Check for updates

Stress induced proinflammatory adaptations: Plausible mechanisms for the link between stress and cardiovascular disease

Aaron L. Slusher[1,2]* and Edmund O. Acevedo[3]

[1]Department of Pediatrics, Yale University School of Medicine, New Haven, CT, United States, [2]Department of Athletics, Yale University, New Haven, CT, United States, [3]Department of Kinesiology and Health Sciences, Virginia Commonwealth University, Richmond, VA, United States

Initiating from Hans Selye's conceptualization of stress physiology, to our present understanding of allostatic load as the cumulative burden of chronic psychological stress and life events, investigators have sought to identify the physiological mechanisms that link stress to health and disease. Of particular interest has been the link between psychological stress and cardiovascular disease (CVD), the number one cause of death in the United States. In this regard, attention has been directed toward alterations in the immune system in response to stress that lead to increased levels of systemic inflammation as a potential pathway by which stress contributes to the development of CVD. More specifically, psychological stress is an independent risk factor for CVD, and as such, mechanisms that explain the connection of stress hormones to systemic inflammation have been examined to gain a greater understanding of the etiology of CVD. Research on proinflammatory cellular mechanisms that are activated in response to psychological stress demonstrates that the ensuing low-grade inflammation mediates pathways that contribute to the development of CVD. Interestingly, physical activity, along with its direct benefits to cardiovascular health, has been shown to buffer against the harmful consequences of psychological stress by "toughening" the SAM system, HPA axis, and immune system as "cross-stressor adaptations" that maintain allostasis and prevent allostatic load. Thus, physical activity training reduces psychological stress induced proinflammation and attenuates the activation of mechanisms associated with the development of cardiovascular disease. Finally, COVID-19 associated psychological stress and its associated health risks has provided another model for examining the stress-health relationship.

KEYWORDS

stress, allostasis, inflammation, cardiovascular disease, physical activity

Introduction

The term s*tress* is used indiscriminately in modern culture to describe psychological and physiological experiences resulting from the ways in which we live, work, and coexist as members of an increasingly more complex society. *Stress*, and our understanding of the experience, stems in part from the "general-adaptation-syndrome" first proposed by Hans Seyle (1907–1982) in his seminal *Nature* publication over 85 years ago (Seyle, 1936). Over the course of roughly 40 years, Selye built upon the *internal milieu* concept described by Claude Bernard (Bernard, 1879) and Walter Cannon's homeostatic "alarm phase" in response to

emotional and physical duress that involves the release of catecholamines, epinephrine (EPI) and norepinephrine (NOR), from sympathetic nervous system activation of the adrenal medulla [sympathetic adrenal medullary (SAM) system] during a "fight or flight" response (Cannon, 1914a; 1932). In doing so, Selye redefined our understanding of how the body maintains homeostasis in response to a stressor. Additionally, Seyle provided the framework necessary to detail the intricate synchronization of the SAM system with the hypothalamic-pituitary-adrenal (HPA) axis and resulting mechanistic actions linked to the release of catecholamines and glucocorticoids, respectively, in response to chronic stress.

Selye and his colleagues conducted extensive research that led to the understanding that the release of corticotropin releasing hormone (CRH; *via* the hypothalamus) induces the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which in turn stimulates the release of glucocorticoids from the adrenal cortex. Furthermore, Selye's findings provided insight to support his proposed theory that chronic stress, such as prolonged exposure to noxious agents (e.g., extreme temperature, trauma, and various drugs), results in "morphological manifestations of distress" characterized by the "stages of resistance and exhaustion" (Selye, 1936; 1976). More specifically, during the *resistance* stage, Selye detailed that the body prepares for a sustained attack while the immune system increases in activation. However, during the *exhaustion* phase, the body's ability to sustain a response to a stressor is diminished and health begins to deteriorate.

As Selye's work progressed and his knowledge of the physiology of stress developed, his theoretical propositions evolved. For example, his original detailing of the "general adaptation syndrome" included the notion that activation of the HPA axis by a stressor is a "basic reaction pattern irrespective of the agent used to produce stress" (Selye, 1950). In time, this idea progressed to an appreciation that an individual's stress response to a particular stressor is, in part, determined by "how you react to it." In doing so, Selye suggested that the differentiation between "distress" and "eustress" helps to determine the response as being initiated by a negative or positive emotion, respectively (Selye, 1974).

Selye's foundational contribution in the study of the stress response has led to over 1,500 peer-reviewed articles and nearly 40 books related to the subject. Likewise, his relentless advocacy for the acceptance of the term "stress" within the medical community has contributed to the widespread use (and misuse) of "stress" as a general concept. The term is fully integrated within the lexicon of the broader scientific community and into the shared consciousness of the general public. However, his lasting impact may best be observed by the extension and expansion of his original works across a diverse array of research applications within numerous scientific disciplines. Indeed, his collective work served as a foundation for modern fields of psychoneuroendocrinology (PNE) and psychoneuroimmunology (PNI), which collectively, provided a greater appreciation for the psychological aspect of disease pathology.

Acute and chronic stress and cardiovascular disease

Hans Selye's original conceptualization of stress physiology and our present understanding of allostatic load as the cumulative burden of chronic stress and life events have helped to elucidate the physiological mechanisms linking stress to health and disease (Sterling and Eyer, 1988). In response to acute psychological stress, the amygdala, a region within the brain involved in emotional regulation, plays a role in the deactivation of the parasympathetic nervous system and activation of the SAM system and HPA axis (Osborne et al., 2020). Although the SAM system is known to secret many factors, including adenosine triphosphate (ATP), neuropeptide Y, and nitric oxide (MacArthur et al., 2011), SAM system activation is most well-known to initiate the rapid release of the catecholamines EPI and NOR that are observed in circulation throughout the body. Within a similar timeframe, CRH released into portal circulation stimulates ACTH secretion to elicit elevations in plasma cortisol (CORT) within ~15–20 min (Sapolsky et al., 2000). The role of the SAM system in response to stress is vital to prepare the body for a "fight-or-flight" response by increasing heart rate, blood pressure, the diversion of blood flow and metabolic substrate to skeletal muscle and the brain, the regulation of sweat production, and the downregulation of reproduction and digestion (Karemaker, 2017). The half-lives of EPI and NOR are ~1.5 and 2.5 min (LaBrosse et al., 1961; Hagberg, et al., 1979), respectively, and once the stressor has resolved, EPI and NOR are rapidly cleared from circulation. In contrast, the HPA axis serves as a self-regulator with CORT by inhibiting CRH and ACTH production and acting to maintain and regulate the coordinated stress response until well after the stressor has subsided (Gagner and Drouin, 1985; McEwen, 2000). With a half-life of ~60 min (Weitzman et al., 1971), the sustained presence of CORT within circulation returns the body's internal physiological functions to normal (Droste et al., 2008; Ulrich-Lai and Herman, 2009).

The initial "fight-or-flight" response to acute psychological stress was proposed by Walter Cannon to maintain internal stability and functionality of an organism (Cannon, 1914b). Physiological functions, such as pH and body temperature, however, operate within a narrow range of function, and the body's ability to regulate these functions within these narrow ranges are considered necessary to sustain life. In the 1970s, Selye theorized that adaptive mechanisms create new equilibriums within an organism in response to a potential threat, such as defense against a pathogen or an increase in the tolerance of tissue to the pathogen (Selye, 1973; Selye, 1975). Having termed this mechanism *heterostasis,* Selye suggested that fluidity of the body's functional capacity is necessary to artificially increase homeostasis to a new level, and by "resetting the thermostat," equilibrium is reestablished over the long-term through active "exogenous intervention" *via* pharmacological therapies (Selye, 1973; Selye, 1975). As stress research continued to advance, greater emphasis was placed on the understanding that the body can adapt to a sustained or prolonged stressor that is present within an individual's environment. For example, heart rates, blood pressures, plasma glucose concentrations, and many other vital functions can operate within a broad range and adapt to new set points in a manner dependent on the physical and psychological state of an individual (McEwen and Stellar, 1993). This functional fluidity has been termed "allostasis" and is necessary to readjust the body's physiology to maintain internal stability in response to change (McEwen, 1998).

During a "normal" acute stress response, allostasis represents a physiological response reflective of the individual's resilience to the stressor and serves as a temporary protective buffer against a potentially harmful physical or emotional perturbation. In response to chronic exposure to any given stressor or the cumulation of various stressors, the inability to properly manage allostasis can be identified by the increased metabolic activity within the amygdala, augmented EPI and NOR concentrations, and dysregulated CORT concentrations at rest and in response to acute psychological stress (Pike et al., 1997; Schommer et al., 2003; Mischler et al., 2005; Tawakol et al., 2017). These responses are associated with the progressive "wear and tear" on the organism that link stress-reactivity to current CVD and future CVD events (Carroll et al., 2012; Tawakol et al., 2017; Fava et al., 2019). This shift from an effective to an inadequate (or maladaptive) physiological response is referred to as allostatic load (McEwen, 1998; McEwen, 2007). Interest in recognizing and identifying allostatic load among clinical populations has increased over the past decade. For example, Seeman et al. (2001) utilized a combination of cardiovascular, anthropometric, cholesterol, catecholamines, and other plasma biomarkers to measure the cumulative impact of allostatic load on various health outcomes and all-cause mortality. Results revealed that the progressive accumulation of allostatic load predicted decreased physical and cognitive abilities and the increased risk of CVD and all-cause mortality over a 7-year span among healthy 70–79-year-old men and women (Seeman et al., 2001). Similarly, a recent meta-analysis of 17 studies indicates that higher compared to lower indices of allostatic load contributed a 22% increase in risk for all-cause mortality and a 31% increased risk for CVD morality (Parker et al., 2022). These results suggest that the presence of repeated stress or prolonged and continuous exposure to stress, presents a challenge to allostasis and decreases the body's ability to adapt. Thus, similar to the "exhaustion" phase proposed by Selye, the attenuated ability of the body to respond to repeated and persistent negative psychological stressors resulting in allostatic load directly contributes to the onset and progression of CVD pathology (Dar et al., 2019; Levine et al., 2021; Parker et al., 2022).

This evolution of Hans Selye's initial conceptualization of stress has led investigators to examine factors that improve the efficiency of the adaptive response to stressors (allostasis) while minimizing over activation of these systems (allostatic load). Since psychological stress overactivity can result in many of the stress related disorders and common diseases of modern life, the identification of potential interventions that can improve an individual's resiliency to the negative consequences of psychological stress is of increased importance. For example, psychological resiliency, in particular an individual's perception that the stressor is a challenge worth overtaking versus a difficult burden to overcome, in part, can determine the magnitude of the individual's acute response to a stressor (Lazarus, 1974). Furthermore, Felix et al. (2022) indicated that higher resiliency (e.g., family/social networks and optimism) helped mitigate against the adverse cardiovascular health outcomes associated with high allostatic load among African American men, but not women. This appraisal model suggests that when a stressor is viewed from a positive perspective or as a lesser threat, hormone secretion and cardiovascular reactivity remain lower compared to when the stressor is viewed as a burden or a larger threat to survival (Hinton et al., 1991; van Eck et al., 1996; Peters et al., 1998; Fauvel

et al., 2001; Steptoe and Willemsen, 2004; Weinstein et al., 2010). Likewise, differences in perception and associated magnitude of the physiological reaction are directly linked to current and future CVD risk (Chida and Steptoe, 2010; Carroll et al., 2012), with lower CVD risk being attributed to positive perceptions of psychological stress (Dar et al., 2019; Levine et al., 2021). As such, the current level of resilience or ability to develop a more robust resiliency to a particular stressor is likely fundamental to reducing the global health burden associated with CVD health (Levine et al., 2021). Similarly, systemic environmental factors woven into the fabric of societies that disproportionally impact various populations and demographics are critical, and possibly more important, when considering strategies to reduce the adverse impact of daily psychological stress on global health.

Psychological stress and inflammation

General immune response to acute and chronic psychological stress

A key factor linking the etiology of psychological stress to CVD risk includes dysregulation of the immune system (Slavich, 2020). Selye first described the impact of chronic psychological stress on immune function dysregulation by describing atrophy to the thymus and lymph nodes within rodents (Selye, 1936). Similarly, it has been suggested that Hans Selye first identified the anti-inflammatory actions of glucocorticoids during the 1940s and was not provided full credit for his discoveries (Szabo et al., 2012). Nontheless, these initial observations served as the foundation for the field of PNI, a term first described by Robert Ader in 1980, and defines his and his colleagues research conducted throughout their careers (Ader and Cohen, 1975; Ader, 1980).

PNI details the role of the immune system as a mechanism linking mental and emotional stress to EPI, NOR, and CORT concentrations in health and disease (Slavich, 2020). More specifically, brief, yet persistent, challenges to allostasis, and the associated progression into allostatic load, are linked to the continual output of catecholamines and glucocorticoids and the dysregulated activation of the immune system (Marsland et al., 2017). In response to acute psychological stress, transient immune responses are commonly examined via changes in circulating concentrations of pro-inflammatory and anti-inflammatory cytokines. Another common measure of immune dysfunction includes identifying shifts in the distribution of immune cell types and their respective subsets examined via flow cytometry. Lastly, isolating innate immune cells, such as monocytes, is frequently utilized to examine changes in the sensitivity of their inflammatory signaling pathways following exposure to known inflammatory agents, such as lipopolysaccharide (LPS) or phytohaemagglutinin. In this regard, increased attention has been directed toward alterations in the psychobiological mechanisms linking acute and chronic psychological stress to dysregulation of the immune system which help explain the association of allostatic load and CVD (Acevedo and Slusher, 2017; Huang et al., 2017).

Acute models of psychological stress are currently limited to laboratory-induced or naturalistic stressors. Laboratory stressors typically occur in a controlled environment using established

protocols known to activate the SAM system and HPA axis, such as the Trier Social Stress Test (TSST). In contrast, naturalistic stressors are real-life experiences, such as major life events or natural disasters, known to induce psychological stress and its associated physiological response. For both psychological and physical stimuli, acute stressors alter allostasis by increasing SAM system and HPA axis activation necessary to stimulate cardiovascular reactivity. In response to acute psychological stress, a recent meta-analysis examining over 30 publications details that among a large array of pro-inflammatory proteins, concentrations of interleukin-6 (IL-6) were also elevated within 40–50 min and remained elevated for at least 2 h following cessation of the stressor. Similar, yet more transient, increases were also exhibited for IL-1β, whereas tumor necrosis factor alpha (TNF-α), IL-2, and the anti-inflammatory cytokine IL-10 exhibited small, albeit significant, increases in circulation during the recovery periods under investigations (often up to 2 h; Marsland et al., 2017). Interestingly, the magnitude of the pro-inflammatory immune response, such as IL-6, has been shown to be greater in healthy compared to clinical populations (Marsland et al., 2017). These findings suggest that the immune response a vital component of the physiological stress response. Likewise, populations with chronic low-grade levels of systemic pro-inflammation at baseline, or rest, may exhibit a different threshold for, or altered magnitude of, an immune response compared to healthy populations that serve as a "control" group for a particular study. As such, the health and disease statuses of various populations must be considered when measuring a psychological stress-induced immune response (Furman et al., 2019).

Examining the mobilization of immune cell populations and associated subsets allows for mechanistic investigations into how various immune cell types respond to protect the host from psychological perturbations. EPI is a potent mobilizer of immune cells, characterized by the transient increase in the number and redistribution of various immune cells and their respective subsets, including the trafficking of monocytes to the vascular endothelium (Dimitrov et al., 2010). More specifically, monocytes are the predominant immune cell population responsible for pro- and anti-inflammatory cytokine production in response to acute psychological stress (Bierhaus et al., 2003). Monocytes are identified by the pattern of cell surface markers CD14 and CD16, and their inflammatory reactivity is determined by expression of the transmembrane pattern recognition receptor Toll-like receptor 4 (TLR4; Hailman et al., 1994; Slusher et al., 2018). There are three primary subsets of monocytes that are determined by the distribution patterns of the CD14 and CD16 receptors: *classical* (CD14$^{+bright}$CD16$^-$), *intermediate* (CD14$^{+bright}$CD16^{+dim}), and *non-classical* (CD14^{+dim}CD16$^{+bright}$; Passlick et al., 1989). Furthermore, *classical* monocytes express low levels of the TLR4 receptors, account for up to 80% of all monocytes, and are typically associated with IL-6 and IL-10 cytokine production (Frankenberger et al., 1996; Slusher et al., 2018). In contrast, *intermediate* and *non-classical* account for about 5% and 15% of all monocytes observed in circulation, respectively, express progressively higher levels of TLR4 receptors at the cell membrane, and are primarily responsible for IL-1β and TNF-α secretion (Frankenberger et al., 1996; Belge et al., 2002; Slusher et al., 2018). Additionally, both *intermediate* and *non-classical* monocyte

subsets are preferentially mobilized in response to acute psychological stress, and thus, serve as one mechanism responsible for the increased inflammatory reactivity of monocyte observed in circulation (Dimitrov et al., 2010).

Changes in monocyte distribution patterns and inflammatory responsiveness have further enabled researchers to identify the specific molecular pathways and how they respond to acute psychological stressors. For example, although CD14 is necessary to initiate an LPS-induced inflammatory response *via* TLR4 (Wright et al., 1990; Kim and Kim, 2014), TLR4 receptors on monocytes also interact with CD16 in response to LPS stimulation at the cell surface to trigger an intracellular signaling cascade that stimulates the activation of the nuclear factor-κB (NF-κB) transcription factor (Akashi et al., 2003; Shalova et al., 2012). As a result, NF-κB undergoes a translocation from the cytoplasm to the nucleus as the primary transcription factor responsible for the synthesis of numerous inflammatory proteins in response to acute psychological stress, including IL-1β, IL-6, IL-10, and TNF-α (Bierhaus et al., 2003). Similarly, TLR4-mediated activation of NF-κB within monocytes increases activation of the Nod-like receptor pyrin containing 3 (NLRP3) inflammasome, an intracellular mulitprotein complex that is responsible for release of numerous pro-inflammatory cytokines in response to psychological stress, including IL-1β and IL-18 (Kaufmann et al., 2017). Although NLRP3-induced IL-1β expression and release has been shown to occur in an ATP-dependent manner within the hippocampus to improve symptoms of depression (Iwata et al., 2016), the release from the monocytes in peripheral circulation; and following recruitment to the brain in response to acute and psychological stress; and its role in the inflammatory response, requires additional research (Alcocer-Gómez et al., 2014). Non-etheless, Kuebler et al. (2015) further demonstrated that NF-κB binding activity increased immediately following the TSST and remained elevated for up to 1 h into recovery among healthy males aged 20–50 years. This rapid activation of the intracellular inflammatory signaling pathway was further shown to be associated with the increased expression of mRNA of various inflammatory cytokines, including IL-1β and IL-6 (Kuebler et al., 2015), which are in turn, released by immune cells as an initial mechanism to protect the host from potential tissue damage associated with the acute stress reactivity.

Marsland et al. (2017) further highlights that the *ex vivo* secretion of the pro-inflammatory cytokines IL-6 and TNF-α from isolated monocytes occurs rapidly (within about 10–30 min) and is soon followed by the secretion of IL-1β (within 30–50 min) among monocytes isolated and cultured immediately following acute psychological stress. Although the rapid release of these inflammatory proteins was observed under culture conditions and might not accurately reflect the secretion kinetics of immune cells *in vivo*, these responses are augmented greatly when stimulated in the presence of LPS, thus supporting the key functional role of the TLR4-NF-κB inflammatory pathway as initially demonstrated by Bierhaus et al. (2003). These findings suggest that the increased reactivity of pro-inflammatory pathway in combination with the transient shift towards the *intermediate* and *non-classical* subsets following an acute psychological stressor primes monocytes to elicit a robust innate immune response upon inflammatory stimulation. Likewise, these research findings are key to understanding the pathology of disease progression because the inflammatory

phenotype of circulating monocytes is thought to reflect the tissue-specific microenvironment upon their migration into specific tissue sites and subsequent differentiation into resident macrophages (Bories et al., 2012).

In response to acute psychological stress, activation of the vascular endothelium results in the secretion of numerous chemokines known to attract circulating leukocytes, mainly monocytes and neutrophils, to the site of inflammation (Redwine et al., 2003; Redwine et al., 2004; Hinterdobler et al., 2021a). Similarly, vascular endothelial cells express adhesion molecules which interact with their receptors on the surface of circulating immune cells that are recruited, in part, by local NOR production within the endothelium (Hinterdobler et al., 2021a; Hinterdobler et al., 2021b). The tethering of pro-inflammatory monocytes and neutrophils and their slow rolling along the vascular endothelium eventually results in their firm adherence (arrest) and subsequent migration (extravasation) through the endothelium (Silvestre-Roig et al., 2020; Mauersberger et al., 2022). Once monocytes have transmigrated through the vascular endothelium, they differentiate into resident tissue macrophages that also exhibit a pro-inflammatory phenotype (Swirski et al., 2009; Silvestre-Roig et al., 2020). As a result, these pro-inflammatory resident macrophages, often referred to as M1-macrophages, ingest cholesterol particles, form foam cells, and can contribute, along with neutrophils, to the development of unstable plaques that prolong and exacerbate the pro-inflammatory microenvironment characteristic of atherosclerosis and coronary heart disease (Wilbert-Lampen et al., 2008; Silvestre-Roig et al., 2020; Hinterdobler et al., 2021a; Hinterdobler et al., 2021b; Gerhardt et al., 2022; Mauersberger et al., 2022).

Interaction of catecholamines and cortisol on immune cell inflammatory pathways

The interaction of the central nervous system and the inflammatory signaling pathway in response to acute psychological stress is in part determined by the interaction of EPI and NOR with various adrenergic receptors (ADRs) located on the surface of immune cells (monocytes). For example, Bierhaus et al. (2003) demonstrated that NOR interacts with α_1-ADRs on the surface of monocytes to increase NF-κB expression. To the contrary, EPI has been shown to interact with β_2-ADRs to downregulate regulate TLR4 and the intracellular pro-inflammatory signaling pathway (Kizaki et al., 2008; Wang et al., 2009; Dimitrov et al., 2013; Hong et al., 2015). These interactions are important to augment the ability of immune cells to travel to various tissues and mount an immune response appropriate to protect the host in response to perceived psychological stress. Shortly after the cessation of the stressor, the HPA axis mediated release of CORT acts on the glucocorticoid receptor within the cytosol, where it subsequently translocates into the nucleus to inhibit NF-κB, downregulate the pro-inflammatory immune response, and increase transcription of the anti-inflammatory cytokine IL-10 within monocytes (Barnes, 1998; McKay and Cidlowski, 1999). The cellular sensitivity to glucocorticoids aids in returning the host to a normal physiological level once the stressor and threat to allostasis has subsided. Interestingly, glucocorticoids have been shown to enhance

ATP-dependent NLRP3 expression within culture monocyte/macrophages to promote pro-inflammation, whereas more recent investigations suggest an inhibitory role within murine macrophages stimulated with LPS (Wu et a., 2020). Although the precise role of glucocorticoids remains yet to be fully elucidated, the synchronization of SAM system and HPA axis activation serve as vital mechanisms necessary to prepare and recover from a fight or flight response.

Over time, repeated exposure to acute stressors or the persistent threat to an individual's safety or wellbeing, such as race- and obesity-related discrimination, low socioeconomic status, neighborhood safety, and/or occupational hazards, to suggest a few, contributes to the accumulation of chronic stress (Schnorpfeil et al., 2003; Nelson et al., 2007; Juster et al., 2010; Seeman et al., 2010; Tan et al., 2017; Suvarna et al., 2020). As a result, alterations of hormone concentrations at baseline and altered responsiveness to an acute psychological stressor (such as an augmented, blunted, or prolonged elevation of hormone concentrations) cause immune system dysregulation characterized by low-grade elevations in systemic inflammatory cytokine concentrations and increases in the pro-inflammatory reactivity of monocytes (Maydych et al., 2017). The prolonged exposure of monocytes to LPS increases α_1-ADR expression on the cell surface of monocytes (Heijnen et al., 1996; Rouppe van der Voort et al., 1999; Rouppe van der Voort et al., 2000), and in parallel, β_2-ADR sensitivity has been shown to decrease in individuals with indices of chronic levels of psychological stress and low-grade pro-inflammatory profiles (Euteneuer et al., 2012; Hong et al., 2014). Furthermore, the expression and sensitivity of glucocorticoid receptors to CORT within monocytes/macrophages is diminished in individuals with chronic elevated levels of psychological stress (Stark et al., 2001; Miller et al., 2008). Increased metabolic activity within the amygdala is also associated with increased hematopoietic stem cell activity within the bone marrow and the increased number of circulating leukocytes (Tawakol et al., 2017). These indices of chronic psychological stress contribute to the prolonged activation of the pro-inflammatory response of immune cells in circulation and within the vascular endothelium following an acute psychological stressor, and consequently, the progression of low-grade pro-inflammatory profiles in circulation and the progression of atherosclerotic inflammation involved in the development of CVD (Rodriguez et al., 2016; Tawakol et al., 2017; Kivimäki and Steptoe, 2018).

Psychological stress adaptations to physical activity and exercise

Physical activity improves resiliency to psychological stress and immune function

Physical activity (any action or movement of the body that requires skeletal muscle activation) and exercise (a subcategory of physical activity that is organized and planned) are two important behavioral strategies that serve as positive physical stressors to protect against the potential negative consequence of acute and chronic psychological stress (Hamer and Steptoe, 2007; Hamer, 2012; Acevedo and Slusher, 2017; Huang et al., 2017). Richard

Dienstbier (1989) has proposed that "active toughening", an adaptation to aerobic exercise training, results in the enhanced regulation of the SAM system activation (EPI and NOR concentrations and cellular ADR sensitivity) and suppression of the CORT response initiated from the HPA axis. As a result, the improved coordination of these physiological responses works in unison to increase stress tolerance, improve emotional control, and enhance immune function (Dienstbier, 1989).

Soon thereafter, Sothmann et al. (1996) provided the framework for the "cross-stressor adaptation" hypothesis. The cross-stressor adaptation hypothesis suggests that individuals with higher participation rates in routine physical activity and/or elevated cardiorespiratory fitness levels (indicated as maximal oxygen uptake; VO_{2max}) experience generalized adaptations that are integrated across physiological systems. These adaptations work to make the collective actions of these systems more resilient to the negative consequences of acute stress reactivity and the hallmark health consequences of chronic stress (Sothmann et al., 1996). Similar to Dienstbier's physiological toughening hypothesis, Sothmann et al. (1996) suggested that routine physical activity, and in particular aerobic exercise training, enhances the function and communication among the SAM system, HPA axis, and cardiovascular and muscular systems to minimize disruptions to homeostasis and allostasis during acute physical activity. Moreover, the capacity of these beneficial adaptations to physical activity to protect against the potentially harmful consequences of acute and chronic psychological stress are largely a factor of the intensity, duration, and frequency and type of activity (Mücke et al., 2018). However, just as an appropriate amount of physical activity can positively regulate indicators of psychological stress, Selye also specified that an excessive amount of exercise should be considered adverse and can contribute to the negative health consequences of chronic psychological stress (Selye, 1936). As such, physical activity and exercise recommendations suggest obtaining sufficient amounts of moderate intensity (150 min/week) or high-intensity (75 min/week) physical activity for optimal physical and psychological health while warning against excessive amounts (up to about 300 min/week) on a consistent basis (Nieman, 2020). It is evident that further investigations into the specific exercise guidelines for enhancing the cross-stressor adaptation and reducing stress related allostatic load are warranted.

In support of the physiological toughening and cross-stressor adaptation hypotheses, regular participation in physical activity is a well-known anti-inflammatory behavior, and the resultant anti-inflammatory milieu helps to lower the risk of developing CVD (Gleeson et al., 2011; Pedersen, 2017). In response to acute and chronic psychological stress, the benefits of physical activity also extend beyond buffering against adverse cardiovascular and hormonal reactivity to more favorably regulating the systemic and cellular immune responses. For example, Hamer and Steptoe (2007) initially examined the relationship between physical fitness and the systemic inflammatory cytokine response following mental stress. Results demonstrated that healthy men and women with increased performance on a submaximal cycle ergometer test exhibited lower cardiovascular reactivity (i.e., lower heart rates) and less pronounced increases in plasma IL-6 and TNF-α compared to low fit individuals during recovery from an acute psychological stressor (Hamer and Steptoe, 2007). Since this hallmark publication, increased participation in physical activity and elevated cardiorespiratory fitness levels routinely exhibit a more regulated systemic and cellular immune response to acute psychological stress as well as lower indices of inflammation when faced with chronic life stress (Puterman et al., 2018; Simpson et al., 2021).

The cellular mechanisms by which the immune system is positively regulated through physical activity participation and exercise training are vast. For example, shifts in the proportion of circulating monocytes in favor of *classical* compared to the more pro-inflammatory *intermediate* and *non-classical* subsets are typical (Timmerman et al., 2008), resulting in a lower concentration of monocytes producing pro-inflammatory proteins upon stimulation. In addition, TLR4 receptor expression is reduced, contributing to a decrease in the activation of the LPS-stimulated intracellular signaling pathway on any given subset of monocyte (Timmerman et al., 2008). Consistent with these findings, Khakroo Abkenar et al. (2019) demonstrated that although acute, high intensity exercise increases peripheral blood mononuclear cell NLRP3 gene expression as well as circulating IL-1β and IL-18 concentrations, 3-month of aerobic exercise training was sufficient to prevent these intracellular and systemic pro-inflammatory responses. Interestingly, Hong et al. (2014) has shown that monocytes exhibited increased cellular β2-ADR sensitivity that could play a role in downregulating the TLR4-mediated inflammatory response. Likewise, glucocorticoid receptor sensitivities within the cytosol and their ability to inhibit NF-κB activation have been shown to increase in response to regular aerobic exercise training (Duclos et al., 2003). As a result, the proportion of pro-inflammatory monocytes is decreased and the overall inflammatory sensitivity of individual monocytes to LPS is significantly lower in physically active and aerobically trained compared to inactive and untrained individuals (Timmerman et al., 2008; Slusher et al., 2018). Cumulatively, the reduced systemic and cellular inflammatory reactivity observed in physically active compared to inactive populations in response to psychological stress serve as a primary mechanism by which physical activity and exercise maintain cardiovascular health and prevent the onset of CVD during the aging process (Merino et al., 2011; Slusher et al., 2019; Simpson et al., 2021).

Physical activity and COVID-19-associated psychological stress

In December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged and spread globally. As a result, local and national stay-at home orders limited access to social connections, increased food insecurities, and prevented access to important health services, such as routine healthcare and exercise gyms/facilities (Fallon, 2020; Killgore et al., 2020; Parekh et al., 2021; Tuczyńska et al., 2021; Völker, 2023). Consequently, the role of physical activity gained attention as a safe and effective public health initiate to reduce the psychological stress associated with the initial and persistent confinement associated with lock-down orders (López-Bueno et al., 2020; Meira Jr. et al., 2020; Wolf et al., 2021). Unfortunately, physical activity tended to decrease during the initial stages of SARS-CoV-2 pandemic related restrictions (Meyer et al., 2020; Tison et al., 2020). In addition, decreased

physical activity levels during the SARS-CoV-2 pandemic appeared to be more pronounced for low socioeconomic communities and children, who were out of school and void of physical education courses (Moore et al., 2020; Spencer et al., 2020). Furthermore, lack of access to safe locations for physical activity engagement may have contributed to this reduction in physical activity (Barr-Anderson et al., 2021). As a result, the SARS-CoV-2 global pandemic disproportionately impacted marginalized communities, and key avenues to make public health services more equitable were highlighted (Okonkwo et al., 2020; Hasson et al., 2022).

The SARS-CoV-2 pandemic also highlighted the unique relationship that exists between physical activity/exercise and psychological stress. For example, Salari et al. (2020) indicated that the prevalence of psychological stress, anxiety, and depression ranged from 30% to 34%, respectively, among the general public during the early months of the SARS-CoV-2 pandemic. In addition, Marashi et al. (2021) demonstrated that physical activity levels dropped in parallel with increased perceptions of psychological stress over a 6-month period among a large Canadian population. Similarly, Creese et al. (2021) suggested that indices of loneliness and decreased physical activity levels were predictors of poor mental health experienced during the SARS-CoV-2 pandemic compared to the 5-year period before the pandemic lockdown among adults 50 years of age or older. It is possible that the stress associated with the SARS-CoV-2 pandemic made it difficult to cope with the significant disruptions to daily life, as many who reported being less physically active indicated that lack of social support, increased feelings of anxiety, and lack of motivation were barriers to engagement in physical activity (Marashi et al., 2021). Upon infection, symptoms of psychological stress, including depression, anxiety, and post-traumatic stress, were more likely to be observed among COVID-19 patients compared to non-infected controls (Guo et al., 2020), as well as patients with severe compared to those with mild or less severe cases (Dong et al., 2021). More worrisome, the severity of psychological stress-related mental health issues predicted elevated plasma concentrations of the pro-inflammatory marker C-reactive protein (Guo et al., 2020). These findings suggest that the exacerbation of pro-inflammatory profiles among individuals infected with COVID-19 is associated with poorer health outcomes, including death (Lamontagne et al., 2021). Similar observations have also been documented with chronic psychological stress in patients with CVD and in patients with other low-grade pro-inflammatory conditions (Papava et al., 2022).

Active engagement in physical activity and exercise proved to be a vital mechanism for the preservations of psychological wellbeing associated with stay-at-home orders during the initial stages of the SARS-CoV-2 pandemic. For example, Wolf et al. (2021) conducted a preliminary review during the early stages of the SARS-CoV-2 pandemic and concluded that increased total time spent engaging in moderate to vigorous physical activity/exercise presented with lower depressive and anxiety-like symptoms. In support of these findings, Marashi et al. (2021) demonstrated that individuals who remained physically active or actively increased engagement in physically activity referenced the associated mental health benefits as the primary motivational factor obtained from regular physical activity participation. These findings suggest that although higher indices of psychological stress

prevented regular engagement in physical activity, personal commitment to physical activity and/or increased motivation for the resultant mental health benefits supported regular physical activity engagement. As a result, consistent physical activity helped to maintain indices of mental health and attenuate levels of psychological stress during the SARS-CoV-2 pandemic. Thus, these results highlight the critical need for approaches that provided social support and direct individuals toward increased physical activity as a behavioral health strategy to maintain mental and emotional health and potentially minimize COVID-19 severity upon infection.

Lower levels of physical activity and cardiorespiratory fitness also emerged as a risk factor for infection severity, hospitalization, intensive care unit admission, and risk of premature death (Christensen et al., 2021; Sallis et al., 2021; Jimeno-Almazán et al., 2022; Nieman and Sakaguchi, 2022). A possible mechanism for this benefit of physical activity relates to the anti-inflammatory role of physical activity and exercise (Zbinden-Foncea et al., 2020; De Sousa et al., 2021). In addition to the capacity of physical activity to facilitate the inflammatory microenvironments described above, regular physical activity and exercise have also been shown to activate the ACE2 receptor within the lungs. ACE2 receptor activation stimulates the production of angiotensin 1–7 (Ang1-7) from angiotensin II (AngII) within pulmonary endothelial cells as an anti-inflammatory mechanism that helps maintain lung health (Prata et al., 2017; De Sousa et al., 2021). To the contrary, COVID-19 binds the ACE2 receptor and prevents Ang1-7 production from AngII, thereby creating an imbalance in the ratio of AngII to Ang1-7 that is associated with the COVID-19-asscociated pro-inflammatory response within the lungs (Zbinden-Foncea et al., 2020; De Sousa et al., 2021).

Another potential mechanism by which regular physical activity and exercise serve to protect against COVID-19 involves increasing the capacity of the immune system to prevent infection (Simpson et al., 2020). Although there is ongoing debate regarding the role that exercise intensity has on minimizing infection risk (Simpson et al., 2020), moderate physical activity and exercise have been shown to regulate immune function and increase the capacity of the immune system to prevent and fight against bacterial and viral infection by improving immunosurveillance (Nieman, 2020; Baker et al., 2023). Similarly, physical activity has been shown to increase vaccine effectiveness (Pascoe et al., 2014), which may play a role in decreasing anxiety associated with not just pandemic-specific vaccinations development, but also vaccine effectiveness upon administration (Bendau et al., 2021; Hallam et al., 2022). As an example, Ledo et al. (2020) previously demonstrated that neutralizing antibodies to seasonal influenza vaccination was greater among elite athletes, and Kohut et al. (2004) observed that 10 months of moderate intensity exercise increased antibody titer in response to influenza immunizations among adults 65 years of age and older. More recently, Hallam et al. (2022) has demonstrated that a single session of moderate intensity cycling (90 min), among aerobically trained individuals, can increase antibody titer without impacting vaccine-associated side effects. More recently, Batatinha et al. (2022) demonstrated that recent vaccination against COVID-19 infection did not alter the cardiorespiratory or neuroendocrine response to moderate and intense physical activity among endurance trained athletes.

Therefore, these results support the increase in messaging about the benefits of acute and chronic physical activity and exercise as a behavioral mechanism to improve the immune responses to safe and effective vaccine administration (Hallam et al., 2022), which in turn, might help to lower pandemic-associated psychological stress.

Summary

Stress today is woven into society and is important to the overall health and wellness of nearly every individual across the globe. From a broader perspective, psychological stress is an important evolutionary driver that has been integral for the survival of our species throughout history and will continue to be a critical driver of our evolution into the future. Hans Selye expanded upon science's previous understanding of stress physiology and laid a critically important foundation for the field that contributed to relationships of acute and chronic stress and the deleterious outcomes related to cardiovascular health. Building upon his work, Bruce McEwen described the roles of allostasis and allostatic load as two mechanisms linking psychological stress to the pathophysiological progression of CVD. Simultaneously, Dienstbier and Sothmann separately described the capacity of physical activity to buffer against the harmful consequences of psychological stress by "toughening" the SAM system, HPA axis, and immune system as "cross-stressor adaptations" that maintain allostasis and prevent allostatic load. Finally, the "new normal" that has emerged during the ongoing SARS-CoV-2 global pandemic has provided a lens through which scientists can once again appreciate the tremendous contributions of Han Selye's work on stress and health, and how his contributions have impacted worldwide public health policy.

Author contributions

AS and EA contributed jointly to the development of the content presented in this article. Each has provided critical intellectual content, rigorously reviewed the manuscript for accuracy, and approve all content for publication. AS and EA agree to be accountable for all aspects of this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Acevedo, E. O., and Slusher, A. L. (2017). Physiological activation to acute mental challenge: Implications for cardiovascular health. *Kinesiol. Rev.* 6, 120–133.

Ader, R., and Cohen, N. (1975). Behaviorally conditioned immunosuppression. *Psychosom. Med.* 37, 333–340.

Ader, R. (1980). Presidential address--1980. Psychosomatic and psychoimmunologic research. *Psychosom. Med.* 42, 307–321. doi:10.1097/00006842-198005000-00001

Akashi, S., Saitoh, S., Wakabayashi, Y., Kikuchi, T., Takamura, N., Nagai, Y., et al. (2003). Lipopolysaccharide interaction with cell surface toll-like receptor 4-MD-2: Higher affinity than that with MD-2 or CD14. *J. Exp. Med.* 198, 1035–1042. doi:10.1084/jem.20031076

Alcocer-Gómez, E., de Miguel, M., Casas-Barquero, N., Núñez-Vasco, J., Sánchez-Alcazar, J. A., Fernández-Rodríguez, A., et al. (2014). NLRP3 inflammasome is activated in mononuclear blood cells from patients with major depressive disorder. *Brain Behav. Immun.* 36, 111–117. doi:10.1016/j.bbi.2013.10.017

Baker, F. L., Zúñiga, T. M., Smith, K. A., Batatinha, H., Kulangara, T. S., Seckeler, M. D., et al. (2023). Exercise mobilizes diverse antigen specific T-cells and elevates neutralizing antibodies in humans with natural immunity to SARS CoV-2. *Brain Behav. Immun. Health.* 28, 100600. doi:10.1016/j.bbih.2023.100600

Barnes, P. J. (1998). Anti-inflammatory actions of glucocorticoids: Molecular mechanisms. *Clin. Sci. (Lond).* 94, 557–572. doi:10.1042/cs0940557

Barr-Anderson, D. J., Hazzard, V. M., Hahn, S. L., Folk, A. L., Wagner, B. E., and Neumark-Sztainer, D. (2021). Stay-at-Home orders during COVID-19: The influence on physical activity and recreational screen time change among diverse emerging adults and future implications for health promotion and the prevention of widening health disparities. *Int. J. Environ. Res. Public Health.* 18, 13228. doi:10.3390/ijerph182413228

Batatinha, H., Baker, F. L., Smith, K. A., Zúñiga, T. M., Pedlar, C. R., Burgess, S. C., et al. (2022). Recent COVID-19 vaccination has minimal effects on the physiological responses to graded exercise in physically active healthy people. *J. Appl. Physiol.* 132, 275–282. doi:10.1152/japplphysiol.00629.2021

Belge, K. U., Dayyani, F., Horelt, A., Siedlar, M., Frankenberger, M., Frankenberger, B., et al. (2002). The proinflammatory CD14$^+$CD16$^+$DR^{++} monocytes are a major source of TNF. *J. Immunol.* 168, 3536–3542. doi:10.4049/jimmunol.168.7.3536

Bendau, A., Plag, J., Petzold, M. B., and Ströhle, A. (2021). COVID-19 vaccine hesitancy and related fears and anxiety. *Int. Immunopharmacol.* 97, 107724. doi:10.1016/j.intimp.2021.107724

Bernard, C. (1879). *Leçons sur les phénomènes de la vie commune aux animaux et aux végétaux*, vol. 2. Paris, France. Baillière.

Bierhaus, A., Wolf, J., Andrassy, M., Rohleder, N., Humpert, P. M., Petrov, D., et al. (2003). A mechanism converting psychosocial stress into mononuclear cell activation. *Proc. Natl. Acad. Sci. U. S. A.* 100, 1920–1925. doi:10.1073/pnas.0438019100

Bories, G., Caiazzo, R., Derudas, B., Copin, C., Raverdy, V., Pigeyre, M., et al. (2012). Impaired alternative macrophage differentiation of peripheral blood mononuclear cells from obese subjects. *Diab. Vasc. Dis. Res.* 9, 189–195. doi:10.1177/1479164111430242

Cannon, W. B. (1914a). The emergency function of the adrenal medulla in pain and the major emotions. *Am. J. Physiol.-Legacy Content.* 33, 356–372. doi:10.1152/ajplegacy.1914.33.2.356

Cannon, W. B. (1914b). *The wisdom of the body*. New York, NY: W.W. Nortin & Company.

Carroll, D., Ginty, A. T., Der, G., Hunt, K., Benzeval, M., and Philips, A. C. (2012). Increased blood pressure reactions to acute mental stress are associated with 16-year cardiovascular disease mortality. *Psychophysiology* 49, 1444–1448. doi:10.1111/j.1469-8986.2012.01463.x

Chida, Y., and Steptoe, A. (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status a meta-analysis of prospective evidence. *Hypertension* 55, 1026–1032. doi:10.1161/HYPERTENSIONAHA.109.146621

Christensen, R. A. G., Arneja, J., Cyr, St.K., Sturrock, S. L., and Brooks, J. D. (2021). The association of estimated cardiorespiratory fitness with COVID-19 incidence and mortality: A cohort study. *PLoS One* 16, e0250508. doi:10.1371/journal.pone.0250508

Creese, B., Khan, Z., Henley, W., O'Dwyer, S., Corbett, A., Vasconcelos Da Silva, M., et al. (2021). Loneliness, physical activity, and mental health during COVID-19: A longitudinal analysis of depression and anxiety in adults over the age of 50 between 2015 and 2020. *Int. Psychogeriatr.* 33, 505–514. doi:10.1017/S1041610220004135

Dar, T., Radfar, A., Abohashem, S., Pitman, R. K., Tawakol, A., and Osborne, M. T. (2019). Psychosocial stress and cardiovascular disease. *Curr. Treat. Options Cardiovasc. Med.* 21, 23. doi:10.1007/s11936-019-0724-5

De Sousa, R. A. L., Improta-Caria, A. C., Aras-Júnior, R., de Oliveira, E. M., Soci, Ú. P. R., and Cassilhas, R. C. (2021). Physical exercise effects on the brain during COVID-19 pandemic: Links between mental and cardiovascular health. *Neurol. Sci.* 42, 1325–1334. doi:10.1007/s10072-021-05082-9

Dienstbier, R. A. (1989). Arousal and physiological toughness: Implications for mental and physical health. *Psychol. Rev.* 96, 84–100. doi:10.1037/0033-295x.96.1.84

Dimitrov, S., Lange, T., and Born, J. (2010). Selective mobilization of cytotoxic leukocytes by epinephrine. *J. Immunol.* 184, 503–511. doi:10.4049/jimmunol.0902189

Dimitrov, S., Shaikh, F., Pruitt, C., Green, M., Wilson, K., Beg, N., et al. (2013). Differential TNF production by monocyte subsets under physical stress: Blunted mobilization of proinflammatory monocytes in prehypertensive individuals. *Brain Behav. Immun.* 27, 101–108. doi:10.1016/j.bbi.2012.10.003

Dong, F., Liu, H. L., Dai, N., Yang, M., and Liu, J. P. (2021). A living systematic review of the psychological problems in people suffering from COVID-19. *J. Affect. Disord.* 292, 172–188. doi:10.1016/j.jad.2021.05.060

Droste, S. K., de Groote, L., Atkinson, H. C., Lightman, S. L., Reul, J. M., and Linthorst, A. C. (2008). Corticosterone levels in the brain show a distinct ultradian rhythm but a delayed response to forced swim stress. *Endocrinology* 149, 3244–3253. doi:10.1210/en.2008-0103

Duclos, M., Gouarne, C., and Bonnemaison, D. (2003). Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. *J. Appl. Physiol.* 94, 869–875. doi:10.1152/japplphysiol.00108.2002

Euteneuer, F., Mills, P. J., Rief, W., Ziegler, M. G., and Dimsdale, J. E. (2012). Association of *in vivo* β-adrenergic receptor sensitivity with inflammatory markers in healthy subjects. *Psychosom. Med.* 74, 271–277. doi:10.1097/PSY.0b013e318245d762

Fallon, K. (2020). Exercise in the time of COVID-19. *Aust. J. Gen. Pract.* 49. doi:10.31128/AJGP-COVID-13

Fauvel, J. P., Quelin, P., Ducher, M., Rakotomalala, H., and Laville, M. (2001). Perceived job stress but not individual cardiovascular reactivity to stress is related to higher blood pressure at work. *Hypertension* 38, 71–75. doi:10.1161/01.hyp.38.1.71

Fava, G. A., McEwen, B. S., Guidi, J., Gostoli, S., Offidani, E., and Sonino, N. (2019). Clinical characterization of allostatic overload. *Psychoneuroendocrinology* 108, 94–101. doi:10.1016/j.psyneuen.2019.05.028

Felix, A. S., Nolan, T. S., Glover, L. M., Sims, M., Addison, D., Smith, S. A., et al. (2022). The modifying role of resilience on allostatic load and cardiovascular disease risk in the jackson heart study. *J. Racial Ethn. Health Disparities* 22. doi:10.1007/s40615-022-01392-6

Frankenberger, M., Sternsdorf, T., Pechumer, H., Pforte, A., and Ziegler-Heitbrock, H. W. (1996). Differential cytokine expression in human blood monocyte subpopulations: A polymerase chain reaction analysis. *Blood* 87, 373–377. doi:10.1182/blood.v87.1.373.bloodjournal871373

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., et al. (2019). Chronic inflammation in the etiology of disease across the life span. *Nat. Med.* 25, 1822–1832. doi:10.1038/s41591-019-0675-0

Gagner, J-P., and Drouin, J. (1985). Opposite regulation of proopiomelanocortin gene transcription by glucocorticoids and CRH. *Mol. Cell. Endocrinol.* 40, 25–32. doi:10.1016/0303-7207(85)90154-6

Gleeson, M., Bishop, N. C., Stensel, D. J., Lindley, M. R., Mastana, S. S., and Nimmo, M. A. (2011). The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. *Nat. Rev. Immunol.* 11, 607–615. doi:10.1038/nri3041

Hagberg, J. M., Hickson, R. C., McLane, J. A., Ehsani, A. A., and Winder, W. W. (1979). Disappearance of norepinephrine from the circulation following strenuous exercise. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.* 47, 1311–1314. doi:10.1152/jappl.1979.47.6.1311

Hailman, E., Lichenstein, H. S., Wurfel, M. M., Miller, D. S., Johnson, D. A., Kelley, M., et al. (1994). Lipopolysaccharide (LPS)-binding protein accelerates the binding of LPS to CD14. *J. Exp. Med.* 179, 269–277. doi:10.1084/jem.179.1.269

Hallam, J., Jones, T., Alley, J., and Kohut, M. L. (2022). Exercise after influenza or COVID-19 vaccination increases serum antibody without an increase in side effects. *Brain Behav. Immun.* 102, 1–10. doi:10.1016/j.bbi.2022.02.005

Hamer, M. (2012). Psychosocial stress and cardiovascular disease risk: The role of physical activity. *Psychosom. Med.* 74, 896–903. doi:10.1097/PSY.0b013e31827457f4

Hamer, M., and Steptoe, A. (2007). Association between physical fitness, parasympathetic control, and proinflammatory responses to mental stress. *Psychosom. Med.* 69, 660–666. doi:10.1097/PSY.0b013e318148c4c0

Hasson, R., Sallis, J. F., Coleman, N., Kaushal, N., Nocera, V. G., and Keith, N. (2022). COVID-19: Implications for physical activity, health disparities, and health equity. *Am. J. Lifestyle Med.* 16, 420–433. doi:10.1177/15598276211029222

Heijnen, C. J., Rouppe van der Voort, C., Wulffraat, N., van der Net, J., Kuis, W., and Kavelaars, A. (1996). Functional alpha 1-adrenergic receptors on leukocytes of patients with polyarticular juvenile rheumatoid arthritis. *J. Neuroimmunol.* 71, 223–226. doi:10.1016/s0165-5728(96)00125-7

Hinterdobler, J., Schott, S., Jin, H., Meesmann, A., Steinsiek, A. L., Zimmermann, A. S., et al. (2021a). Acute mental stress drives vascular inflammation and promotes plaque destabilization in mouse atherosclerosis. *Eur. Heart J.* 42, 4077–4088. doi:10.1093/eurheartj/ehab371

Hinterdobler, J., Schunkert, H., Kessler, T., and Sager, H. B. (2021b). Impact of acute and chronic psychosocial stress on vascular inflammation. *Antioxid. Redox Signal.* 35, 1531–1550. doi:10.1089/ars.2021.0153

Hinton, J. W., Rotheiler, E. A., Gemmell, M., and Shewan, D. (1991). Heart rate, anxiety, anger, and arousal reactions to enforced time-wasting: Dependence on reactive uncontrol, work involvement, and dominance factors of 'type A. *Int. J. Psychophysiol.* 11, 115–124. doi:10.1016/0167-8760(91)90003-g

Hong, S., Dimitrov, S., Cheng, T., Redwine, L., Pruitt, C., Mills, P. J., et al. (2015). Beta-adrenergic receptor mediated inflammation control by monocytes is associated with blood pressure and risk factors for cardiovascular disease. *Brain Behav. Immun.* 50, 31–38. doi:10.1016/j.bbi.2015.08.012

Hong, S., Dimitrov, S., Pruitt, C., Shaikh, F., and Beg, N. (2014). Benefit of physical fitness against inflammation in obesity: Role of beta-adrenergic receptors. *Brain Behav. Immun.* 39, 113–120. doi:10.1016/j.bbi.2013.12.009

Huang, C-J., McAllister, M. J., and Slusher, A. L. (2017). *The roles of psychological stress, physical activity, and dietary modifications on cardiovascular health implications.* Oxford Research Encyclopeadia of Psychology.

Iwata, M., Ota, K. T., Li, X. Y., Sakaue, F., Li, N., Dutheil, S., et al. (2016). Psychological stress activates the inflammasome via release of adenosine triphosphate and stimulation of the purinergic type 2X7 receptor. *Biol. Psychiatry* 80, 12–22. doi:10.1016/j.biopsych.2015.11.026

Jimeno-Almazán, A., Martínez-Cava, A., Buendía-Romero, Á., Franco-López, F., Sánchez-Agar, J. A., Sánchez-Alcaraz, B. J., et al. (2022). Correction to: Relationship between the severity of persistent symptoms, physical fitness, and cardiopulmonary function in post-COVID-19 condition. A population-based analysis. *Intern. Emerg. Med.* 17, 2199–2208. doi:10.1007/s11739-022-03089-4

Juster, R. P., McEwen, B. S., and Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci. Biobehav. Rev.* 35, 2–16. doi:10.1016/j.neubiorev.2009.10.002

Karemaker, J. M. (2017). An introduction into autonomic nervous function. *Physiol. Meas.* 38, R89–R118. doi:10.1088/1361-6579/aa6782

Kaufmann, F. N., Costa, A. P., Ghisleni, G., Diaz, A. P., Rodrigues, A. L. S., Peluffo, H., et al. (2017). NLRP3 inflammasome-driven pathways in depression: Clinical and preclinical findings. *Brain Behav. Immun.* 64, 367–383. doi:10.1016/j.bbi.2017.03.002

Khakroo Abkenar, I., Rahmani-Nia, F., and Lombardi, G. (2019). The effects of acute and chronic aerobic activity on the signaling pathway of the inflammasome NLRP3 complex in young men. *Med. Kaunas.* 55, 105. doi:10.3390/medicina55040105

Killgore, W. D. S., Cloonan, S. A., Taylor, E. C., Miller, M. A., and Dailey, N. S. (2020). Three months of loneliness during the COVID-19 lockdown. *Psychiatry Res.* 293, 113392. doi:10.1016/j.psychres.2020.113392

Kim, D., and Kim, J. Y. (2014). Anti-CD14 antibody reduces LPS responsiveness via TLR4 internalization in human monocytes. *Mol. Immunol.* 57, 210–215. doi:10.1016/j.molimm.2013.09.009

Kivimäki, M., and Steptoe, A. (2018). Effects of stress on the development and progression of cardiovascular disease. *Nat. Rev. Cardiol.* 15, 215–229. doi:10.1038/nrcardio.2017.189

Kizaki, T., Izawa, T., Sakurai, T., Haga, S., Taniguchi, N., Tajiri, H., et al. (2008). Beta2-adrenergic receptor regulates Toll-like receptor-4-induced nuclear factor-kappaB activation through beta-arrestin 2. *Immunology* 124, 348–356. doi:10.1111/j.1365-2567.2007.02781.x

Kohut, M. L., Arntson, B. A., Lee, W., Rozeboom, K., Yoon, K. J., Cunnick, J. E., et al. (2004). Moderate exercise improves antibody response to influenza immunization in older adults. *Vaccine* 22, 2298–2306. doi:10.1016/j.vaccine.2003.11.023

Kuebler, U., Zuccarella-Hackl, C., Arpagaus, A., Wolf, J. M., Farahmand, F., von Känel, R., et al. (2015). Stress-induced modulation of NF-κB activation, inflammation-associated gene expression, and cytokine levels in blood of healthy men. *Brain Behav. Immun.* 46, 87–95. doi:10.1016/j.bbi.2014.12.024

LaBrosse, E. H., Mann, J. D., and Kety, S. S. (1961). The phsiological and psychological effects of intravenously administered epinephrine, and its metabolism, in normal and schizophrenic men. III. Metabolism of 7-H3-epinephrine as determined in studies on blood and urine. *J. Psychiatr. Res.* 1, 68–75. doi:10.1016/0022-3956(61)90007-3

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

Lazarus, R. S. (1974). Psychological stress and coping in adaptation and illness. *Int. J. Psychiatry Med.* 5, 321–333. doi:10.2190/T43T-84P3-QDUR-7RTP

Ledo, A., Schub, D., Ziller, C., Enders, M., Stenger, T., Gärtner, B. C., et al. (2020). Elite athletes on regular training show more pronounced induction of vaccine-specific T-cells

and antibodies after tetravalent influenza vaccination than controls. *Brain Behav. Immun.* 83, 135–145. doi:10.1016/j.bbi.2019.09.024

Levine, G. N., Cohen, B. E., Commodore-Mensah, Y., Fleury, J., Huffman, J. C., Khalid, U., et al. (2021). Psychological health, well-being, and the mind-heart-body connection: A scientific statement from the American heart association. *Circulation* 143, e763–e783. doi:10.1161/CIR.0000000000000947

López-Bueno, R., Calatayud, J., Ezzatvar, Y., Casajús, J. A., Smith, L., Andersen, L. L., et al. (2020). Association between current physical activity and current perceived anxiety and mood in the initial phase of COVID-19 confinement. *Front. Psychiatry* 11, 729. doi:10.3389/fpsyt.2020.00729

Macarthur, H., Wilken, G. H., Westfall, T. C., and Kolo, L. L. (2011). Neuronal and non-neuronal modulation of sympathetic neurovascular transmission. *Acta. Physiol. (Oxf).* 203, 37–45. doi:10.1111/j.1748-1716.2010.02242.x

Marashi, M. Y., Nicholson, E., Ogrodnik, M., Fenesi, B., and Heisz, J. J. (2021). A mental health paradox: Mental health was both a motivator and barrier to physical activity during the COVID-19 pandemic. *PLoS One* 16, e0239244. doi:10.1371/journal.pone.0239244

Marsland, A. L., Walsh, C., Lockwood, K., and John-Henderson, N. A. (2017). The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis. *Brain Behav. Immun.* 64, 208–219. doi:10.1016/j.bbi.2017.01.011

Mauersberger, C., Hinterdobler, J., Schunkert, H., Kessler, T., and Sager, H. B. (2022). Where the action is-leukocyte recruitment in atherosclerosis. *Front. Cardiovasc. Med.* 11, 813984. doi:10.3389/fcvm.2021.813984

Maydych, V., Claus, M., Dychus, N., Ebel, M., Damaschke, J., Diestel, S., et al. (2017). Impact of chronic and acute academic stress on lymphocyte subsets and monocyte function. *PLoS ONE* 12, e0188108. doi:10.1371/journal.pone.0188108

McEwen, B. S. (2000). Allostasis and allostatic load: Implications for neuropsychopharmacology. *Neuropsychopharmacology* 22, 108–124. doi:10.1016/S0893-133X(99)00129-3

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiol. Rev.* 87, 873–904. doi:10.1152/physrev.00041.2006

McEwen, B. S., and Stellar, E. (1993). Stress and the individual. Mechanisms leading to disease. *Arch. Intern. Med.* 153, 2093–2101. doi:10.1001/archinte.153.18.2093

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Ann. N. Y. Acad. Sci.* 840, 33–44. doi:10.1111/j.1749-6632.1998.tb09546.x

McKay, L. I., and Cidlowski, J. A. (1999). Molecular control of immune/inflammatory responses: Interactions between nuclear factor-kappa B and steroid receptor-signaling pathways. *Endocr. Rev.* 20, 435–459. doi:10.1210/edrv.20.4.0375

Meira, C. M., Jr., Meneguelli, K. S., Leopoldo, M. P. G., and Florindo, A. A. (2020). Anxiety and leisure-domain physical activity frequency, duration, and intensity during covid-19 pandemic. *Front. Psychol.* 11, 603770. doi:10.3389/fpsyg.2020.603770

Merino, A., Buendia, P., Martin-Malo, A., Aljama, P., Ramirez, R., and Carracedo, J. (2011). Senescent CD14$^+$CD16$^+$ monocytes exhibit proinflammatory and proatherosclerotic activity. *J. Immunol.* 186, 1809–1815. doi:10.4049/jimmunol.1001866

Meyer, J., McDowell, C., Lansing, J., Brower, C., Smith, L., Tully, M., et al. (2020). Changes in physical activity and sedentary behavior in response to COVID-19 and their associations with mental health in 3052 US adults. *Int. J. Environ. Res. Public Health* 17, 6469. doi:10.3390/ijerph17186469

Miller, G. E., Chen, E., Sze, J., Marin, T., Arevalo, J. M., Doll, R., et al. (2008). A functional genomic fingerprint of chronic stress in humans: Blunted glucocorticoid and increased NF-kappaB signaling. *Biol. Psychiatry* 64, 266–272. doi:10.1016/j.biopsych.2008.03.017

Mischler, K., Fischer, J. E., Zgraggen, L., Kudielka, B. M., Preckel, D., and von Känel, R. (2005). The effect of repeated acute mental stress on habituation and recovery responses in hemoconcentration and blood cells in healthy men. *Life Sci.* 77, 1166–1179. doi:10.1016/j.lfs.2005.03.006

Moore, S. A., Faulkner, G., Rhodes, R. E., Brussoni, M., Chulak-Bozzer, T., Ferguson, L. J., et al. (2020). Impact of the COVID-19 virus outbreak on movement and play behaviours of Canadian children and youth: A national survey. *Int. J. Behav. Nutr. Phys. Act.* 17, 85. doi:10.1186/s12966-020-00987-8

Mücke, M., Ludyga, S., College, F., and Gerber, M. (2018). Influence of regular physical activity and fitness on stress reactivity as measured with the trier social stress test protocol: A systematic review. *Sports Med.* 48, 2607–2622. doi:10.1007/s40279-018-0979-0

Nelson, K. M., Reiber, G., Kohler, T., and Boyko, E. J. (2007). Peripheral arterial disease in a multiethnic national sample: The role of conventional risk factors and allostatic load. *Ethn. Dis.* 17, 669–675.

Nieman, D. C. (2020). Coronavirus disease-2019: A tocsin to our aging, unfit, corpulent, and immunodeficient society. *J. Sport Health Sci.* 9, 293–301. doi:10.1016/j.jshs.2020.05.001

Nieman, D. C., and Sakaguchi, C. A. (2022). Physical activity lowers the risk for acute respiratory infections: Time for recognition. *J. Sport Health Sci.* 11, 648–655. doi:10.1016/j.jshs.2022.08.002

Okonkwo, N. E., Aguwa, U. T., Jang, M., Barré, I. A., Page, K. R., Sullivan, P. S., et al. (2020). COVID-19 and the US response: Accelerating health inequities. *B.M.J. Evid. Based Med.* 26, 176–179. doi:10.1136/bmjebm-2020-111426

Osborne, M. T., Shin, L. M., Mehta, N. N., Pitman, R. K., Fayad, Z. A., and Tawakol, A. (2020). Disentangling the links between psychosocial stress and cardiovascular disease. *Circ. Cardiovasc. Imaging13* 13, e010931. doi:10.1161/CIRCIMAGING.120.010931

Papava, I., Dehelean, L., Romosan, R. S., Bondrescu, M., Dimeny, C. Z., Domuta, E. M., et al. (2022). The impact of hyper-acute inflammatory response on stress adaptation and psychological symptoms of COVID-19 patients. *Int. J. Environ. Res. Public Health* 19, 6501. doi:10.3390/ijerph19116501

Parekh, N., Ali, S. H., O'Connor, J., Tozan, Y., Jones, A. M., Capasso, A., et al. (2021). Food insecurity among households with children during the COVID-19 pandemic: Results from a study among social media users across the United States. *Nutr. J.* 20, 73. doi:10.1186/s12937-021-00732-2

Parker, H. W., Abreu, A. M., Sullivan, M. C., and Vadiveloo, M. K. (2022). Allostatic load and mortality: A systematic review and meta-analysis. *Am. J. Prev. Med.* 63, 131–140. doi:10.1016/j.amepre.2022.02.003

Pascoe, A. R., Fiatarone Singh, M. A., and Edwards, K. M. (2014). The effects of exercise on vaccination responses: A review of chronic and acute exercise interventions in humans. *Brain Behav. Immun.* 39, 33–41. doi:10.1016/j.bbi.2013.10.003

Passlick, B., Flieger, D., and Ziegler-Heitbrock, H. W. (1989). Identification and characterization of a novel monocyte subpopulation in human peripheral blood. *Blood* 74, 2527–2534. doi:10.1182/blood.v74.7.2527.bloodjournal7472527

Pedersen, B. K. (2017). Anti-inflammatory effects of exercise: Role in diabetes and cardiovascular disease. *Eur. J. Clin. Invest.* 47, 600–611. doi:10.1111/eci.12781

Peters, M. L., Godaert, G. L., Ballieux, R. E., van Vliet, M., Willemsen, J. J., Sweep, F. C., et al. (1998). Cardiovascular and endocrine responses to experimental stress: Effects of mental effort and controllability. *Psychoneuroendocrinology* 23, 1–17. doi:10.1016/s0306-4530(97)00082-6

Pike, J. L., Smith, T. L., Hauger, R. L., Nicassio, P. M., Patterson, T. L., McClintick, J., et al. (1997). Chronic life stress alters sympathetic, neuroendocrine, and immune responsivity to an acute psychological stressor in humans. *Psychosom. Med.* 59, 447–457. doi:10.1097/00006842-199707000-00015

Prata, L. O., Rodrigues, C. R., Martins, J. M., Vasconcelos, P. C., Oliveira, F. M., Ferreira, A. J., et al. (2017). Original research: ACE2 activator associated with physical exercise potentiates the reduction of pulmonary fibrosis. *Exp. Biol. Med. (Maywood).* 242, 8–21. doi:10.1177/1535370216665174

Redwine, L., Mills, P. J., Sada, M., Dimsdale, J., Patterson, T., and Grant, I. (2004). Differential immune cell chemotaxis responses to acute psychological stress in Alzheimer caregivers compared to non-caregiver controls. *Psychosom. Med.* 66, 770–775. doi:10.1097/01.psy.0000138118.62018.87

Redwine, L., Snow, S., Mills, P., and Irwin, M. (2003). Acute psychological stress: Effects on chemotaxis and cellular adhesion molecule expression. *Psychosom. Med.* 65, 598–603. doi:10.1097/01.psy.0000079377.86193.a8

Rodriguez, J. M., Monsalves-Alvarez, M., Henriquez, S., Llanos, M. N., and Troncoso, R. (2016). Glucocorticoid resistance in chronic diseases. *Steroids* 115, 182–192. doi:10.1016/j.steroids.2016.09.010

Rouppe van der Voort, C., Kavelaars, A., van de Pol, M., and Heijnen, C. J. (1999). Neuroendocrine mediators up-regulate alpha1b- and alpha1d-adrenergic receptor subtypes in human monocytes. *J. Neuroimmunol.* 95, 165–173. doi:10.1016/s0165-5728(99)00011-9

Rouppe van der Voort, C., Kavelaars, A., van de Pol, M., and Heijnen, C. J. (2000). Noradrenaline induces phosphorylation of ERK-2 in human peripheral blood mononuclear cells after induction of alpha(1)-adrenergic receptors. *J. Neuroimmunol.* 108, 82–91. doi:10.1016/s0165-5728(00)00253-8

Salari, N., Hosseinian-Far, A., Jalali, R., Vaisi-Raygani, A., Rasoulpoor, S., Mohammadi, M., et al. (2020). Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: A systematic review and meta-analysis. *Glob. Health* 16, 57. doi:10.1186/s12992-020-00589-w

Sallis, R., Young, D. R., Tartof, S. Y., Sallis, J. F., Sall, J., Li, Q., et al. (2021). Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: A study in 48 440 adult patients. *Br. J. Sports Med.* 55, 1099–1105. doi:10.1136/bjsports-2021-104080

Sapolsky, R. M., Romero, L. M., and Munch, A. U. (2000). How do glucocorticoids influence stress response? Integrating permissive, suppressive, stimulatory, and preparative actions 1. *Endocr. Rev.* 21, 55–89. doi:10.1210/edrv.21.1.0389

Schnorpfeil, P., Noll, A., Schulze, R., Ehlert, U., Frey, K., and Fischer, J. E. (2003). Allostatic load and work conditions. *Soc. Sci. Med.* 57, 647–656. doi:10.1016/s0277-9536(02)00407-0

Schommer, N. C., Hellhammer, D. H., and Kirschbaum, C. (2003). Dissociation between reactivity of the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medullary system to repeated psychosocial stress. *Psychosom. Med.* 65, 450–460. doi:10.1097/01.psy.0000035721.12441.17

Seeman, T. E., McEwen, B. S., Rowe, J. W., and Singer, B. H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc. Natl. Acad. Sci. U. S. A.* 98, 4770–4775. doi:10.1073/pnas.081072698

Seeman, T., Epel, E., Gruenewald, T., Karlamangla, A., and McEwen, B. S. (2010). Socio-economic differentials in peripheral biology: Cumulative allostatic load. *Ann. N. Y. Acad. Sci.* 1186, 223–239. doi:10.1111/j.1749-6632.2009.05341.x

Selye, H. (1936). A syndrome produced by diverse nocuous agents. *Nature* 138, 32. doi:10.1038/138032a0

Selye, H. (1973). Homeostasis and heterostasis. *Perspect. Biol. Med.* 16, 441–445. doi:10.1353/pbm.1973.0056

Selye, H. (1975). Stress and distress. *Compr. Ther.* 1, 9–13.

Selye, H. (1950). Stress and the general adaptation syndrome. *Br. Med. J.* 1, 1383–1392. doi:10.1136/bmj.1.4667.1383

Selye, H. (1974). *Stress without distress*. Philadelphia, PA: J. B. Lippincott.

Shalova, I. N., Kajiji, T., Lim, J. Y., Gómez-Piña, V., Fernández-Ruíz, I., Arnalich, F., et al. (2012). CD16 regulates TRIF-dependent TLR4 response in human monocytes and their subsets. *J. Immunol.* 188, 3584–3593. doi:10.4049/jimmunol.1100244

Silvestre-Roig, C., Braster, Q., Ortega-Gomez, A., and Soehnlein, O. (2020). Neutrophils as regulators of cardiovascular inflammation. *Nat. Rev. Cardiol.* 17, 327–340. doi:10.1038/s41569-019-0326-7

Simpson, R. J., Boßlau, T. K., Weyh, C., Niemiro, G. M., Batatinha, H., Smith, K. A., et al. (2021). Exercise and adrenergic regulation of immunity. *Brain Behav. Immun.* 97, 303–318. doi:10.1016/j.bbi.2021.07.010

Simpson, R. J., Campbell, J. P., Gleeson, M., Krüger, K., Nieman, D. C., Pyne, D. B., et al. (2020). Can exercise affect immune function to increase susceptibility to infection? *Exerc. Immunol. Rev.* 26, 8–22.

Slavich, G. M. (2020). "Psychoneuroimmunology of stress and mental health," in *The Oxford handbook of stress and mental health*. Editors K. Harkness and E. P. Hayden (New York: Oxford University Press).

Slusher, A. L., Zúñiga, T. M., and Acevedo, E. O. (2019). Inflamm-aging is associated with lower plasma PTX3 concentrations and an impaired capacity of PBMCs to express hTERT following LPS stimulation. *Mediat. Inflamm.* 2019, 2324193, doi:10.1155/2019/2324193

Slusher, A. L., Zúñiga, T. M., and Acevedo, E. O. (2018). Maximal exercise alters the inflammatory phenotype and response of mononuclear cells. *Med. Sci. Sports Exerc.* 50, 675–683. doi:10.1249/MSS.0000000000001480

Sothmann, M. S., Buckworth, J., Claytor, R. P., Cox, R. H., White-Welkley, J. E., and Dishman, R. K. (1996). Exercise training and the cross-stressor adaptation hypothesis. *Exerc. Sport Sci. Rev.* 24, 267–288. doi:10.1249/00003677-199600240-00011

Spencer, L. H., Lynch, M., Lawrence, C. L., and Edwards, R. T. (2020). A scoping review of how income affects accessing local green space to engage in outdoor physical activity to improve well-being: Implications for post-COVID-19. *Int. J. Environ. Res. Public Health.* 17, 9313. doi:10.3390/ijerph17249313

Stark, J. L., Avitsur, R., Padgett, D. A., Campbell, K. A., Beck, F. M., and Sheridan, J. F. (2001). Social stress induces glucocorticoid resistance in macrophages. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 280, R1799–R1805. doi:10.1152/ajpregu.2001.280.6.R1799

Steptoe, A., and Willemsen, G. (2004). The influence of low job control on ambulatory blood pressure and perceived stress over the working day in men and women from the Whitehall II cohort. *J. Hypertens.* 22, 915–920. doi:10.1097/00004872-200405000-00012

Sterling, P., and Eyer, J. (1988). "Allostasis: A new paradigm to explain arousal pathology," in *Handbook of life stress, cognition and health* (John Wiley & Sons), 629–649.

Suvarna, B., Suvarna, A., Phillips, R., Juster, R. P., McDermott, B., and Sarnyai, Z. (2020). Health risk behaviours and allostatic load: A systematic review. *Neurosci. Biobehav. Rev.* 108, 694–711. doi:10.1016/j.neubiorev.2019.12.020

Swirski, F. K., Weissleder, R., and Pittet, M. J. (2009). Heterogeneous *in vivo* behavior of monocyte subsets in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 29, 1424–1432. doi:10.1161/ATVBAHA.108.180521

Szabo, S., Tache, Y., and Somogyi, A. (2012). The legacy of Hans Selye and the origins of stress research: A retrospective 75 years after his landmark brief "letter" to the editor# of nature. *Stress* 15, 472–478. doi:10.3109/10253890.2012.710919

Tan, M., Mamun, A., Kitzman, H., Mandapati, S. R., and Dodgen, L. (2017). Neighborhood disadvantage and allostatic load in african American women at risk for obesity-related diseases. *Prev. Chronic Dis.* 14, E119. doi:10.5888/pcd14.170143

Tawakol, A., Ishai, A., Takx, R. A., Figueroa, A. L., Ali, A., Kaiser, Y., et al. (2017). Relation between resting amygdalar activity and cardiovascular events: A longitudinal and cohort study. *Lancet* 389, 834–845. doi:10.1016/S0140-6736(16)31714-7

Timmerman, K. L., Flynn, M. G., Coen, P. M., Markofski, M. M., and Pence, B. D. (2008). Exercise training-induced lowering of inflammatory (CD14$^+$CD16$^+$) monocytes: A role in the anti-inflammatory influence of exercise? *J. Leukoc. Biol.* 84, 1271–1278. doi:10.1189/jlb.0408244

Tison, G. H., Avram, R., Kuhar, P., Abreau, S., Marcus, G. M., Pletcher, M. J., et al. (2020). Worldwide effect of COVID-19 on physical activity: A descriptive study. *Ann. Intern. Med.* 173, 767–770. doi:10.7326/M20-2665

Tuczyńska, M., Matthews-Kozanecka, M., and Baum, E. (2021). Accessibility to non-COVID health services in the world during the COVID-19 pandemic: Review. *Front. Public Health* 9, 760795. doi:10.3389/fpubh.2021.760795

Turner, A. I., Smyth, N., Hall, S. J., Torres, S. J., Hussein, M., Jayasinghe, S. U., et al. (2020). Psychological stress reactivity and future health and disease outcomes: A systematic review of prospective evidence. *Psychoneuroendocrinology* 114, 104599. doi:10.1016/j.psyneuen.2020.104599

Ulrich-Lai, Y. M., and Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nat. Rev. Neurosci.* 10, 397–409. doi:10.1038/nrn2647

van Eck, M., Berkhof, H., Nicolson, N., and Sulon, J. (1996). The effects of perceived stress, traits, mood states, and stressful daily events on salivary cortisol. *Psychosom. Med.* 58, 447–458. doi:10.1097/00006842-199609000-00007

Völker, B. (2023). Networks in lockdown: The consequences of COVID-19 for social relationships and feelings of loneliness. *Soc. Netw.* 72, 1–12. doi:10.1016/j.socnet.2022.08.001

Wang, W., Xu, M., Zhang, Y. Y., and He, B. (2009). Fenoterol, a beta(2)-adrenoceptor agonist, inhibits LPS-induced membrane-bound CD14, TLR4/CD14 complex, and inflammatory cytokines production through beta-arrestin-2 in THP-1 cell line. *Acta Pharmacol. Sin.* 30, 1522–1528. doi:10.1038/aps.2009.153

Weinstein, A. A., Deuster, P. A., Francis, J. L., Bonsall, R. W., Tracy, R. P., and Kop, W. J. (2010). Neurohormonal and inflammatory hyper-responsiveness to acute mental stress in depression. *Biol. Psychol.* 84, 228–234. doi:10.1016/j.biopsycho.2010.01.016

Weitzman, E. D., Fukushima, D., Nogeire, C., Roffwarg, H., Gallagher, T. F., and Hellman, L. (1971). Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J. Clin. Endocrinol. Metab.* 33, 14–22. doi:10.1210/jcem-33-1-14

Wilbert-Lampen, U., Leistner, D., Greven, S., Pohl, T., Sper, S., Völker, C., et al. (2008). Cardiovascular events during world cup soccer. *N. Engl. J. Med.* 358, 475–483. doi:10.1056/NEJMoa0707427

Wolf, S., Seiffer, B., Zeibig, J. M., Welkerling, J., Brokmeier, L., Atrott, B., et al. (2021). Is physical activity associated with less depression and anxiety during the COVID-19 pandemic? A rapid systematic review. *Sports Med.* 51, 1771–1783. doi:10.1007/s40279-021-01468-z

Wright, S. D., Ramos, R. A., Tobias, P. S., Ulevitch, R. J., and Mathison, J. C. (1990). CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. *Science* 249, 1431–1433. doi:10.1126/science.1698311

Wu, L., Zhou, C., Wu, J., Chen, S., Tian, Z., and Du, Q. (2020). Corticosterone inhibits LPS-induced NLRP3 inflammasome priming in macrophages by suppressing xanthine oxidase. *Mediat. Inflamm.* 18, 6959741. doi:10.1155/2020/6959741

Zbinden-Foncea, H., Francaux, M., Deldicque, L., and Hawley, J. A. (2020). Does high cardiorespiratory fitness confer some protection against proinflammatory responses after infection by SARS-CoV-2? *Obes. (Silver Spring)* 28, 1378–1381. doi:10.1002/oby.22849