020). Anti-TNF therapy is under consideration to treat COVID-19 patients (Feldmann et al., 2020), owing to its efficacy in preventing a cytokine cascade (namely, IL-6 and IL-1 release) in other conditions, like rheumatoid arthritis (Charles et al., 1999). Given that elevations in TNF-α production are observed following chronic stress (Li et al., 2008), as well as in people with PTSD (Gill, Vythilingam, & Page, 2008) and MDD (Dowlati et al., 2010), anti-TNF treatment could be particularly critical in COVID-19 patients with these pre-existing conditions. Furthermore, chronic stress-induced TNF-α and IL-1β transmission is associated with hyperinflammatory pulmonary responses (Curry et al., 2010), which is particularly relevant to its role in ARDS-mediated fatality in COVID-19 patients. Specifically, in addition to increasing serum TNF-α, IL-1β, and IL-6 levels, social defeat stress produces a significant increase in TNF-α and IL-1β lung mRNA (Curry et al., 2010; Quan et al., 2001), pointing to a role of these mediators in initiating a proinflammatory environment within the lungs after stress. Critically, the same social defeat paradigm enhances pulmonary inflammation during infection with the influenza A virus, causing respiratory distress and increasing mortality (Stark et al., 2001). This inflammatory reaction occurs despite elevated CORT levels, implicating the development of glucocorticoid resistance in immune cells of stressed animals (Stark et al., 2001).

5 | FUTURE DIRECTIONS

5.1 | Effects of SARS-CoV-2 on glucocorticoid transmission

Recent findings from Tan et al. (2020) show increased CORT transmission in COVID-19 patients within 48 h of hospitalization. This study is the first to show compelling changes in glucocorticoid profiles following SARS-CoV-2 infection. As previously mentioned, additional research is needed to understand temporal dynamics of CORT in COVID-19 patients since hypercytokinemia occurs later in the disease progression. Importantly, future research must also examine molecular mimicry of ACTH molecules in SARS-CoV-2, given that this could shed light on the course of HPA dysregulation (researchers are currently examining this mechanism: Chinese Clinical Trial Registry, ChiCTR20000301150). Understanding how this virus affects stress-regulatory mechanisms will elucidate how CORT, cytokines, or alternative mechanisms are involved in glucocorticoid resistance, resulting in hypercytokinemia. This is particularly important, given that several mental health disorders are characterized by HPA dysregulation and hyperinflammation. Notably, depression is commonly precipitated by stress (Pizzagalli, 2014) and is associated with hypercortisolism (Carroll et al., 2007) and hyperinflammation (Raison et al., 2006). Indeed, even among psychiatrically healthy participants, plasma IL-6 is linked to volumetric decreases in stress-regulatory brain regions implicated in MDD, such as the hippocampus and amygdala (Ironside et al., 2019). Given a predisposition to dysregulated stress and immune responses, we postulate that individuals with depression are likely prone to negative COVID-19-related outcomes. In support of this hypothesis, emerging literature shows greater self-reported depression and lower quality of life in COVID-19 patients relative to healthy controls (Nguyen et al., 2020). Although research in this domain is scarce, over 50% of SARS and Middle East Respiratory Syndrome coronavirus patients experienced depressive episodes during hospitalization (Kim, Yoo, Lee, Lee, & Shin, 2018; Mak, Chu, Pan, Yiu, & Chan, 2009), suggesting that the virus negatively impacts mental health. Importantly, stressful life events predict MDD onset (Kendler, Gardner, & Prescott, 2002) and recurrence (Monroe, Anderson, & Harkness, 2019), findings that are especially salient in the context of current public fear and economic uncertainty: the current social milieu in most countries, therefore, is increasing the risk for depression and, by association, worse health outcomes. Thus, elucidating the effects of SARS-CoV-2 on stress reactivity is pertinent to our understanding of stress-related pathology in COVID-19 patients.

5.2 | COVID-19 in the brain: A role for the endocannabinoid system

In addition to its devastating impact in the periphery, COVID-19 may produce long-term central nervous system (CNS) deficits, including neurodegeneration (De Felice, Tovar-Moll, Moll, Munoz, & Ferreira, 2020). Emerging research highlights neurological complications following infection (e.g., stroke, haemorrhage and encephalitis; Varatharaj et al., 2020), which could reflect viral infection within the CNS (Mesci et al., 2020). Specifically, the virus appears to impair synaptogenesis and cause necrosis of cortical neurons, both of which can be reversed with the antiviral drug, Sofosbuvir (Mesci et al., 2020). Although SARS-CoV-2 has been detected in cortical neurons in autopsy reports (Song et al., 2020), the viral load is minimal and inconsistently detected (Paniz- Mondolfi et al., 2020); it is also absent from cerebrospinal fluid (Al Saiegh et al., 2020). Future research should elucidate whether the virus produces neurological syndromes through direct infection or an alternative, perhaps indirect, route.

Some suggest that COVID-19-induced CNS deficits may occur through systemic hyperinflammation that degrades the blood-brain barrier, leading to neuroinflammation and associated neurological syndromes (De Felice et al., 2020). The endocannabinoid system (ECS), which plays a critical role in neuroinflammation (Edwards & Abizaid, 2016), is likely recruited under these conditions. Specifically, ECS dysregulation is associated with increased inflammatory responses in the CNS (Boorman, Zajkowska, Ahmed, Pariante, & Zunszain, 2016) and neuroinflammation increases ECS activity, inducing upregulation of the cannabinoid type-2 (CB2) receptors on activated microglia and cells of immune origin (Pacher & Mechoulam, 2011). One assumption is that CB2 receptors are recruited in response to neuroinflammation, suppressing immune responses in a number of pathological conditions (Nagarkatti, Pandey, Rieder, Hegde, & Nagarkatti, 2009). This may include stress, which exerts an effect, at least partially, through the ECS (Balsevich, Abizaid, Chen, Karatsoreos, & Schmidt, 2019). Indeed, systemic injections of a CB2 receptor agonist in mice inhibit chronic stress-induced hypersecretion of proinflammatory cytokines and protect against neuroinflammatory responses in the frontal cortex (Zoppi et al., 2014).

Given the anti-inflammatory properties of cannabinoids and their potential to deter a cytokine storm syndrome (D'Elia, Harrison, Oyston, Lukaszewski, & Clark, 2013), some researchers advocate therapeutic use of the non-psychotropic cannabidiol (CBD) for COVID-19 patients (e.g., Byrareddy & Mohan, 2020). This is based on evidence that CBD, through activation of CB2 receptors, modulates immune cell migration (Miller & Stella, 2008) and inhibits cytokine production (Ehrhart et al., 2005) (see Figure 2).

Furthermore, preclinical studies report that CB2 receptor knockout mice show potentiated inflammatory responses to an influenza virus (Buchweitz, Karmaus, Williams, Harkema, & Kaminski, 2008), pointing to an important role of this receptor in immune regulation following viral infection. Critically, chronic stress upregulates CB2 receptor expression in the mouse hippocampus (Robertson et al., 2017), which could provide neuroprotective effects on inflammation-induced alterations in HPA functioning. As such, CBD treatment could protect against CNS atrophy in COVID-19 patients with a history of chronic stress. The efficacy of CBD to treat COVID-19 has yet to be tested, but its strong safety profile (Iffland & Grotenhermen, 2017) offers a promising avenue for future therapeutic research. Thus, we call for researchers to examine a potential role for CB2 receptor agonism in preserving CNS function in COVID-19 patients, specifically due to its role in suppressing glial and astrocyte activation (Sheng et al., 2005). Currently, there are no studies that examine the effects of CBD use in COVID-19 patients, but recent analyses shed light on its therapeutic potential (see Wang et al., 2020).

6 | RISK MITIGATION

Given the role of CORT in modulating inflammatory responses, stress-reduction practices could promote better immunity and recovery from COVID-19. Meditation is among the many recommended stress management practices during quarantine (Yanyu et al., 2020). In particular, mindfulness meditation has the ability to modulate CORT (Turakitwanakan, Mekseepralard, & Busarakumtragul, 2013) and reduce inflammatory responses (Creswell et al., 2016). Notably, it is particularly effective in reducing IL-6 levels during acute stress exposure (Hoge et al., 2018) and in trauma-exposed women (Gallegos, Lytle, Moynihan, & Talbot, 2015). Furthermore, pandemic-related isolation and confinement promotes a sedentary lifestyle comprised of inactivity and a lack of physical exercise (Burtscher, Burtscher, & Millet, 2020). Not only has physical exercise been associated with reduced anxiety and depression during the COVID-19 pandemic (Fu et al., 2020), but it robustly modulates CORT (Moraes, Deslandes, Cevada, Souza, & Laks, 2012) and viral immunity (Nieman & Wentz, 2019). Burtscher et al. (2020) argue that the public should seriously consider the benefits of physical activity in mitigating poor COVID-19 outcomes, particularly as chronic stress, immunity and inactivity are heavily interconnected.

Relatedly, current mass quarantine strategies (including stay-at-home orders and travel restrictions) are promoting social isolation (Jordan, Adab, & Cheng, 2020), which elevates IL-6 levels synergistically in those with depression (particularly in men; Häfner et al., 2011). Among older adults, social isolation increases risk for cardiovascular and immune diseases, as well as depression (Armitage & Nellums, 2020). A novel framework conceptualizes an important biological basis for social bonding (i.e., Social Safety Theory), positing that threats to social safety (e.g., isolation) promote negative health outcomes, such as viral infection and inflammatory-related diseases (Slavich, 2020). Thus, social relationships could protect against COVID-19-related complications, pointing to the importance of physical, as opposed to social, distancing during self-isolation. On this basis, virtual communication is an effective alternative to physical contact (Colasante, Lin, DeFrance, & Hollenstein, 2020) in that digital emotional support is as effective as in-person support for regulating negative emotions. Notably, these benefits do not apply, solely, to

those with a tendency toward social isolation or avoidance (Colasante et al., 2020), suggesting that online interaction (e.g., video calls, texting) could be beneficial to the broader population. Relatedly, internet-based cognitive behavioural therapy has numerous benefits over traditional face-to-face therapy (Webb, Rosso, & Rauch, 2017), which offers those with MDD an effective alternative to in-person treatment during self-isolation.

Currently, there is no effective pharmacotherapy for SARS-CoV-2, though clinical trials are rapidly advancing. Glucocorticoid administration to COVID-19 patients could prevent or suppress a cytokine storm syndrome, owing to its ability to restrain IL-6 transmission (Ruzek et al., 1999). Indeed, a recent clinical trial found that dexamethasone, a synthetic glucocorticoid, reduces mortality rate in severe COVID-19 patients who require ventilation (Horby et al., 2020). Given that sustained hypercortisolism (as seen in MDD) is associated with GR resistance (Raison & Miller, 2003), it is unclear whether dexamethasone would be effective for COVID-19 patients with a history of chronic stress. In fact, in the absence of careful dosing and monitoring of serum CORT during tapering (Scaroni, Armigliato, & Cannavò, 2020), steroid treatment in COVID-19 patients with adrenal insufficiency could be detrimental (Isidori et al., 2020). An alternative intervention strategy might involve direct modulation of cytokine release, namely IL-6. Early studies show promise for Tocilizumab, an IL-6 receptor antagonist, which appears to improve clinical outcomes in severe cases by preventing a cytokine storm syndrome (Zhang et al., 2020b). Importantly, preclinical research suggests that IL-6 is critical in initiating a preliminary response to infection, and that deficiencies in IL-6 increase the risk for mortality (Dienz et al., 2012). Certain populations, including those with MDD (Dowlati et al., 2010), PTSD (Jiang et al., 2019), as well as the elderly (Kiecolt-Glaser et al, 1996), are also at higher risk for viral infection, due to elevated cytokine levels. Thus, the timing of drug intervention could be a crucial factor in determining its efficacy in treating COVID-19, particularly for those with predispositions to hypercytokinemia.

7 | CONCLUSION

In an effort to develop safe and effective interventions, infectious disease experts implore scientists of all specializations to conduct 'robust research to understand the basic biology of new organisms and our susceptibilities to them' (Fauci, Lane, & Redfield, 2020). With respect to the latter, we show similar mechanisms in chronic stress-induced inflammation and SARS-CoV-2, which might interact synergistically to increase the risk of complications and mortality. Little is known about the pathogenicity of the virus, but overwhelming evidence points to exaggerated immune responses, like IL-6 hypersecretion, leading to severe health consequences. Hence, chronic stress should be regarded as a significant risk factor for poor COVID-19 prognosis, but further empirical research is needed in this domain. Specifically, researchers should examine the complex interactions between SARS-CoV-2 and chronic stress-related HPA dysregulation and hypercytokinemia. Though inflammation appears to characterize the pathogenesis of the virus, it remains unclear how symptoms differentially manifest based on such predispositions. For instance, emerging findings implicate similar immune disturbances in COVID-19-positive children who develop a hyperinflammatory syndrome (multisystem inflammatory syndrome in children: rash, peeling skin, stomach pain) but rarely suffer respiratory issues (Riphagen, Gomez, Gonzalez-Martinez, Wilkinson, & Theocharis, 2020). Relatedly, inflammatory skin lesions ('COVID toes') manifest in some otherwise asymptomatic COVID-19-positive adults (Landa, Mendieta-Eckert, Fonda-Pascual, & Aguirre, 2020). These findings suggest that a hyperinflammatory response is present in most or all cases, but it may differentially manifest in its symptomatology and severity. Further research is needed to uncover how predisposing inflammatory factors might produce alternative COVID-19 disease profiles. Resiliency factors might also protect people from chronic stress-induced harm, which could elucidate the heterogeneity observed in COVID-19 symptom severity and disease prognosis.

ACKNOWLEDGMENTS

This work was supported by a Discovery Grant from the Natural Sciences and Engineering Research Council (NSERC) of Canada to MCO (203707), and by an NSERC Alexander Graham Bell Graduate Scholarship and a Michael Smith Foreign Study Supplement to SJL. DAP was partially supported by R37 MH068376 and R01 MH095809 from the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of NSERC or the National Institutes of Health.

CONFLICT OF INTEREST STATEMENT

Steven J. Lamontagne and Mary C. Olmstead declare no competing interests. Over the past 3 years, Diego A. Pizzagalli has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Otsuka Pharmaceuticals and Takeda Pharmaceuticals; one honorarium from Alkermes, and research funding from NIMH, Dana Foundation, Brain and Behavior Research Foundation, Millennium Pharmaceuticals. In addition, he has received stock options from BlackThorn Therapeutics. No funding from these entities was used to support the current work.

ORCID

Steven J. Lamontagne https://orcid.org/0000-0002-7933-5027

REFERENCES

Al Saiegh, F., Ghosh, R., Leibold, A., Avery, M. B., Schmidt, R. F., Theofanis, T., & Rincon, F. (2020). Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. *Journal of Neurology, Neurosurgery & Psychiatry*, *91*(8), 846–848.

Álvarez-Troncoso, J., Larrauri, M. Z., Vega, M. D. M., Vallano, R. G., Peláez, E. P., Rojas-Marcos, P. M. … Esteban, E. T. (2020). Case report: COVID-19 with bilateral adrenal hemorrhage. *The American Journal of Tropical Medicine and Hygiene*, *103*(3), 1156–1157.

Angileri, F., Legare, S., Gammazza, A. M., de Macario, E. C., Macario, A. J., & Cappello, F. (2020). Molecular mimicry may explain multi-organ damage in COVID-19. *Autoimmunity Reviews*, *19*(8), 102591.

Armitage, R., & Nellums, L. B. (2020). COVID-19 and the consequences of isolating the elderly. *The Lancet Public Health*, *5*(5), 256.

Assaf, A. M., Al-Abbassi, R., & Al-Binni, M. (2017). Academic stress-induced changes in Th1-and Th2-cytokine response. *Saudi Pharmaceutical Journal*, *25*(8), 1237–1247.

Avitsur, R., Stark, J. L., Dhabhar, F. S., Padgett, D. A., & Sheridan, J. F. (2002). Social disruption-induced glucocorticoid resistance: Kinetics and site specificity. *Journal of Neuroimmunology*, *124*(2), 54–61.

Avitsur, R., Stark, J. L., & Sheridan, J. F. (2001). Social stress induces glucocorticoid resistance in subordinate animals. *Hormones and Behavior*, *39*(4), 247–257.

Balsevich, G., Abizaid, A., Chen, A., Karatsoreos, I. N., & Schmidt, M. V. (2019). Stress and glucocorticoid modulation of feeding and metabolism. *Neurobiology of Stress*, *11*(100171), 1–6.

Bergström, A., Jayatissa, M. N., Thykjaer, T., & Wiborg, O. (2007). Molecular pathways associated with stress resilience and drug resistance in the chronic mild stress rat model of depression—a gene expression study. *Journal of Molecular Neuroscience*, *33*(2), 201–215.

Bestle, D., Heindl, M. R., Limburg, H., Pilgram, O., Moulton, H., Stein, D. A. … Klenk, H. D. (2020). TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. *Life Science Alliance*, *3*(9), 1–14.

Black, P. H., & Garbutt, L. D. (2002). Stress, inflammation and cardiovascular disease. *Journal of Psychosomatic Research*, *52*(1), 1–23.

Bo, H. X., Li, W., Yang, Y., Wang, Y., Zhang, Q., Cheung, T. … Xiang, Y. T. (2020). Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China. *Psychological Medicine*, 1–2. https://doi.org/10.1017/S0033291720000999

Bonanno, G. A. (2004). Loss, trauma, and human resilience: Have we underestimated the human capacity to thrive after extremely aversive events? *American Psychologist*, *59*(1), 20–28.

Boonen, E., Vervenne, H., Meersseman, P., Andrew, R., Mortier, L., Declercq, P. E. … Langouche, L. (2013). Reduced cortisol metabolism during critical illness. *New England Journal of Medicine*, *368*(16), 1477–1488.

Boorman, E., Zajkowska, Z., Ahmed, R., Pariante, C. M., & Zunszain, P. A. (2016). Crosstalk between endocannabinoid and immune systems: A potential dysregulation in depression? *Psychopharmacology*, *233*(9), 1591–1604.

Brydon, L., & Steptoe, A. (2005). Stress-induced increases in interleukin-6 and fibrinogen predict ambulatory blood pressure at 3-year follow-up. *Journal of Hypertension*, *23*(5), 1001–1007.

Buchweitz, J. P., Karmaus, P. W., Williams, K. J., Harkema, J. R., & Kaminski, N. E. (2008). Targeted deletion of cannabinoid receptors CB1 and CB2 produced enhanced inflammatory responses to influenza A/PR/8/34 in the absence and presence of Δ9-tetrahydrocannabinol. *Journal of Leukocyte Biology*, *83*(3), 785–796.

Burtscher, J., Burtscher, M., & Millet, G. P. (2020). Indoor) isolation, stress and physical inactivity: Vicious circles accelerated by Covid-19? *Scandinavian Journal of Medicine & Science in Sports*, *30*(8), 1544–1545.

Byrareddy, S. N., & Mohan, M. (2020). SARS-CoV2 induced respiratory distress: Can Cannabinoids be added to anti-viral therapies to reduce lung inflammation? *Brain, Behavior, and Immunity* 2020 Apr 28, *87*, 120–121. https://doi.org/10.1016/j.bbi.2020.04.079

Carpenter, L. L., Gawuga, C. E., Tyrka, A. R., Lee, J. K., Anderson, G. M., & Price, L. H. (2010). Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology*, *35*(13), 2617–2623.

Carroll, B. J., Cassidy, F., Naftolowitz, D., Tatham, N. E., Wilson, W. H., Iranmanesh, A. … Veldhuis, J. D. (2007). Pathophysiology of hypercortisolism in depression. *Acta Psychiatrica Scandinavica*, *115*, 90–103.

Charles, P., Elliott, M. J., Davis, D., Potter, A., Kalden, J. R., Antoni, C. … Feldmann, M. (1999). Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-α therapy in rheumatoid arthritis. *The Journal of Immunology*, *163*(3), 1521–1528.

Chen, X., Zhao, B., Qu, Y., Chen, Y., Xiong, J., Feng, Y. … Ding, J. (2020). Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clinical Infectious Diseases* 2020 Apr 17, *71*(8), 1937–1942. https://doi.org/10.1093/cid/ciaa449/5821311

Chiappelli, F., Manfrini, E., Franceschi, C., Cossarizza, A., & Black, K. L. (1994). Steroid regulation of cytokines. Relevance for TH1-to-TH2 shift? *Annals of the New York Academy of Sciences*, *746*(1), 204–215.

Cohen, H. J., Pieper, C. F., Harris, T., Rao, K. M. K., & Currie, M. S. (1997). The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *52*(4), 201–208.

Colasante, T., Lin, L., DeFrance, K., & Hollenstein, T. (2020). *Transcending time and space with digital emotional support* PsyArXiv. 2020 Apr 06. https://doi.org/10.31234/osf.io/cehtk

Cole, S. W. (2014). Human social genomics. *PLoS Genetics*, *10*(8), 1–7.

Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. (2020). The species Severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. *Nature Microbiology*, *5*(4), 536–544.

Creswell, J. D., Taren, A. A., Lindsay, E. K., Greco, C. M., Gianaros, P. J., Fairgrieve, A. … Ferris, J. L. (2016). Alterations in resting-state functional connectivity link mindfulness meditation with reduced interleukin-6: A randomized controlled trial. *Biological Psychiatry*, *80*(1), 53–61.

Curry, J. M., Hanke, M. L., Piper, M. G., Bailey, M. T., Bringardner, B. D., Sheridan, J. F., & Marsh, C. B. (2010). Social disruption induces lung inflammation. *Brain, Behavior, and Immunity*, *24*(3), 394–402.

D'Elia, R. V., Harrison, K., Oyston, P. C., Lukaszewski, R. A., & Clark, G. C. (2013). Targeting the "cytokine storm" for therapeutic benefit. *Clinical and Vaccine Immunology*, *20*(3), 319–327.

De Felice, F. G., Tovar-Moll, F., Moll, J., Munoz, D. P., & Ferreira, S. T. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the central nervous system. *Trends in Neurosciences* 2020 Apr 21, *43*(6), 355–357. https://doi.org/10.1016/j.tins.2020.04.004

De Mello, V. D. F., Lankinen, M., Schwab, U., Kolehmainen, M., Lehto, S., Seppänen-Laakso, T. … Erkkilä, A. T. (2009). Link between plasma ceramides, inflammation and insulin resistance: Association with serum IL-6 concentration in patients with coronary heart disease. *Diabetologia*, *52*(12), 2612–2615.

Deak, T., Kudinova, A., Lovelock, D. F., Gibb, B. E., & Hennessy, M. B. (2017). A multispecies approach for understanding neuroimmune mechanisms of stress. *Dialogues in Clinical Neuroscience*, *19*(1), 37–53.

Dhabhar, F. S., & McEwen, B. S. (1997). Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: A potential role for leukocyte trafficking. *Brain, Behavior, and Immunity*, *11*(4), 286–306.

Dhabhar, F. S., Miller, A. H., McEwen, B. S., & Spencer, R. L. (1996). Stress-induced changes in blood leukocyte distribution. Role of adrenal steroid hormones. *The Journal of Immunology*, *157*(4), 1638–1644.

Di Lorenzo, G. (2020). Re: Silke Gillessen Sommer, Thomas Powles. Advice for medical oncology care of urological cancer patients during the COVID-19 pandemic. *European Urology* In press: Is It Always Correct to Continue Androgen Receptor Signaling Inhibitors in the COVID-19 Era? https://doi.org/10.1016/j.eururo.2020.03.026 24 Apr 2020.

Dienz, O., Rud, J. G., Eaton, S. M., Lanthier, P. A., Burg, E., Drew, A., & Rincon, M. (2012). Essential role of IL-6 in protection against H1N1 influenza virus by promoting neutrophil survival in the lung. *Mucosal Immunology*, *5*(3), 258–266.

Dimitrov, S., Benedict, C., Heutling, D., Westermann, J., Born, J., & Lange, T. (2009). Cortisol and epinephrine control opposing circadian rhythms in T cell subsets. *Blood*, *113*(21), 5134–5143.

Ding, Y., He, L., Zhang, Q., Huang, Z., Che, X., Hou, J., & Geng, J. (2004). Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: Implications for pathogenesis and virus transmission pathways. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*, *203*(2), 622–630.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, *67*(5), 446–457.

Edwards, A., & Abizaid, A. (2016). Driving the need to feed: Insight into the collaborative interaction between ghrelin and endocannabinoid systems in modulating brain reward systems. *Neuroscience & Biobehavioral Reviews*, *66*, 33–53.

Edwards, L. D., Heyman, A. H., & Swidan, S. (2011). Hypocortisolism: An evidence-based review. *Integrative Medicine*, *10*(4), 30–37.

Ehrhart, J., Obregon, D., Mori, T., Hou, H., Sun, N., Bai, Y., & Shytle, R. D. (2005). Stimulation of cannabinoid receptor 2 (CB 2) suppresses microglial activation. *Journal of Neuroinflammation*, *2*(1), 1–13.

Farsalinos, K., Niaura, R., Le Houezec, J., Barbouni, A., Tsatsakis, A., Kouretas, D., & Poulas, K. (2020). Nicotine and SARS-CoV-2: COVID-19 may be a disease of the nicotinic cholinergic system. *Toxicology Reports*, *7*, 658–663.

Fauci, A. S., Lane, H. C., & Redfield, R. R. (2020). Covid-19—navigating the uncharted. *New England Journal of Medicine*, *382*, 1268–1269.

Feldmann, M., Maini, R. N., Woody, J. N., Holgate, S. T., Winter, G., Rowland, M., & Hussell, T. (2020). Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *The Lancet*, *395*(10234), 1407–1409.

Franceschi, C., & Campisi, J. (2014). Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, *69*(1), 4–9.

Fu, W., Wang, C., Zou, L., Guo, Y., Lu, Z., Yan, S., & Mao, J. (2020). Psychological health, sleep quality, and coping styles to stress facing the COVID-19 in Wuhan, China. *Translational Psychiatry*, *10*(1), 1–9.

Gallegos, A. M., Lytle, M. C., Moynihan, J. A., & Talbot, N. L. (2015). Mindfulness-based stress reduction to enhance psychological functioning and improve inflammatory biomarkers in trauma-exposed women: A pilot study. *Psychological Trauma: Theory, Research, Practice, and Policy*, *7*(6), 525–532.

Gill, J., Vythilingam, M., & Page, G. G. (2008). Low cortisol, high DHEA, and high levels of stimulated TNF-α, and IL-6 in women with PTSD. *Journal of Traumatic Stress: Official Publication of The International Society for Traumatic Stress Studies*, *21*(6), 530–539.

Gouin, J. P., Glaser, R., Malarkey, W. B., Beversdorf, D., & Kiecolt-Glaser, J. (2012). Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychology*, *31*(2), 264–268.

Gouin, J. P., Hantsoo, L., & Kiecolt-Glaser, J. K. (2008). Immune dysregulation and chronic stress among older adults: A review. *Neuroimmunomodulation*, *15*(4–6), 251–259.

Gunnar, M. R., & Vazquez, D. M. (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. *Development and Psychopathology*, *13*(3), 515–538.

Hadjadj, J., Yatim, N., Barnabei, L., Corneau, A., Boussier, J., Pere, H., & Carlier, N. (2020). Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients. *MedRxiv*, *369*, 718–724. https://doi.org/10.1101/2020.04.19.20068015

Häfner, S., Emeny, R. T., Lacruz, M. E., Baumert, J., Herder, C., & Koenig, W., & KORA Study Investigators (2011). Association between social isolation and inflammatory markers in depressed and non-depressed individuals: Results from the MONICA/KORA study. *Brain, Behavior, and Immunity*, *25*(8), 1701–1707.

Harmer, D., Gilbert, M., Borman, R., & Clark, K. L. (2002). Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Letters*, *532*(1–2), 107–110.

Hayashi, T., Bunai, Y., Ago, K., Ago, M., & Ogata, M. (2011). Thymus and adrenal glands in elder abuse. *The American Journal of Forensic Medicine and Pathology*, *32*(4), 368–371.

Heim, C., Newport, D. J., Bonsall, R., Miller, A. H., & Nemeroff, C. B. (2001). Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *American Journal of Psychiatry*, *158*(4), 575–581.

Hennessy, M. B., Deak, T., & Schiml-Webb, P. A. (2001). Stress-induced sickness behaviors: An alternative hypothesis for responses during maternal separation. *Developmental Psychobiology: The Journal of the International Society for Developmental Psychobiology*, *39*(2), 76–83.

Himmerich, H., Fischer, J., Bauer, K., Kirkby, K. C., Sack, U., & Krügel, U. (2013). Stress-induced cytokine changes in rats. *European Cytokine Network*, *24*(2), 97–103.

Hirano, T., & Murakami, M. (2020). COVID-19: A new virus, but a familiar receptor and cytokine release syndrome. *Immunity*, *52*(5), 731–733.

Hoge, E. A., Bui, E., Palitz, S. A., Schwarz, N. R., Owens, M. E., Johnston, J. M. … Simon, N. M. (2018). The effect of mindfulness meditation training on biological acute stress responses in generalized anxiety disorder. *Psychiatry Research*, *262*, 328–332.

Horby, P., Lim, W. S., Emberson, J., Mafham, M., Bell, J., Linsell, L., … Landray, M. (2020). Dexamethasone in hospitalized patients with COVID-19: Preliminary report. *The New England Journal of Medicine*, 1–20. https://doi.org/10.1101/2020.06.22.20137273

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y. … Cheng, Z. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*(10223), 497–506.

Hueston, C. M., Barnum, C. J., Eberle, J. A., Ferraioli, F. J., Buck, H. M., & Deak, T. (2011). Stress-dependent changes in neuroinflammatory markers observed after common laboratory stressors are not seen following acute social defeat of the Sprague Dawley rat. *Physiology & Behavior*, *104*(2), 187–198.

Iffland, K., & Grotenhermen, F. (2017). An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. *Cannabis and Cannabinoid Research*, *2*(1), 139–154.

Ironside, M., Admon, R., Maddox, S. A., Mehta, M., Douglas, S., Olson, D. P., & Pizzagalli, D. A. (2019). Inflammation and depressive phenotypes: Evidence from medical records from over 12 000 patients and brain morphology. *Psychological Medicine*, *16*, 1–9. https://doi.org/10.1017/S0033291719002940

Isidori, A. M., Arnaldi, G., Boscaro, M., Falorni, A., Giordano, C., Giordano, R. … Sbardella, E. (2020). COVID-19 infection and glucocorticoids: Update from the Italian Society of endocrinology expert opinion on steroid replacement in adrenal insufficiency. *Journal of Endocrinological Investigation*, *43*, 1141–1147.

Jiang, T., Farkas, D. K., Ahern, T. P., Lash, T. L., Sørensen, H. T., & Gradus, J. L. (2019). Posttraumatic stress disorder and incident infections: A nationwide cohort study. *Epidemiology*, *30*(6), 911–917.

Jordan, R. E., Adab, P., & Cheng, K. K. (2020). Covid-19: Risk factors for severe disease and death. *BMJ* 2020 Mar 26, *368*, 1–2. https://doi.org/10.1136/bmj.m1198

Joseph, J. J., & Golden, S. H. (2017). Cortisol dysregulation: The bidirectional link between stress, depression, and type 2 diabetes mellitus. *Annals of the New York Academy of Sciences*, *1391*(1), 20–34.

Karlović, D., Serretti, A., Vrkić, N., Martinac, M., & Marčinko, D. (2012). Serum concentrations of CRP, IL-6, TNF-α and cortisol in major depressive disorder with melancholic or atypical features. *Psychiatry Research*, *198*(1), 74–80.

Kendler, K. S., Gardner, C. O., & Prescott, C. A. (2002). Toward a comprehensive developmental model for major depression in women. *American Journal of Psychiatry*, *159*(7), 1133–1145.

Kiecolt-Glaser, J. K., Glaser, R., Gravenstein, S., Malarkey, W. B., & Sheridan, J. (1996). Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proceedings of the National Academy of Sciences*, *93*(7), 3043–3047.

Kim, H. C., Yoo, S. Y., Lee, B. H., Lee, S. H., & Shin, H. S. (2018). Psychiatric findings in suspected and confirmed middle east respiratory syndrome patients quarantined in hospital: A retrospective chart analysis. *Psychiatry Investigation*, *15*(4), 355–360.

Koo, J. W., Russo, S. J., Ferguson, D., Nestler, E. J., & Duman, R. S. (2010). Nuclear factor-kappaB is a critical mediator of stress-impaired neurogenesis and depressive behavior. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(6), 2669–2674.

Krüger, K., Agnischock, S., Lechtermann, A., Tiwari, S., Mishra, M., Pilat, C. … Mooren, F. C. (2011). Intensive resistance exercise induces lymphocyte apoptosis via cortisol and glucocorticoid receptor-dependent pathways. *Journal of Applied Physiology*, *110*(5), 1226–1232.

Laing, A. G., Lorenc, A., Del Barrio, I. D. M., Das, A., Fish, M., Monin, L. … Kamdar, S. (2020). A consensus Covid-19 immune signature combines immuno-protection with discrete sepsis-like traits associated with poor prognosis. *medRxiv* 2020 Jun 09. https://doi.org/10.1101/2020.06.08.20125112

Landa, N., Mendieta-Eckert, M., Fonda-Pascual, P., & Aguirre, T. (2020). Chilblain-like lesions on feet and hands during the COVID-19 Pandemic. *International Journal of Dermatology*, *59*, 739–743.

Ledingham, I. M., & Watt, I. (1983). Influence of sedation on mortality in critically ill multiple trauma patients. *The Lancet*, *321*(8336), 1270.

Lee, E. K., & Choi, M. H. (2015). Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. *BMB Reports*, *48*(4), 209–216.

Leow, M. K. S., Kwek, D. S. K., Ng, A. W. K., Ong, K. C., Kaw, G. J. L., & Lee, L. S. U. (2005). Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). *Clinical Endocrinology*, *63*(2), 197–202.

Li, X., Geng, M., Peng, Y., Meng, L., & Lu, S. (2020a). Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of Pharmaceutical Analysis*, *10*(2), 102–108.

Liu, K., Chen, Y., Lin, R., & Han, K. (2020). Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. *Journal of Infection*, *80*(6), 14–18.

Li, S., Wang, C., Wang, W., Dong, H., Hou, P., & Tang, Y. (2008). Chronic mild stress impairs cognition in mice: From brain homeostasis to behavior. *Life Sciences*, *82*(17–18), 934–942.

Maes, M., Song, C., Lin, A., De Jongh, R., Van Gastel, A., Kenis, G. … Demedts, P. (1998). The effects of psychological stress on humans: Increased production of pro-inflammatory cytokines and Th1-like response in stress-induced anxiety. *Cytokine*, *10*(4), 313–318.

Mak, I. W. C., Chu, C. M., Pan, P. C., Yiu, M. G. C., & Chan, V. L. (2009). Long-term psychiatric morbidities among SARS survivors. *General Hospital Psychiatry*, *31*(4), 318–326.

Marshall, G. D. , Jr, Agarwal, S. K., Lloyd, C., Cohen, L., Henninger, E. M., & Morris, G. J. (1998). Cytokine dysregulation associated with exam stress in healthy medical students. *Brain, Behavior, and Immunity*, *12*(4), 297–307.

Mastorakos, G., Weber, J. S., Magiakou, M. A., Gunn, H. A. N. N., & Chrousos, G. P. (1994). Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: Potential implications for the syndrome of inappropriate vasopressin secretion. *Journal of Clinical Endocrinology & Metabolism*, *79*(4), 934–939.

Mathew, D., Giles, J. R., Baxter, A. E., Greenplate, A. R., Wu, J. E., Alanio, C. … Manne, S. (2020). Deep immune profiling of COVID-19 patients reveals patient heterogeneity and distinct immunotypes with implications for therapeutic interventions. *bioRxiv* 2020 May 23. https://doi.org/10.1101/2020.05.20.106401

McEwen, B. S., & Seeman, T. (1999). Protective and damaging effects of mediators of stress: Elaborating and testing the concepts of allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *896*(1), 30–47.

Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. *The Lancet*, *395*(10229), 1033–1034.

Mesci, P., Macia, A., Saleh, A., Martin-Sancho, L., Yin, X., Snethlage, C., & Muotri, A. (2020). Sofosbuvir protects human brain organoids against SARS-CoV-2. *bioRxiv*. https://doi.org/10.1101/2020.05.30.125856

Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychology*, *21*(6), 531–541.

Miller, A. M., & Stella, N. (2008). CB2 receptor-mediated migration of immune cells: It can go either way. *British Journal of Pharmacology*, *153*(2), 299–308.

Mizoguchi, K., Yuzurihara, M., Ishige, A., Sasaki, H., Chui, D. H., & Tabira, T. (2001). Chronic stress differentially regulates glucocorticoid negative feedback response in rats. *Psychoneuroendocrinology*, *26*(5), 443–459.

Monroe, S. M., Anderson, S. F., & Harkness, K. L. (2019). Life stress and major depression: The mysteries of recurrences. *Psychological Review*, *126*(6), 791–816.

Moraes, H. S., Deslandes, A. C., Cevada, T., Souza, A. C. F. M., & Laks, J. (2012). The effect of physical exercise on cortisol levels in older adults: A systematic review. *Rev Bras Ativ Fis Saude*, *17*, 314–320.

Morey, J. N., Boggero, I. A., Scott, A. B., & Segerstrom, S. C. (2015). Current directions in stress and human immune function. *Current Opinion in Psychology*, *5*, 13–17.

Munhoz, C. D., Lepsch, L. B., Kawamoto, E. M., Malta, M. B., de Sá Lima, L., Avellar, M. C. W. … Scavone, C. (2006). Chronic unpredictable stress exacerbates lipopolysaccharide-induced activation of nuclear factor-κB in the frontal cortex and hippocampus via glucocorticoid secretion. *Journal of Neuroscience*, *26*(14), 3813–3820.

Murray, D. R., Haselton, M. G., Fales, M., & Cole, S. W. (2019). Subjective social status and inflammatory gene expression. *Health Psychology*, *38*(2), 182–186.

Nagarkatti, P., Pandey, R., Rieder, S. A., Hegde, V. L., & Nagarkatti, M. (2009). Cannabinoids as novel anti-inflammatory drugs. *Future Medicinal Chemistry*, *1*(7), 1333–1349.

Nemeroff, C. B., Krishnan, K. R. R., Reed, D., Leder, R., Beam, C., & Dunnick, N. R. (1992). Adrenal gland enlargement in major depression: A computed tomographic study. *Archives of General Psychiatry*, *49*(5), 384–387.

Nguyen, H. C., Nguyen, M. H., Do, B. N., Tran, C. Q., Nguyen, T. T., Pham, K. M. … Duong, T. H. (2020). People with suspected COVID-19 symptoms were more likely depressed and had lower health-related quality of life: The potential benefit of health literacy. *Journal of Clinical Medicine*, *9*(4), 965–983.

Nieman, D. C., & Wentz, L. M. (2019). The compelling link between physical activity and the body's defense system. *Journal of sport and health science*, *8*(3), 201–217.

Pace, T. W., Hu, F., & Miller, A. H. (2007). Cytokine-effects on glucocorticoid receptor function: Relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain, Behavior, and Immunity*, *21*(1), 9–19.

Pace, T. W., Mletzko, T. C., Alagbe, O., Musselman, D. L., Nemeroff, C. B., Miller, A. H., & Heim, C. M. (2006). Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *American Journal of Psychiatry*, *163*(9), 1630–1633.

Pacher, P., & Mechoulam, R. (2011). Is lipid signaling through cannabinoid 2 receptors part of a protective system? *Progress in Lipid Research*, *50*(2), 193–211.

Panesar, N. S. (2008). What caused lymphopenia in SARS and how reliable is the lymphokine status in glucocorticoid-treated patients? *Medical Hypotheses*, *71*(2), 298–301.

Paniz-Mondolfi, A., Bryce, C., Grimes, Z., Gordon, R. E., Reidy, J., Lednicky, J. … Fowkes, M. (2020). Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *Journal of Medical Virology*, *92*(7), 699–702.

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: Classical theories and new developments. *Trends in Neurosciences*, *31*(9), 464–468.

Park, E. J., Lee, J. H., Yu, G. Y., He, G., Ali, S. R., Holzer, R. G. … Karin, M. (2010). Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell*, *140*(2), 197–208.

Paskitti, M. E., McCreary, B. J., & Herman, J. P. (2000). Stress regulation of adrenocorticosteroid receptor gene transcription and mRNA expression in rat hippocampus: Time-course analysis. *Molecular Brain Research*, *80*(2), 142–152.

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: Toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, *10*, 393–423.

Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y. … Tian, D. S. (2020). Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clinical Infectious Diseases* 2020 12 Mar, *71*(15), 762–768. https://doi.org/10.1093/cid/ciaa248

Quan, N., Avitsur, R., Stark, J. L., He, L., Shah, M., Caligiuri, M. … Sheridan, J. F. (2001). Social stress increases the susceptibility to endotoxic shock. *Journal of Neuroimmunology*, *115*(1–2), 36–45.

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*(1), 24–31.

Raison, C. L., & Miller, A. H. (2003). When not enough is too much: The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *American Journal of Psychiatry*, *160*(9), 1554–1565.

Riphagen, S., Gomez, X., Gonzalez-Martinez, C., Wilkinson, N., & Theocharis, P. (2020). Hyperinflammatory shock in children during COVID-19 pandemic. *The Lancet* 2020 May 07, *395*(10237), 1607–1608. https://doi.org/10.1016/S0140-6736(20)31094-1

Riviere, G., Michaud, A., Breton, C., VanCamp, G., Laborie, C., Enache, M. … Vieau, D. (2005). Angiotensin-converting enzyme 2 (ACE2) and ACE activities display tissue-specific sensitivity to undernutrition-programmed hypertension in the adult rat. *Hypertension*, *46*(5), 1169–1174.

Robertson, J. M., Achua, J. K., Smith, J. P., Prince, M. A., Staton, C. D., Ronan, P. J … Summers, C. H. (2017). Anxious behavior induces elevated hippocampal Cb2 receptor gene expression. *Neuroscience*, *352*, 273–284.

Ruzek, M. C., Pearce, B. D., Miller, A. H., & Biron, C. A. (1999). Endogenous glucocorticoids protect against cytokine-mediated lethality during viral infection. *The Journal of Immunology*, *162*(6), 3527–3533.

Rygula, R., Abumaria, N., Flügge, G., Fuchs, E., Rüther, E., & Havemann-Reinecke, U. (2005). Anhedonia and motivational deficits in rats: Impact of chronic social stress. *Behavioural Brain Research*, *162*(1), 127–134.

Savignac, H. M., Hyland, N. P., Dinan, T. G., & Cryan, J. F. (2011). The effects of repeated social interaction stress on behavioural and physiological parameters in a stress-sensitive mouse strain. *Behavioural Brain Research*, *216*(2), 576–584.

Scaroni, C., Armigliato, M., & Cannavò, S. (2020). COVID-19 outbreak and steroids administration: Are patients treated for Sars-cov-2 at risk of adrenal insufficiency? *Journal of Endocrinological Investigation*, *43*, 1035–1036.

Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*, *130*(4), 601–630.

Sheng, W. S., Hu, S., Min, X., Cabral, G. A., Lokensgard, J. R., & Peterson, P. K. (2005). Synthetic cannabinoid WIN55, 212-2 inhibits generation of inflammatory mediators by IL-1β-stimulated human astrocytes. *Glia*, *49*(2), 211–219.

Slavich, G. M. (2020). Social safety theory: A biologically based evolutionary perspective on life stress, health, and behavior. *Annual Review of Clinical Psychology*, *16*, 265–295.

Somasundaram, N. P., Ranathunga, I., Ratnasamy, V., Wijewickrama, P. S. A., Dissanayake, H. A., Yogendranathan, N. … Grossman, A. B. (2020). The impact of SARS-cov-2 virus infection on the endocrine system. *Journal of the Endocrine Society*, *4*(8), 1–22.

Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Sprado, A., Skriabine, S., & Szigeti-Buck, K. (2020). Neuroinvasion of SARS-CoV-2 in human and mouse brain. *bioRxiv* https://doi.org/10.1101/2020.06.25.169946

Stark, J. L., Avitsur, R., Padgett, D. A., Campbell, K. A., Beck, F. M., & Sheridan, J. F. (2001). Social stress induces glucocorticoid resistance in macrophages. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, *280*(6), 1799–1805.

Steenblock, C., Todorov, V., Kanczkowski, W., Eisenhofer, G., Schedl, A., Wong, M. L. … Bornstein, S. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the neuroendocrine stress axis. *Molecular Psychiatry*, *25*, 1–7. https://doi.org/10.1038/s41380-020-0758-9

Stewart, A. M., Roy, S., Wong, K., Gaikwad, S., Chung, K. M., & Kalueff, A. V. (2015). Cytokine and endocrine parameters in mouse chronic social defeat: Implications for translational 'cross-domain' modeling of stress-related brain disorders. *Behavioural Brain Research*, *276*, 84–91.

Tan, T., Khoo, B., Mills, E. G., Phylactou, M., Patel, B., Eng, P. C. … Comninos, A. N. (2020). Association between high serum total cortisol concentrations and mortality from COVID-19. *The Lancet Diabetes & Endocrinology*, *8*(8), 659–660.

Tarcic, N., Ovadia, H., Weiss, D. W., & Weidenfeld, J. (1998). Restraint stress-induced thymic involution and cell apoptosis are dependent on endogenous glucocorticoids. *Journal of Neuroimmunology*, *82*(1), 40–46.

Toben, C., & Baune, B. T. (2015). An act of balance between adaptive and maladaptive immunity in depression: A role for T lymphocytes. *Journal of Neuroimmune Pharmacology*, *10*(4), 595–609.

Tufan, A., Guler, A. A., & Matucci-Cerinic, M. (2020). COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. *Turkish Journal of Medical Sciences*, *50*(1), 620–632.

Turakitwanakan, W., Mekseepralard, C., & Busarakumtragul, P. (2013). Effects of mindfulness meditation on serum cortisol of medical students. *Medical Journal of the Medical Association of Thailand*, *96*(1), 90–95.

Ulrich-Lai, Y. M., Figueiredo, H. F., Ostrander, M. M., Choi, D. C., Engeland, W. C., & Herman, J. P. (2006). Chronic stress induces adrenal hyperplasia and hypertrophy in a subregion-specific manner. *American Journal of Physiology-Endocrinology and Metabolism*, *291*(5), 965–973.

Usher, K., Bhullar, N., & Jackson, D. (2020). Life in the pandemic: Social isolation and mental health. *Journal of Clinical Nursing*, *395*(10228), 945–947.

Varatharaj, A., Thomas, N., Ellul, M. A., Davies, N. W., Pollak, T. A., Tenorio, E. L., & Coles, J. P. (2020). Neurological and neuropsychiatric complications of COVID-19 in 153 patients: A UK-wide surveillance study. *The Lancet Psychiatry*, *7*(10), 875–882.

Vedhara, K., Cox, N. K., Wilcock, G. K., Perks, P., Hunt, M., Anderson, S., & Shanks, N. M. (1999). Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *The Lancet*, *353*(9153), 627–631.

Wang, B., Kovalchuk, A., Li, D., Ilnytskyy, Y., Kovalchuk, I., & Kovalchuk, O. (2020). Search of preventative strategies: Novel anti-inflammatory high-CBD cannabis sativa extracts modulate ACE2 expression in COVID-19 gateway tissues. 17 April 2020. https://doi.org/10.20944/preprints202004.0315.v1

Webb, C. A., Rosso, I. M., & Rauch, S. L. (2017). Internet-based cognitive behavioral therapy for depression: Current progress & future directions. *Harvard Review of Psychiatry*, *25*(3), 114–122.

Wheatland, R. (2004). Molecular mimicry of ACTH in SARS–implications for corticosteroid treatment and prophylaxis. *Medical Hypotheses*, *63*(5), 855–862.

WHO (2020a). *Coronavirus disease (COVID-19) situation reports*. Retrieved from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

WHO (2020b). *Director-general's opening remarks at the media briefing on COVID-19 (16 March 2020)*. Retrieved from https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—16-march-2020

Wood, S. K., Wood, C. S., Lombard, C. M., Lee, C. S., Zhang, X. Y., Finnell, J. E., & Valentino, R. J. (2015). Inflammatory factors mediate vulnerability to a social stress-induced depressive-like phenotype in passive coping rats. *Biological Psychiatry*, *78*(1), 38–48.

World Health Organization (WHO). (2020). *Influenza & COVID-19: Similarities and differences*. Retrieved from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza#

Wu, C., Chen, X., Cai, Y., Zhou, X., Xu, S., Huang, H. … Song, J. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Internal Medicine* 2020 Mar 13, *180*(7), 934–943. https://doi.org/10.1001/jamainternmed.2020.0994

Xu, J., Zhao, S., Teng, T., Abdalla, A. E., Zhu, W., Xie, L. … Guo, X. (2020). Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses*, *12*(2), 244–261.

Yanyu, J., Xi, Y., Huiqi, T., Bangjiang, F., Bin, L., Yabin, G. … Changsheng, D. (2020). Meditation-based interventions might be helpful for coping with the Coronavirus disease 2019 (COVID-19) 2020 Apr 23. https://doi.org/10.31219/osf.io/f3xzq

Yorulmaz, A., Akın, F., Sert, A., Ağır, M. A., Yılmaz, R., & Arslan, Ş. (2018). Demographic and clinical characteristics of patients with serum sickness-like reaction. *Clinical Rheumatology*, *37*(5), 1389–1394.

Zhang, W., Zhao, Y., Zhang, F., Wang, Q., Li, T., Liu, Z. … Zeng, X. (2020b). The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. *Clinical Immunology*, *214*(108393), 1–5.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z. … Guan, L. (2020b). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *The Lancet*, *395*(10229), 1054–1062.

Zoppi, S., Madrigal, J. L., Caso, J. R., García-Gutiérrez, M. S., Manzanares, J., Leza, J. C., & García-Bueno, B. (2014). Regulatory role of the cannabinoid CB2 receptor in stress-induced neuroinflammation in mice. *British Journal of Pharmacology*, *171*(11), 2814–2826.

How to cite this article: Lamontagne, S. J., Pizzagalli, D. A., & Olmstead, M. C. (2021). Does inflammation link stress to poor COVID-19 outcome? *Stress and Health*, *37*(3), 401–414. https://doi.org/10.1002/smi.3017