# Worried Sick: Understanding the Implications of Stress on a Physiological Level

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**Abstract**

Stress is prevalent among many individuals in today's society. A literature review was conducted to investigate the physiological effects of stress, including the biomarkers of stress and how these interact with various body systems. The stress response is a protective mechanism to prepare the body to adequately respond to a perceived threat. However, when this response is prolonged, it begins to have a maladaptive effect on the body and can cause more harm than good. This literature review sought to compile what is known regarding the general effects of chronic stress and its impact on the nervous, immune, digestive, and cardiovascular systems.

**Worried Sick: Understanding the Implications of Stress on a Physiological Level**

The last two decades have seen an increase in the prevalence of chronic stress (stress). A comparison of adults between the ages of 25 and 64 years in the U.S. showed a 40% increase in psychological distress from 1999-2000 to 2017-2018 (Daly, 2022). This is likely due to a combination of work and non-work-related stressors. Specifically, concerns about disease, social support, and general work situations contribute most drastically to levels of perceived stress (Sørensen, Lasgaard, Willert, & Larsen, 2021). Although the word "stress" can be an ambiguous term, in this work, it will be defined as any objective or perceived occurrence that is associated with negative effects for the individual experiencing it (Cohen, Miller, & Rabin, 2001). "Stress" and "distress" will be used interchangeably, as an analysis has shown their definitions to be indistinguishable (Bienertova-Vasku, Lenart, & Scheringer, 2020).

One concern regarding chronic stress on already increasing prevalence is the COVID-19 pandemic of 2020. Lockdowns and social isolation, loss of job security, and general fear surrounding the pandemic are just some of the variables that had potential to negatively affect individuals' mental health. While there was an initial spike of perceived stress, many studies indicate that after the first wave of the pandemic, stress levels approached baseline again (LaCaille, Hooker, Marshall, LaCaille, & Owens, 2021; Riehm et al., 2021; Twenge & Joiner, 2020). Compared to 2018 statistics, eight times as many adults in April 2020 fit criteria for experiencing serious mental distress, and three times as many fit criteria for experiencing moderate or serious distress (Twenge & Joiner, 2020). This data was significant across all demographics, and it was found that in April 2020 one in four adults fit criteria for serious mental distress and two out of three reported moderate or serious distress (Twenge & Joiner, 2020).

Despite the sharp rise in stress during the first wave of the pandemic, the stress levels correlate with that of other disasters: an initial increase in stress, followed by a decline until reaching normal or baseline levels (Riehm et al., 2021). A study compared reported levels of mental distress on March 11, 2020, marking the beginning of the pandemic, to that of the first of every month until August 2020 (Riehm et al., 2021). The odds of mental distress were almost twice as likely in April and May, but by August, the odds lowered to 0.80 times as likely to experience mental distress compared to March (Riehm et al., 2021). A study researching changes in perceived stress in first-year college students during the COVID-19 pandemic found increases in stress throughout the year but could not attribute the rise in stress to the pandemic, as the levels were consistent with previous research (LaCaille et al., 2021). These studies reinforce the fact that a rise in stress levels among the population is occurring despite the stress from the pandemic, not because of it.

**Inclusion and Exclusion Criteria**

Due to the prevalence of stress, a literature review was conducted to understand more about the physiological mechanisms and implications of stress under chronic conditions. In order to compile research, databases such a Science Direct, Academic Search Plus, MEDLINE Ultimate (EBSCO) and EBSCO Quick Search were used. Boolean searches were used with peer-reviewed and scholarly filters applied in most cases, with some supporting literature used for background information. Key words, such as stress and cortisol, were used in addition to specific organ systems to narrow the results. Organ systems were chosen based on the frequency in which they appeared in research relating to the effects that chronic stress poses on them. Both literary reviews and primary research were used to collect background information as well as supporting evidence through recent studies. Sources cited in research that was found as a result of a search

was also used to expand on summarized information. While the origin for this research topic was inspired in a college setting, no specific demographic parameters were used in the research, and both the mechanisms of stress and its chronic implications throughout this study apply to the general population. The aim of this paper is to explore some of the pathophysiology that can occur when stress is present for prolonged periods of time.

**The Stress Mechanism**

The stress response is an innate mechanism that is initiated when a threat is perceived. The stress response can be activated in two ways: the sympathetic adrenomedullary axis (SAM) or the hypothalamic-pituitary-adrenal (HPA) axis. The former is the first component of the stress response and activates the sympathetic branch of the autonomic nervous system (Becker & Rohleder, 2019). A perceived threat stimulates the amygdala and subsequently the hypothalamus, which triggers autonomic nervous system (ANS) activation and stimulates catecholamine release from the adrenal glands (O'Connor, Thayer, & Vedhara, 2021). Norepinephrine is released first to activate internal organs, followed by epinephrine which advances the preparation for a fight-or-flight response (O'Connor et al., 2021). This results in an increase in respiration rate, increased cardiac output with more frequent and forceful contractions, pupil dilation to allow more light in, and slowing of the gastrointestinal (GI) tract so more blood can be allocated to muscles (O'Connor et al., 2021)

The primary way in which the stress response is stimulated and maintained, however, is through the second step of initiation via the HPA axis. Upon receiving stimuli that can be perceived as a stressor or threat, the neurons carrying this excitatory input converge in the hypothalamic paraventricular nucleus in the brain (Cranston, 2014). The amygdala stimulates the paraventricular nucleus in response to stress, which then produces corticotrophin-releasing

hormone (CRH). CRH is released into the hypophyseal portal where it stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH reaches the adrenal cortex of the adrenal glands via the bloodstream and cortisol is released as a result (Cranston, 2014).

Cortisol is the main glucocorticoid found in humans. It can bind to mineralcorticoid (MR) and glucocorticoid receptors (GR). Glucocorticoids can bind to GRs in the cytoplasm, which will then translocate to the nucleus and can alter the transcription of many metabolic, immune and inflammatory proteins (Zefferino, Di Gioia, & Conese, 2021). Cortisol is able to bind to these receptors because it can pass through the blood brain barrier. Once in the brain, it can bind to the MR in the hippocampus and prefrontal cortex or the GR that are found throughout the brain (Becker & Rohleder, 2019; Otte et al., 2015). Glucocorticoid binding can then result in anti-inflammatory effects such as apoptosis in immune cells such as monocytes, macrophages, and T cells (Amsterdam, Tajima, & Sasson, 2002; Zefferino et al., 2021). The role of cortisol in response to stress is to increase blood glucose levels by inducing production of glucose so the body is in a prime energy state to react to a threat (Stephens & Wand, 2012). This is accomplished by increasing access to energy stores through protein and fat mobilization and the release of glycogen in both the liver and muscle tissue. These compounds are metabolized to produce glucose that the brain and the muscles can use (O'Connor et al., 2021). When bound to a GR, cortisol can impact cardiovascular function, immune responses and inflammation, arousal, learning and memory (Stephens & Wand, 2012).

However, stress is not the only stimulus for cortisol secretion. Cortisol is naturally released in the body throughout the day as a part of normal function. The concentration fluctuates in a daily cycle known as the circadian rhythm. The circadian rhythm is regulated by a

pacemaker in the suprachiasmatic nucleus that activates the HPA axis so that cortisol levels are at their lowest around midnight, with its highest peak in the morning (Zefferino et al., 2021). This peak that occurs in the morning is known as the cortisol awakening response (CAR), where cortisol levels increase rapidly within 30 minutes of arousal and then drop to baseline levels (Duan et al., 2013; Pruessner et al., 1997).

In the normal physiological process, the initial response to stress is activation of the sympathetic nervous system, resulting in release of adrenaline and noradrenaline which can indirectly affect cognitive processing. A couple minutes following the initial onset of stress, the HPA axis is activated to release cortisol, which will directly affect neural pathways (Becker & Rohleder, 2019; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). This process is terminated by the release of cortisol inhibiting continued stimulation of the HPA axis. This negative feedback is accomplished by cortisol suppressing the hypothalamus, pituitary gland, hippocampus and medial prefrontal cortex to inhibit CRH release and therefore downregulate HPA axis activity (Cranston, 2014; Di, Malcher-Lopes, Halmos, & Tasker, 2003). This collective process occurs in the presence of acute-onset stress and is designed to be the body's adaptive response to these events (Noushad et al., 2021). This is known as allostasis, which can be defined as the protective mechanism that maintains homeostasis by stimulating the release of glucocorticoids, catecholamines, and cytokines (Zefferino et al., 2021). Any changes in allostasis in relation to the HPA axis can injure brain reward pathways, thus contributing to depressed moods and cravings (Stephens & Wand, 2012).

**Pathological Effects of Chronic Stress**

While the stress mechanism and release of cortisol is a beneficial aspect of human physiology in acute circumstances, chronic stress can become detrimental to overall health. This

is known as allostatic overload, in which too much of a good thing becomes a bad thing when it is no longer a necessary or adequate response and can induce damage by neuroendocrine mediators (McEwen, Bruce S., 2008; Zefferino et al., 2021). Chronic stress can be defined as a sustained sympathetic response to a stressor that is not corrected by the parasympathetic nervous system (PSNS), which translates to continued activation of the sympathetic response and the HPA axis (Sandrini, Ieraci, Amadio, Zarà, & Barbieri, 2020). The HPA axis plays a key role in the release of cortisol to maintain homeostasis; when this mechanism is activated for too long, the high levels of cortisol are not needed and can cause damage to the body.

### *Biomarkers of Chronic Stress and Influencing Factors*

As the final product of the stress response pathway, cortisol is the classic indicator of an activation of the stress response. The ANS is the means by which this process occurs. While the HPA axis dominates the stress response, the SAM axis also plays a role through direct stimulation of the adrenal medulla through the nervous system, rather than the hormones involved in the HPA axis. Since catecholamines such as epinephrine and norepinephrine are released in response to activation of the SAM axis, these molecules are significant biomarkers for ANS activity. Investigation of these biomarkers can reveal the prevalence of an individual's stress (Noushad et al., 2021).

Research has shown interactions between stress and the cortisol awakening response (CAR). In normal physiology, cortisol levels rise quickly in the 30 minutes following arousal, and then decrease to baseline levels an hour later (Duan et al., 2013; Pruessner et al., 1997). A higher CAR can be found in situations where more energy is needed to meet the demands of the day. Elevated CAR is commonly seen in prolonged stressful situations (Duan et al., 2013). However, a flattened CAR has also been noted in some instances of chronic stress (Duan et al.,

2013). This particular study used male students taking a competitive test for graduate school admission and males not taking the exam, which were studied one month before and after the test (Duan et al., 2013). Saliva samples were used, and participants' chronic stress levels were evaluated using the self-reported 10-item Perceived Stress Score (PSS) (Cohen & Williamson, 1988). PSS and self-reported anxiety levels found to be higher in the experimental exam group (Duan et al., 2013). The CAR of the exam group proved to be significantly lower than the control group and was most evident among individuals who had higher PSS scores, which is indicative of HPA axis down-regulation due to chronic stress (Duan et al., 2013). This could also be attributed to an overproduction of cortisol while sleeping among students with higher stress, as the exam group had higher waking cortisol levels. This can result from stress modifying the production of cortisol in late-stage sleep (Duan et al., 2013). It is also important to note that CAR has not been associated with amount of sleep or specific waking times, as it is primarily affected by stress and not sleep patterns (Duan et al., 2013).

Cortisol is able to inhibit glucocorticoid receptors in the hypothalamus and pituitary glands, as well as the mineralocorticoid receptors in the hippocampus via negative feedback. Hair cortisol concentration (HCC) is another way to measure cortisol levels in the body. Unlike the cortisol levels found in saliva which reflect changes throughout the day, HCC is not affected by daily fluctuations, or diurnal variations, but rather shows the average cortisol levels from the previous few months (Koumantarou Malisiova et al., 2021). One research study sought to measure HCC to discover whether it was associated with stress-related psychological components and if any differences in these factors occurred between men and women (Kim et al., 2021). It was demonstrated that this feedback loop is slower for women than for men (Kim et al., 2021). This finding was attributed to the fact that women have been shown to have fewer

glucocorticoid receptors in the brain than men (Bangasser, 2013). The study also showed that cortisol levels were affected by psychological elements such as depression, anxiety and emotion regulation (Kim et al., 2021). As the participants were all young adults between the ages of eighteen and thirty years old, the researchers controlled for age, education level, and stress-related psychological factors (Kim et al., 2021). Given these controls, the only significant findings were that only emotion dysregulation was affiliated with HCC, and that this connection was only observed in women (Kim et al., 2021).

Garcia-Leon et al., 2018 conducted a study among healthy adults in the Spanish population and tested the relationship between HCC and age, education, employment status, exercise, hair dye, and the use of contraceptives (Garcia-Leon et al., 2018). It was concluded that there were no statistical differences between men and women among the factors being assessed, excluding the use of contraceptives that was specific to females (Garcia-Leon et al., 2018). Higher HCC was also found in individuals who reported regular physical exercise, had higher education, and females who used hormonal contraceptives (Garcia-Leon et al., 2018). The authors note that these results differ from other studies on the use of hair dye as well as contraceptives, as the dosage and levels of estrogen can have different effects (Garcia-Leon et al., 2018).

As this research explores the implications of chronic stress, understanding biomarkers can play an important role in identifying stress as a causative agent of various pathologies. If significant elevations or depressions of CAR or high HCC are found, measures can be taken to decrease the chronic stress in order to treat the root of the issue. It is also important to note some factors that can influence these biomarkers independent of chronic stress to have a full understanding of the individual and their condition. As both CAR and HCC are only affected in

cases of chronic stress and do not change under acute stress, these parameters can be used in future medical practices to better treat conditions if stress is suspected to be the underlying issue of other diseases.

**Effects of Chronic Stress on the Brain**

Given that cortisol is involved in the neuroendocrine interactions of the body and HPA axis activation is integrated in the brain via amygdala and hypothalamus activation, it is likely that chronically elevated cortisol levels due to chronic stress will affect the brain and neurological processes (O'Connor et al., 2021).

The hippocampus is the primary region of the brain that is most responsible for memory. This includes the conversion of short-term memory to long-term memory. This region of the brain has the highest density of GR, and therefore is the most responsive to stress in the brain due to the high levels of glucocorticoid or more specifically, cortisol binding, stimulated from HPA axis activation (Scoville & Milner, 1957; Yaribeygi, Panahi, Sahraei, Johnston, & Sahebkar, 2017). The hippocampus experiences decreased neurogenesis in response to stress, which is caused by glucocorticosteroids affecting the cellular metabolism of neurons (Lawrence & Sapolsky, 1994; Yaribeygi et al., 2017). Increasing the sensitivity of the cells in the hippocampus to stimulatory amino acids or increasing the amount of extracellular glutamate can also account for the effect on neurogenesis (Sapolsky & Pulsinelli, 1985). Other structural and, as a result, functional changes, such as a decline in the number of dendritic branches and neurons and changes in the structure of synaptic terminals results of stress (McEwen, B. S., 1999). Because of the role of the hippocampus in memory storage, chronically elevated glucocorticosteroid levels can atrophy the region and cause memory disorders (Lupien & Lepage, 2001; Yaribeygi et al., 2017).

The hippocampus is also the location in the brain where cognitive learning takes place, whereas habit-based learning takes place in the dorsal striatum and the basolateral amygdala (Stephens & Wand, 2012). In response to the cortisol secreted during stress, memory retrieval can be blocked. In this instance, habit-based learning (as opposed to cognitive learning) that is promoted by cortisol secretion encourages consolidation of emotionally arousing information. Because of this pathway, cortisol can used be as a tool to predict predisposition to and management of addictions such as alcoholism (Stephens & Wand, 2012).

Chronic stress can also cause changes in the brain that are comparative to that of mental health disorders, such as anxiety and depression. The negative feedback that would occur from cortisol secretion to suppress HPA activation has been shown to be diminished during chronic stress (Cranston, 2014; Römer et al., 2009). Chronic stress can cause insufficient cortisol levels when acute stress is triggered. The HPA axis will be altered and not be able to be suppressed, and behavioral adaptation will become more and more inefficient. A correlation between cortisol levels and depression have been found. A decrease in the activity of cortisol-deactivating enzymes and an increase in cortisol are found in people who have clinical depression in comparison to healthy people (Cranston, 2014; Römer et al., 2009). High corticosterone levels found with chronic stress can increase CRH expression in the central amygdala with the shortening of dendrites in the prefrontal cortex and growth in that of the amygdala, which can play a role in anxiety-like behaviors (McEwen, 2008; Stephens & Wand, 2012).

One study by Nowacka-Chmielewska et al., 2022 studied the brains of female rats in response to western diet and chronic stress, both separately and together. The researchers found that chronic stress can lead to both physiological and neuroendocrine alterations that result in changes in food intake and appetite, as well as fat distribution. HPA axis dysregulation was

shown to be involved with obesity development (Adam & Epel, 2007; Nowacka-Chmielewska et al., 2022). CRH release from the stress response can also play a role in neurological pathologies such as Parkinson's and Alzheimer's—stress-induced CRH release causes mast cells to degranulate, and these granules can cross the blood-brain barrier and affect the brain (Atsushi Kanamori et al., 2022).

In order to study the effects of chronic stress on the brain, a global proteomic analysis was used (Nowacka-Chmielewska et al., 2022). After inducing chronic social instability in the female rats, protein expression was shown to be altered in the temporal cortex of these rats, where learning and memory processes take place in the rat (Nowacka-Chmielewska et al., 2022). While changes were observed with the chronic stress group, the researchers found a strong synergistic effect when inducing chronic stress and a western diet (Nowacka-Chmielewska et al., 2022). 27 proteins with the chronic stress group and 30 proteins in the western diet/chronic stress group were found to be down-regulated, including synaptic, mitochondrial, regulatory, metabolic, transport, and signaling proteins (Nowacka-Chmielewska et al., 2022). These are involved in neurotransmitter secretion, learning and memory, neurogenesis, and synaptic transmission in the temporal complex (Nowacka-Chmielewska et al., 2022). These findings are relevant in American culture as the typical diet often follows the western diet and consists of high calorie and processed foods, with a high proportion of carbohydrates and fats. With evidence that a western diet can exacerbate the negative effects of stress, making lifestyle changes to eat more whole foods that are lower in calories and less processed may be a way to counter some of the effects of chronic stress and maintain adequate protein expression in the brain.

**Glucocorticoids and the immune system**

Dysregulation of the immune system can lead to an overstimulation or lack of function, both of which can be harmful. Two key players in the immune system are B- and T-lymphocytes. B cells function by releasing antibodies in response to antigen binding, while cytotoxic T cells act more directly by cell-cell contact with a foreign organism. Helper T cells release cytokines in response to antigen binding to direct the appropriate lymphocytes to either make antibodies or to bind to the antigen and initiate cytotoxic effects. These cells mediate adaptive immunity component, while the leukocytes that make up the innate cells are quicker to act, they are not as specific in their identification and targeting of specific pathogens (Punt, Stranford, Jones, & Owen, 2019). Keeping the immune cells in balance and at optimal function is important to maintaining overall health and preventing sickness. Glucocorticoids have been found to impair the immune response as a result of prolonged stress.

A key component of the adaptive immune system is the helper T cell. These cells are important in activating B cells to produce antibodies as a part of the humoral immune response or cytotoxic T cells in the cell-mediated immune response. Helper T cells can be divided into two subclasses: Th1 and Th2. Elenkov and Chrousous summarize the roles of these two subclasses. Th1 cells are involved in the cell-mediated pathway by secreting the cytokines IFN-γ, IL-2, and TNF-β. Th2 cells secrete IL-4, IL-10, and IL-13, which are cytokines involved with the humoral adaptive immune response (Elenkov & Chrousos, 2002).

The cytokine IL-12 is released from activated antigen-presenting cells (APCs). IL-12 release along with TNF-α and INF-γ, from Th1 cells, have shown a synergistic effect in inducing inflammation by stimulating the production of inflammatory compounds. Conversely, the major anti-inflammatory cytokines IL-4 and IL-10 come from Th2 cells and promote humoral immunity. The major proinflammatory cytokines and the major anti-inflammatory cytokines

have an antagonistic relationship, with the dominating pathway inhibiting the other (Elenkov & Chrousos, 2002). Glucocorticoids, such as cortisol, are able to impact the adaptive immune response by interfering with the production of these cytokines. Glucocorticoids inhibit the production of the Th1 pro-inflammatory cytokine IL-12 by APCs (Blotta, DeKruyff, & Umetsu, 1997; Elenkov & Chrousos, 2002). This is also accompanied by an increased production of IL-4 from T cells due to the lack of the antagonistic presence of IL-12 (DeKruyff, Fang, & Umetsu, 1998; Elenkov & Chrousos, 2002). Glucocorticoids are also able to directly upregulate the anti-inflammatory response by increasing lymphocyte production of IL-10 (Elenkov & Chrousos, 2002). Another mechanism by which cortisol favors the anti-inflammatory pathways is by reducing histamine secretion and stabilizing the lysosomal membrane (Stephens & Wand, 2012).

Glucocorticoids, namely cortisol, are also able to impact the immune response by binding to glucocorticoid receptors in the brain. Once bound, the receptor-ligand complex translocates to the nucleus and alters the transcription and ultimately the translation of proteins associated with inflammation and the immune response (Zefferino et al., 2021).

Cortisol can also activate pathways and bind to cellular membranes, such as those belonging to the cells of the immune system. They are able to accomplish their anti-inflammatory effects by inducing apoptosis in monocytes, macrophages and T cells (Amsterdam et al., 2002; Zefferino et al., 2021). Eliminating these cells would decrease the population of leukocytes responding to an area where damage or antigen-encounter has occurred, and thereby reducing inflammation. This could also potentially reduce the cell signaling that would induce further leukocyte migration into the area, which would also minimize inflammation in the area. Under chronic stress conditions and perpetually elevated glucocorticoid levels, however, glucocorticoid resistance may arise. This period may show a decreased response to

glucocorticoids and therefore a decrease in the anti-inflammatory effects of cortisol (Cohen et al., 2012; Zefferino et al., 2021).

Studies have shown that elevated glucocorticoid levels associated with chronic stress can cause a decline in the number of B lymphocytes (McGregor, Murphy, Albano, & Ceballos, 2016). B cells undergo various levels of maturation as they are made from hematopoietic stem cells in the bone marrow and then continue to mature into naïve B cells. At this stage they can be activated by antigen recognition in circulation or secondary lymphoid organs (such as the lymph nodes or spleen), and then begin to produce antibodies as part of the humoral branch of adaptive immunity (Punt et al., 2019).

One study indicates that high glucocorticoid levels are associated with elimination of 30-70% of pro-B, pre-B and immature B cells within a period of 36 hours (Laakko & Fraker, 2002). *in vitro* human studies have also indicated that elevated glucocorticoids can trigger apoptosis in 60% and 80% of CD10+ and CD19+ marrow B cells (Igarashi et al., 2005). McGregor et al conducted a study to determine how the psychological stress of students impacted cortisol levels and the number of B lymphocytes compared to a non-student control group. The study used first year graduate students with an intense final exam as the experimental group, and non-students as the control group. Salivary cortisol and B cell levels were measured throughout the year. CD19+ B lymphocytes declined significantly among the student experimental group compared to the control (McGregor et al., 2016). While levels of daily cortisol levels were not as high among the student group as hypothesized, likely due to too short of a time to experience a sufficient level of chronic stress, students experienced a decreased level of CAR. This group saw a decline from a 23% increase drop to a 2% morning increase over time. This finding was associated with a decrease in B cells and suggests evidence of prolonged stress (McGregor et al., 2016). The

lowering of the number of B cells in circulation can lead to a reduced immune response when a pathogen is encountered, and lead to an increased risk of infection if that pathogen is not adequately cleared.

**Chronic Stress and the Digestive System**

The digestive system integrates both body systems previously discussed, as it has its own component of the nervous system (the enteric nervous system), as well as immune cells within the GI tract. The GI tract is responsible for obtaining nutrients from food and regulating digestion and is also affected by stress.

During digestion and absorption, timing along each part of the GI tract is important, as the body needs adequate time to absorb the nutrients from the diet and any water that is consumed. As the stress response is activated, CRH levels increase triggering an increase in the movement of the distal GI tract (the colon, or large intestine) and a decrease in movement in the proximal GI tract (the stomach and small intestine) (Mönnikes et al., 2001; Yaribeygi et al., 2017). CRH-2 receptors are responsible for causing a delay in stomach emptying, while type 1 CRH receptors are found in the colon and affect the speed of peristalsis (Mönnikes et al., 2001; Yaribeygi et al., 2017).

However, other studies find the opposite effect of stress on the rate of bowel movements. Zhang et al., 2015 conducted an animal study and used noise to induce stress in rats. The stressed group proved to have higher cortisol than the control group as a result. The conclusions showed that noise stress inhibited gastric emptying of rats and accelerated food movement in the small intestine. They also found that stress makes an individual more susceptible to gastric ulcers (Zhang et al., 2015). This conclusion is supported by case studies, such as that of Guo et al., 2009. While previous research indicated that glucocorticoids could enhance the protective

mechanisms of the gastric mucosa during acute stress, other studies have found that glucocorticoids can have a maladaptive effect during prolonged stress. One particular study by Guo et al study found that chronic stress as a result of psychological stressors can lead to alterations in the gastric mucosa allowing for greater colonization of *H. pylori*, which can lead to stomach ulcers (Guo et al., 2009).

The immune system is highly integrated with the GI tract, as the lumen contains many non-self cells from the ingestion of substances that are foreign to the body. Dysregulation of these two systems can result in eosinophilic gastrointestinal disorders (EGIDs), which are chronic allergic diseases that can be identified in the GI tract by eosinophilic inflammation. Kanamori et al., 2022 conducted a study after hypothesizing that psychological stress would worsen non-esophageal EGIDs (Atsushi Kanamori et al., 2022). This disease classification encompasses gastritis, enteritis, and colitis triggered by eosinophilic inflammation (EoG, EoN, EoC, respectively). Activation of the HPA axis can interrupt the production of enteric-derived hormones, ultimately affecting the overall function of the GI system (Zhang et al., 2015). EGIDs, and the stress that exacerbates them, impact the GI system through by stimulating the production of CRH by eosinophils in the intestine. CRH activates mast cells, which can compromise the protective mucosa lining of the stomach by damaging the intestinal epithelium (Atsushi Kanamori et al., 2022).

**Chronic Stress and the Cardiovascular System**

The cardiovascular system consists of the heart, blood vessels, and blood. Maintaining cardiovascular health should be a priority for everyone, given that cardiovascular disease (CVD) is the leading cause of death worldwide (Mozaffarian, 2017). 2015 statistics state that 423 million people across the globe have cardiovascular disease with 19.9 million deaths,

contributing to one-third of deaths worldwide (Mozaffarian, 2017). As discussed with other body systems and functions, stress can also affect heart health in numerous ways. Finding ways to manage and alleviate stress early may be a preventative measure to avoid cardiovascular disease in the future.

As previously specified, the stress response is a function of the ANS, specifically the sympathetic branch. Activation of this branch of the nervous system also has direct effects on the heart and the cardiovascular system, enhancing cardiac output to prepare the body for fight-or-flight. This induces an increase in heart rate and the strength of systolic contractions. Blood vessels are targeted, causing vasodilation in skeletal muscle to increase blood flow in this tissue, and narrowing of veins. Blood flow to the spleen and kidneys is decreased by contracting the arteries, and the kidneys increase sodium reabsorption to increase blood pressure. Endothelial tissue in the blood vessels is altered in the stress response (Rozanski, Blumenthal, & Kaplan, 1999; Yaribeygi et al., 2017), increasing instances of ischemia and thrombosis while also increasing platelet aggregation in the blood. In addition to these effects, Yaribeygi et al. summarizes research concluding psychological stress increases oxygen demand and coronary vasoconstriction, which poses significant risk for myocardial infarction (MI), more commonly known as a heart attack (Yaribeygi et al., 2017).

Many studies show that work stress is a significant predictor and causative agent for the onset of new coronary artery disease, higher fatality rates from cardiometabolic disease, and stroke (Levine, 2022). One proposed mechanism is harmful lifestyle choices that are a result of chronic stress. More research is necessary to explain the mechanisms—however, these behaviors can include smoking, unhealthy eating patterns, a decrease in sleep and exercise, poor compliance with heart medications and treatments, and neglecting follow-ups with medical

professionals and screenings (Levine, 2022). Another way in which stress induces CVD is through cortisol, which leads to increased insulin resistance and blood pressure, and contributes to a central redistribution of adiposity (Levine, 2022).

The relationship between the brain and the cardiovascular system functions in the onset of CVD as a result of stress. The amygdala has been shown to play a significant role in the stress response as shown in a study by Tawakol et al. Under perceived stress conditions, amygdalar activity increases. Increased amygdalar activity is associated with increased bone-marrow activation as well as arterial inflammation, and high amygdalar activity is correlated with a higher risk of cardiovascular events over the course of 3-4 years (Tawakol et al., 2017). The amygdala is so involved in this response largely due to its efferent projections into the brainstem. These projections function in the sympathetic nervous response that arises from stress. High amygdalar activity is linked to perceived stress, as well as CVD events. The incidence of CVD events was mediated by arterial inflammation, which was mediated with an increase in bone-marrow activity, contributing to 46% of the total effect (Tawakol et al., 2017). Arterial inflammation contributed to 39% of CVD events occurring from high amygdala activity (Tawakol et al., 2017). This was shown to be significant even in groups without any pre-clinical evidence of atherosclerosis at baseline (Tawakol et al., 2017). High resting amygdalar activity not only increased the risk of a CVD event occurring but predicted that an event would happen sooner in those with a lower activity (Tawakol et al., 2017).

Additional studies have also linked the occurrence of emotional upset and MI. The onset of intense emotions increases the risk of an MI by a factor of 4.7, while it potentially triggers 18% of MI as shown in a patient case study (Sandrini et al., 2020). Those with pre-existing chronic heart failure and an increased chronic fasting cortisol level are more likely to have a

future cardiac event (Hamer, Endrighi, Venuraju, Lahiri, & Steptoe, 2012). Research has shown that when conventional CVD factors were taken into account, long-term stress added to the increased risk of an acute MI from a ratio of 69:X to X:183 (Popovic et al., 2022).

An acute heart failure syndrome has also been correlated with stress. Known as stress-induced cardiomyopathy (SIC), this condition is characterized by left ventricular dysfunction in both systole and diastole, with wall-motion abnormalities (Popovic et al., 2022). Research also indicates the occurrence of a "dose response" in regard to stress resulting in CVD—periodic stress is associated with some level of risk while chronic stress has a higher risk of incidence (Levine, 2022). In reference to a specific pathology of the cardiovascular system, hypertension was found to increase 15% and 22% in individuals under moderate/high levels of perceived stress compared to those with low stress, measured over the course of seven years (Spruill et al., 2019).

Allostasis occurs in the heart to adapt to stressors, but the beneficial adaptations can turn into allostatic overload under chronic stress. Acute onset stress can stimulate platelet aggregation factors in an attempt to prevent excessive bleeding. While this mechanism is meant to be protective, it can prove to be harmful in patients with CVD who tend to sustain longer periods of platelet activation that can increase the risk of blood clot formation (Sandrini et al., 2020). More enhanced platelet aggregation was found in patients of lower socioeconomic status and higher work demand, further indicating that allostasis can occur under chronic stress conditions (Sandrini et al., 2020). In response to HPA axis activation, cortisol and CRH are able to intensify the ability of thrombin and ADP to promote platelet aggregation. A similar mechanism of activation is also seen in Cushing's syndrome, hallmarked by hypercortisolism (Sandrini et al., 2020).

Depression has been shown to increase the risk of CVD incidence and the chance of a cardiovascular event. An individual with depression that has no CVD diagnosis is 2.7 times more likely to die from coronary artery disease over a period of 8.5 years (Popovic et al., 2022; Surtees et al., 2008). Adults who experience stress in the workplace are 10-40% more likely to develop CVD, with stress strongly associated with early onset CVD in people below and above the age of 50 (Kivimäki & Kawachi, 2015; Popovic et al., 2022; Song et al., 2019). One mechanism by which this can occur is through ANS dysregulation from regular stress. Whether this dysregulation manifests as an exaggerated response or blunted reactivity, Popovic et al summarize significant correlations in alterations in ANS function and hypothalamic pathways: hypertension, coronary artery calcification, and thickening of the carotid intima media (Popovic et al., 2022).

### *Faith, Stress, and the Heart*

Stress can have different impacts on the cardiovascular system according to faith and worldview. A recent study hypothesized that individuals with stronger worldview convictions, such as those proclaiming to be religious or atheists, would have a more positive cardiovascular stress response than those with a greater existential search (Schnell, Fuchs, & Hefti, 2020). Students participating in the study were divided by self-proclaimed worldview: atheist, agnostic, religious, and spiritual. They gave saliva cortisol samples before, directly after, and during the recovery period, and cardiovascular measures included systolic blood pressure (SBP) and heart rate. The results revealed that baseline cortisol levels were higher for spiritual and atheist participants than religious and agnostic individuals (Schnell et al., 2020). The spiritual group also had a higher average SBP and heart rate than those who identified as religious. Religious and agnostic groups experienced an increase in cortisol levels in response to the stressors. However,

the atheist group proved to have a higher overall stress response than that of the religious group. While the hypothesis was partially disproved, the study does give evidence that faith and worldview can influence the effects of stress (Schnell et al., 2020).

A previous study sought to better understand how the different practices of religion can be a protective mechanism to defend against stress (Tartaro, Luecken, & Gunn, 2005). Participants were divided among various levels of religiosity and spirituality: not religious, slightly religious, moderately religious, very religious, with the same categories dividing the spiritual group. Cortisol levels were obtained, and blood pressure was monitored before and after the stressor tasks. The results demonstrated that increased religiosity or spirituality can lessen the overall increase from baseline to post-task cortisol levels (Tartaro et al., 2005). Greater religiosity resulted in less reactivity, while less religiosity had higher overall cortisol levels and higher reactivity. There were no significant associations between cortisol levels and spirituality. More frequent prayer and forgiveness was found to correlate with lower cortisol production, while attendance at services, religious coping mechanisms and meditation had no effect. This study offers evidence that the more personal, lived-out aspects of faith can serve as a protectant against some of the biomarkers and cardiovascular effects of stress (Tartaro et al., 2005).

**Stress Mitigation Methods and Stimulants**

While this research has focused on the effects of stress, there are several methods of stress alleviation that may prevent the excessive activation of stress response and/or the damaging effects of chronic stress. A study was conducted on undergraduate students and compared the duration of stress and the controllability of stress. The findings showed that chronic controllable stress was improved by using the “stress-is-enhancing” mindset (Jenkins, Weeks, & Hard, 2021). The shift in mindset from a belief that stress is debilitating to stress is

enhancing allowed the students to take a proactive approach because they felt they could control the outcome of their stressor (Jenkins et al., 2021). The results suggest that adopting a mindset that stress can motivate productive behavior under stressful times, even due to chronic stressors, can decrease perceived stress and therefore alleviate some of the physical and mental ailments that result from chronic stress (Jenkins et al., 2021).

Many people use exercise as a way of alleviating stress. While the research behind this is somewhat inconclusive, there is some evidence to support the connection. Exercise affects the nervous and endocrine systems in a similar manner as acute stressors: there is an increase in cortisol, epinephrine and norepinephrine, and inflammatory cytokines (Hackney & Lane, 2015; Popovic et al., 2022). This may seem counterintuitive as a means to mitigate stress, but both aerobic and resistance exercise can actually reduce sensitivity to other stressors. This can make an individual more resilient and can reduce the symptoms associated with stress (Ensari et al., 2020; Popovic et al., 2022).

A lack of research on the effect of physical activity in non-clinical populations led to a meta-meta-analysis of the effect of physical activity on symptoms of depression and anxiety in adults (Rebar et al., 2015). Physical activity was defined as bodily movement that required energy to produce skeletal muscle movement and ranged from low-intensity walking to moderate- and high-intensity workouts (Rebar et al., 2015). It was found that physical activity has a therapeutic effect on individuals in non-clinical populations. There was a medium mediating effect on depression and a small mediating effect on anxiety (Rebar et al., 2015). While a lot of variability exists within the type of exercise as well as the symptoms that an individual is experiencing, this evidence shows that physical activity can help to improve some mental health issues that can arise from chronic stress.

Magnesium deficiency has been linked to stress, with each individually causing similar symptoms. Pickering et al identifies the shared symptoms as that of fatigue, irritability, nervousness, GI discomfort, muscle tension, weakness, and cramps, and headache (Pickering et al., 2020). Both stress and magnesium deficiency are causal: stress can cause magnesium deficiency, and magnesium deficiency can cause stress (Pickering et al., 2020). In the U.S., magnesium can be ingested from the diet through vegetables, meat, and milk (Ford & Mokdad, 2003; Pickering et al., 2020). According to a compilation of finding from Pickering et al, loss of magnesium can be caused by high sodium, calcium, and protein in the diet, as well as caffeine and alcohol intake, and the use of diuretics, proton pump inhibitors, and antibiotics (Pickering et al., 2020). A 30% depletion in soil from farming practices over the course of the last 60 years and processed foods common in the western diet contribute an 80-90% loss of magnesium as well (Baaij, Hoenderop, & Bindels, 2015; DiNicolantonio, O'Keefe, & Wilson, 2018; Pickering et al., 2020; Thomas, 2007). In 2015, the Dietary Guidelines Advisory Committee identified it as an under-consumed nutrient in the U.S., with 2.5-15% of the population experiencing mild hypomagnesemia, which can also occur in mid- to long-term stress (Mouw, Latessa, & Sullo, 2005; Pickering et al., 2020). One way in which magnesium mitigates stress is through its interaction with glutamate and γ-aminobutyric acid (GABA). Magnesium inhibits glutamate, which is excitatory in the HPA axis, and stimulates GABA, an inhibitor of the HPA axis, and weakens the response from catecholamines and glucocorticoids to decrease the stress response at multiple points in the pathway (Pickering et al., 2020).

One study used humor as a way to minimize stress. Participants were divided into two groups, one of which watched a funny movie before beginning the stressful task assigned to both groups were to complete. The results showed that the group that watched the movie had

significantly less psychological stress, as shown by salivary cortisol levels taken throughout the study (Froehlich et al., 2021). This indicates that consuming relaxing media before the onset of a stressor can help to minimize the stress response without compromising performance (Froehlich et al., 2021). Conversely, caffeine and nicotine have been found to be stimulators of the HPA axis (Kudielka & Wüst, 2010). Table 1 summarizes these findings. Understanding mechanisms that will either stimulate or alleviate stress can provide individuals with the knowledge needed to best manage and prevent stress and chronic stress-inducing practices.

**Table 1.** A summary of stress mitigation and stress stimulants.

| **Stress Mitigation** | **Stress Stimulant** |
|---|---|
| "stress-is-enhancing" mindset | "stress-is-debilitating" mindest |
| Exercise | Caffeine |
| Magnesium | Nicotine |
| Relaxing or humorous media | |

## Conclusion

The stress response is an amazing design that prepares and protects the body. It is a complex mechanism that results in many physiological changes to enhance performance in a fight-or-flight situation. The problem occurs when this response is unwarranted and unchecked. Chronic shift causes a shift from beneficial allostasis to allostatic overload, during which the body undergoes a lot of wear and tear (McEwen, 2008).

While there is a plethora of further, more in-depth research about chronic stress, this paper was meant to review current research and previous studies that have informed what is currently known about this response. Besides its activation by the neuroendocrine system and its effect on both hormones and the brain, the stress response and its biomarkers can have

pathological effects throughout the body. This is not often something that can be treated quickly, but there are many methods that can alleviate some of the symptoms of chronic stress and allow for overall improved quality of life and healthier lifestyle.

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