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# The Role of Cortisol in the Stress Response

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**ABSTRACT**

Stress is a physiological and psychological response triggered by internal or external stressors that challenge the body's homeostasis. Cortisol, a glucocorticoid hormone released by the adrenal glands in response to stress, plays a pivotal role in modulating this response. Its primary function is to mobilize energy, regulate inflammation, and enhance cognitive processes during acute stress. While cortisol facilitates adaptation by suppressing overactive immune responses and ensuring resource availability, its prolonged elevation can lead to detrimental effects, including metabolic disorders, cardiovascular diseases, and cognitive impairments. Conversely, inadequate cortisol production disrupts the body's ability to manage stress, resulting in conditions like fatigue, hypotension, and impaired recovery. This study explores the dynamic relationship between stress and cortisol, emphasizing how balanced cortisol levels contribute to stress resolution and homeostasis restoration. Understanding cortisol's dual role provides insights into its potential therapeutic applications for managing stress-related disorders.

**Keyword:** stress, cortisol, the role of cortisol, mechanism of cortisol, cortisol and stress hormone

**ABSTRAK**

*Stres adalah respons fisiologis dan psikologis yang dipicu oleh stresor internal atau eksternal yang menantang homeostasis tubuh. Kortisol, hormon glukokortikoid yang dilepaskan oleh kelenjar adrenal sebagai respons terhadap stres, memegang peran penting dalam memodulasi respons ini. Fungsi utamanya adalah untuk memobilisasi energi, mengatur peradangan, dan meningkatkan proses kognitif selama stres akut. Sementara kortisol memfasilitasi adaptasi dengan menekan respons imun yang terlalu aktif dan memastikan ketersediaan sumber daya, peningkatan jangka panjangnya dapat menyebabkan efek merugikan, termasuk gangguan metabolik, penyakit kardiovaskular, dan gangguan kognitif. Sebaliknya, produksi kortisol yang tidak memadai mengganggu kemampuan tubuh untuk mengelola stres, yang mengakibatkan kondisi seperti kelelahan, hipotensi, dan pemulihan yang terganggu. Studi ini mengeksplorasi hubungan dinamis antara stres dan kortisol, menekankan bagaimana kadar kortisol yang seimbang berkontribusi pada resolusi stres dan pemulihan homeostasis. Memahami peran ganda kortisol memberikan wawasan tentang potensi aplikasi terapeutiknya untuk mengelola gangguan terkait stres.*
.

***Kata kunci:*** *stres, kortisol, peran kortisol, mekanisme kortisol, kortisol dan hormon stres*

## 1. Introduction

Stress is an inevitable aspect of life, influencing both physical and mental well-being. Defined as the body's response to any challenge that disrupts homeostasis, stress can manifest acutely or chronically, with varying impacts depending on its intensity and duration. The hypothalamic pituitary adrenal (HPA) axis is central to the stress response, with cortisol as its primary effector hormone [1].

Cortisol, often referred to as the "stress hormone," orchestrates several adaptive responses aimed at helping the body cope with and recover from stress. In the short term, cortisol mobilizes energy reserves by increasing glucose availability, suppresses excessive immune activity, and enhances cognitive functions such as focus and decision-making. These effects are essential for acute stress adaptation, often described as the "fight-or-flight" response [2].

However, the balance of cortisol levels is critical. Chronic stress, which leads to prolonged cortisol elevation, is associated with negative outcomes such as metabolic syndrome, hypertension, and neurocognitive decline. On the other hand, insufficient cortisol production, as seen in conditions like Addison's disease, impairs the body's ability to handle stress, leading to fatigue, hypotension, and increased vulnerability to external stressors [3].

This article delves into the intricate relationship between stress and cortisol, examining how cortisol contributes to stress resolution and discussing the consequences of dysregulated cortisol levels. By exploring these dynamics, the study highlights cortisol's potential as a therapeutic target in managing stress-related disorders and promoting overall resilience.

## 2. Methods

This systematic review was performed by online searches of PubMed Google Scholar, Sciencedirect and Mendeley databases. The descriptors “cortisol and stres response”, “stres hormone”, “stress and stressor “the role of cortisol”. The inclusion criteria were research articles on role of cortisol to stres response. The search returned 185 articles and the preselection was made by reading the abstracts and fulltext research publications, while excluding reviews. The preferred reporting items for systematic and meta-analysis (PRISMA) framework used data collection for this review is shown in Figure 1.

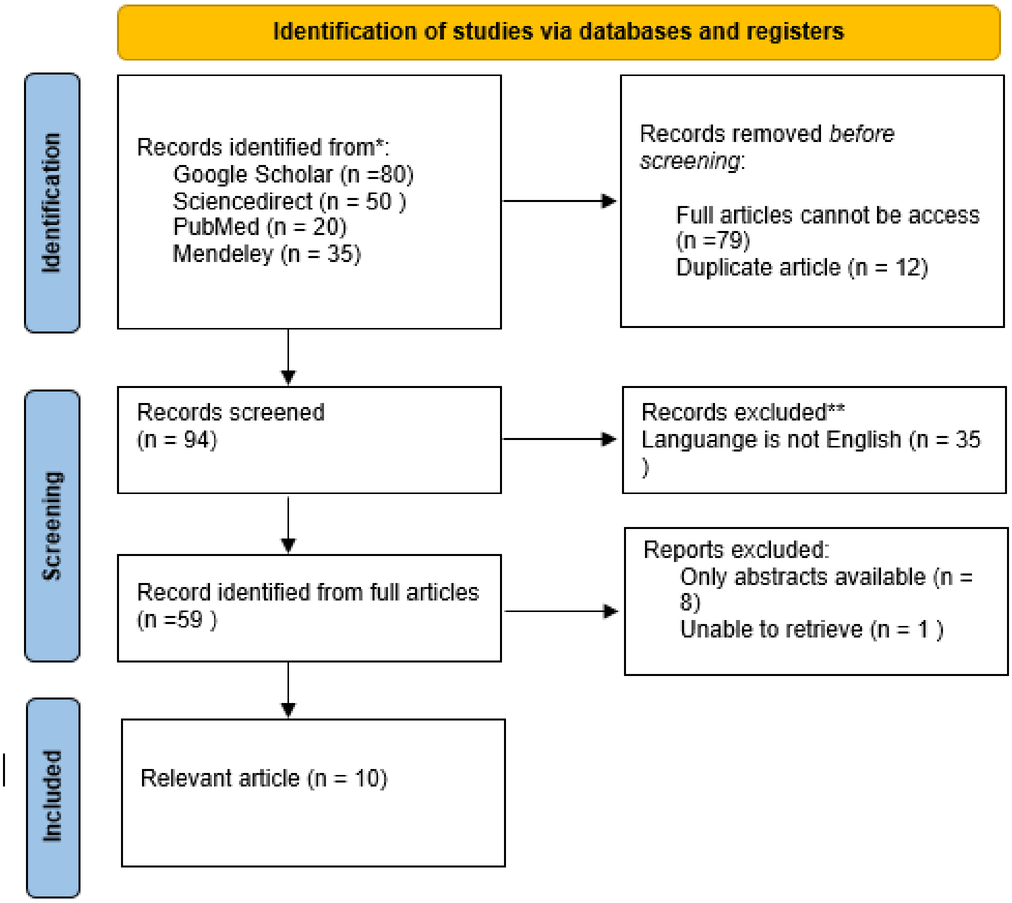


Figure 1. PRISMA flowchart for the review methodology.

## 3. Result and discussion

Studies that have been selected in this review demonstrate that role of cortisol in the stress response that used to systematic literature review by using PRISMA at Table 1.

Table 1. Data Systematic Literature Review

| Reference | Highlight Result |
|---|---|
| Sapolsky, R. M. (2020). Cortisol's Role in Acute and Chronic Stress Responses. | The crucial role of cortisol, a key stress hormone, in how we respond to stress, both in the short term and over the long run. Sapolsky explains that cortisol helps the body handle acute stress by mobilizing energy and boosting the fight-or-flight response, allowing people to deal with immediate threats. However, when stress becomes chronic, sustained high levels of cortisol can have harmful effects on various bodily systems, such as the immune, cardiovascular, and nervous systems. |
| Funder, J. W., et al. (2020). The Physiology of Cortisol Secretion | The article offers an in-depth explanation of how cortisol secretion is regulated and its physiological functions in the body. It describes how cortisol, a crucial glucocorticoid hormone produced by the adrenal glands, is released in reaction to stress via the hypothalamic-pituitary-adrenal (HPA) axis. The article also highlights the various impacts of cortisol on metabolism, immune function, and the body's ability to adapt to stress. |
| Thau, L., Gandhi, J., & Sharma, S. (2021). Physiology, Cortisol | Cortisol levels follow a diurnal pattern, typically peaking in the morning shortly after waking and declining throughout the day. It is regulated by the hypothalamic-pituitary-adrenal (HPA) axis, where the hypothalamus releases corticotropin-releasing hormone (CRH), stimulating the pituitary gland to release adrenocorticotropic hormone (ACTH), which then stimulates cortisol production in the adrenal glands. |
| McEwen, B. S. (2021). Acute Stress Responses in Humans. | The acute stress response is a critical biological process that helps the body react to immediate threats by activating the sympathetic nervous system and the HPA axis. This response is beneficial in the short term, as it boosts alertness and energy to help us survive stressful situations. |
| Herman, J. P., et al. (2021). CRH and the HPA Axis in Stress Regulation | The key role of the CRH and HPA axis in both the physical and mental reactions to stress. CRH, which is produced in the hypothalamus, is essential for initiating the body's stress response. It does so by triggering the release of adrenocorticotropic hormone (ACTH), which in turn prompts the adrenal glands to produce cortisol. This hormonal cascade is vital for mobilizing energy and regulating the body's functions during times of stress. |
| Zefferino, R., Di Gioia, S., & Conese, M. (2021). Molecular links between endocrine, nervous and immune system during chronic stress | The intricate and interdependent functions of the endocrine, nervous, and immune systems in how the body responds to chronic stress, both physiologically and at the molecular level. From the context, it seems the authors suggest that prolonged stress can cause major changes in these systems, triggering a series of biological reactions that ultimately affect overall health. |

| Reference | Highlight Result |
|---|---|
| Dziurkowska, E., & Wesolowski, M. (2021). Cortisol as a Biomarker of Mental Disorder Severity | Consequences of abnormal cortisol secretion. Disorders in cortisol secretion (particularly hypercortisolemia) may cause mental disorders and can be one of the many hormonal disorders accompanying these conditions, for example depression. Increased secretion of cortisol in a stressful situation has consequences for the functioning and condition of our brain. |
| Iqbal, T., Elahi, A., Wijns, W., & Shahzad, A. (2023). Cortisol detection methods for stress monitoring in connected health | The article delves into different methods for detecting cortisol, a key stress biomarker, within the framework of connected health systems. It examines various techniques, with a particular focus on their suitability for real-time stress monitoring and their potential for integration into wearable devices designed for continuous health tracking |
| James, K. A., Stromin, J. I., Steenkamp, N., & Combrinck, M. I. (2023). Understanding the relationships between physiological and psychosocial stress, cortisol and cognition. | The study finds that both physiological and psychosocial stress have a considerable impact on cortisol production, which, in turn, affects cognitive functions. However, the link between cortisol and cognition is complex, as the effects of increased cortisol levels depend on factors like the type and duration of stress, as well as individual differences. Chronic stress and prolonged elevated cortisol can negatively affect cognitive abilities, particularly in memory, attention, and decision-making. Conversely, short-term stress might temporarily boost certain cognitive functions due to the body's adaptive responses. |
| Knezevic, E., Nenic, K., Milanovic, V., & Knezevic, N. N. (2023). The Role of Cortisol in Chronic Stress, Neurodegenerative Diseases, and Psychological Disorders. | Chronic stress can lead to sustained high levels of cortisol, which may impair neuroplasticity, disrupt the hippocampus (a region critical for memory and emotional regulation), and contribute to cognitive decline. This can be particularly evident in disorders like Alzheimer's disease, depression, and anxiety disorders. The study emphasizes that cortisol dysregulation can be a contributing factor to the pathophysiology of these conditions, potentially leading to changes in brain structure and function. |

### 3.1 Stress, Classified and Stressor

Stress is a physiological and psychological response to external or internal demands, often referred to as stressors. These demands challenge an individual's ability to cope and adapt. Stress is not inherently negative; it can be categorized as positive (eustress) or negative (distress) depending on its effects on an individual. Stress arises when there is a mismatch between the demands placed on an individual and their resources to cope with those demands [4].

Stress can be classified into three primary types:

1. Acute Stress is short term stress that occurs in response to immediate threats or challenges. Examples narrowly avoiding an accident, preparing for a presentation. Generally manageable and sometimes beneficial in motivating individuals to perform well [5].
2. Chronic Stress is long term stress resulting from ongoing demands or challenges that do not resolve quickly. The examples is financial difficulties, ongoing workplace conflicts. It can lead to serious health issues like cardiovascular disease, depression, and weakened immunity [6].
3. Episodic Acute Stress is recurring episodes of acute stress often associated with patterns of worry and overcommitment.Examples are requently missing deadlines, consistently feeling overwhelmed by responsibilities. It may lead to tension headaches, migraines, and hypertension [7].
4. Eustress and Distress. Eustress is positive stress that enhances performance and motivation. Distress is negative stress that overwhelms coping abilities and impairs functioning [8].

Stressors are the stimuli or events that trigger a stress response. They can be classified into:

1. Physical Stressors are Environmental factors that cause physical strain on the body for the examples are noise, temperature extremes, physical injuries [9].
2. Psychological Stressors are internal factors, such as thoughts or feelings, that lead to stress. The examples are fear of failure, negative self-talk, and anxiety about the future [10].
3. Social Stressors is stress originating from interpersonal relationships or social situations such as are conflicts with friends or family, social isolation, workplace harassment [11].
4. Daily hassles are minor, recurring stressors in everyday life. Such as are traffic jams, losing keys, or dealing with minor workplace issues [12].

### 3.2 The Effect of Hormones in Stress

Hormones play a pivotal role in regulating the body's response to stress through the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) system. These systems coordinate the release of key hormones to help the body cope with and adapt to stress. Below are the main hormones involved in the stress response and their effects:

1. **Cortisol (The Primary Stress Hormone).** Cortisol is released by the adrenal cortex, is central to the HPA axis and helps the body manage acute and chronic stress.The effects are metabolic regulation is stimulates gluconeogenesis in the liver to increase blood glucose levels, immune modulationcis suppresses pro inflammatory cytokines and adaptive immune responses to prevent excessive inflammation, cardiovascular support is increases blood pressure and cardiac output by enhancing the responsiveness of blood vessels to catecholamines and cognitive enhancement mproves memory and focus during acute stress. Prolonged cortisol elevation can lead to metabolic syndrome, hypertension, immune suppression, and cognitive decline [13].
2. **Adrenaline and Noradrenaline (**Catecholamines**).** These hormones, secreted by the adrenal medulla, are part of the SAM system, which mediates the "fight-or-flight" response. The effects are energy mobilization increases heart rate and respiration to deliver oxygen and glucose to muscles, vasoconstriction is redirects blood flow to vital organs (heart, brain, muscles) by constricting blood vessels in less critical areas. **E**nhanced alertness. Activates the amygdala and prefrontal cortex for quick decision-making and persistent elevation can cause cardiovascular strain and contribute to anxiety disorders [14].
3. **Corticotropin-Releasing Hormone (CRH).** CRH is released by the hypothalamus to activate the HPA axis and stimulate the production of adrenocorticotropic hormone (ACTH). The effects are HPA axis activation. Facilitates cortisol release from the adrenal glands. Appetite Suppression can modulates hunger during stress by interacting with the hypothalamic feeding centers. Chronic Effects are prolonged CRH activity can lead to dysregulated HPA axis responses and mood disorders.

### 3.3 Normal and Stress-Induced Cortisol Levels

Cortisol ($C_{21}H_{30}O_5$), is a steroid hormone with a molecular weight of 362.46 g/mol. Cortisol is a well-known biomarker of psychological and physiological stress. The level of cortisol plays an important part in regulating blood pressure, carbohydrate metabolism and glucose levels. It also contributes to the homeostasis of cardiovascular, renal, immune, endocrine and skeletal systems. Abnormally increased levels of cortisol interfere with blood amino acid and fatty acid levels, resulting in depression of the immune system and inflammation. Severely increased levels of cortisol contribute to the development of symptoms of obesity, bone fragility, and fatigue, while decreased levels of cortisol lead to Addison’s disease manifested by arterial hypotension, weight loss and darkened scars/skinfolds. The most dominating effects of cortisol are indicative of emotional or psychological stress and that is why cortisol is also called the ‘stress hormone [19].

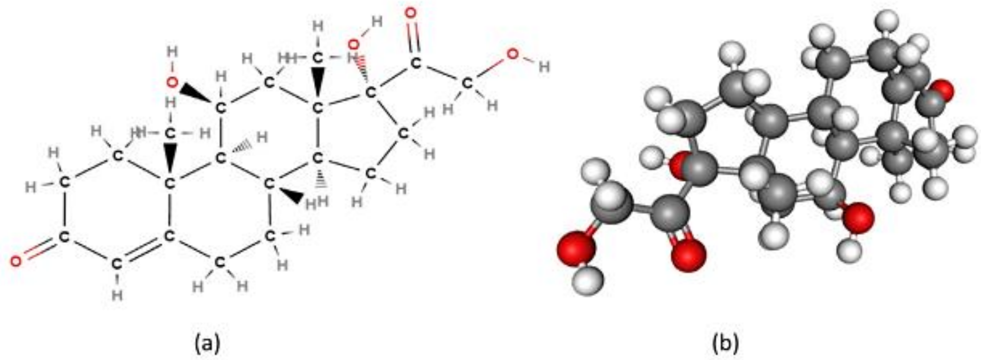


Figure 2. Molecular and 3D structure of Cortisol ($C_{21}H_{30}O_5$). In (a) C is for Carbon, H is for Hydrogen and O is for Oxygen molecule. In (b) Black shows Carbon, grey shows Hydrogen and Red shows Oxygen molecule.

### Normal Cortisol Levels

**C**ortisol levels are typically measured in the blood, saliva, or urine. The levels vary depending on the time of day, as they peak in the early morning and decline throughout the day.

1. **Normal Blood Cortisol Levels [20]:**
   - **Morning (6:00 AM - 8:00 AM):** 10-20 µg/dL (275-555 nmol/L)
   - **Afternoon (4:00 PM - 6:00 PM):** 3-10 µg/dL (80-275 nmol/L)
2. **Normal Salivary Cortisol Levels [21]:**
   - **Morning:** 0.15-0.6 µg/dL (4.14-16.56 nmol/L)
   - **Afternoon:** 0.05-0.2 µg/dL (1.38-5.52 nmol/L)
3. **Normal 24-hour Urinary Free Cortisol [22]:**
   - 10-100 µg/day (28-276 nmol/day)

### Cortisol Levels During Stress

During acute or chronic stress, cortisol levels may rise significantly above normal.

1. **Acute Stress.** Blood cortisol levels can increase to **20-40 µg/dL** (555-1110 nmol/L) during acute stress events [23].
2. **Chronic Stress.** Chronic exposure to stressors can elevate cortisol levels persistently or disrupt the diurnal rhythm, leading to flattened curves (e.g., higher evening levels). Urinary free cortisol levels may exceed **100 µg/day** in cases of chronic stress. [24]
3. **Pathological Cortisol Levels. Cushing's Syndrome:** Cortisol >50 µg/dL (1380 nmol/L) and **Addison's Disease (Low Cortisol):** Cortisol <5 µg/dL (138 nmol/L) [25]

### 3.4 Methods for Identifying Cortisol Levels

Cortisol levels are typically measured in blood, saliva, urine, or hair using various analytical techniques. These methods vary in sensitivity, specificity, and practicality depending on the research or clinical context.

Table 2. method for identifying cortisollevels.

| Method | Sample type | sensitivity | specificity | Ease of use | Best use |
|---|---|---|---|---|---|
| ELISA | Saliva, Blood | Moderate | Moderate | Easy | Population studies[26] |
| RIA | Blood, Urine | High | High | Moderate | Clinical and research labs[27] |
| LC-MS/MS | Blood, Saliva, Urine | Very High | Very High | Complex | Research and clinical diagnostics[28] |
| Salivary Cortisol | Saliva | Moderate | Moderate | Very Easy | Stress research, diurnal monitoring [29] |

| | | | | | |
|---|---|---|---|---|---|
| Hair Cortisol | Hair | High | High | Moderate | Chronic stress assessment [30] |
| Urinary Free Cortisol | Urine | High | High | Moderate | Adrenal disorder diagnosis [31] |

### 3.5 The Ainm of Cortisol During Stress

Cortisol, the primary glucocorticoid hormone, is released in response to stress as part of the hypothalamic-pituitary-adrenal (HPA) axis activation. Its increase during stress serves adaptive purposes to help the body cope with and respond to external or internal challenges.

Table 3. The aim of cortisol increase during stress

| Function | Purpose |
|---|---|
| Energy Mobilization | Provides energy to vital organs during stress [32] |
| Immune Modulation | Prevents overactive immune responses and reduces inflammation [33] |
| Cardiovascular Support | Enhances blood pressure and circulation [34] |
| Cognitive and Behavioral Adaptation | Improves focus, memory, and decision-making during stress [35] |
| Stress Recovery and Termination | Self-regulates the stress response through negative feedback mechanisms [36] |

### 3.6 How Cartisol can Decrease Stress Levels

Cortisol, often called the "stress hormone," plays a dual role in stress regulation. While prolonged cortisol elevation is associated with negative effects, short term cortisol release is essential for managing and resolving stress. Cortisol helps the body adapt to stress by regulating various physiological and psychological processes.

### 3.7 Mechanisms of Cortisol in Decreasing Stress Levels

1. Regulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis. The HPA axis governs cortisol production. During stress, the hypothalamus signals the pituitary gland to stimulate cortisol release from the adrenal glands. Cortisol, in turn, exerts a negative feedback effect on the HPA axis, reducing the release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). This feedback loop prevents excessive cortisol secretion and helps restore homeostasis [37].
2. Modulation of Inflammation. Cortisol suppresses the immune response by inhibiting pro-inflammatory cytokines such as IL-6 and TNF-α. This reduces inflammation, which is often elevated during chronic stress. By dampening inflammatory pathways, cortisol alleviates physiological stress and prevents stress-related damage to tissues [38].
3. Energy Mobilization and Recovery. Cortisol facilitates the mobilization of glucose, fats, and amino acids, providing energy to cope with immediate stressors. After the stressor is resolved, cortisol helps in energy restoration, promoting recovery and repair processes [39].
4. Regulation of Mood and Emotional Responses. Cortisol interacts with brain regions like the amygdala and prefrontal cortex, modulating emotional responses to stress. By reducing excessive emotional reactivity, cortisol contributes to psychological resilience and stress recovery [40].
5. Sleep-Wake Regulation. Cortisol levels follow a diurnal rhythm, peaking in the morning and declining at night. This rhythm supports stress recovery by facilitating restorative sleep and preparing the body for daily challenges. Improved sleep, in turn, reduces stress perception and enhances overall resilience [41].

### 3.8 Effects of Cortisol: Increasing and Decreasing Levels

Cortisol, a vital glucocorticoid hormone, plays a crucial role in maintaining homeostasis during stress. However, abnormal increases or decreases in cortisol levels can have significant physiological and psychological effects. The effect of cortisol is shown in Table 4.

Table 4. Effect of cortisol

| Cortisol Level | Short-Term Effects | Long-Term Effects |
|---|---|---|
| **Increased (High)** | Mobilized energy, suppressed inflammation, heightened focus | Insulin resistance, hypertension, cognitive decline |
| **Decreased (Low)** | Hypoglycemia, hypotension, impaired stress response | Fatigue, excessive inflammation, depression |

### 3.9 Diseases Related to Abnormal Cortisol Levels

Abnormal cortisol levels, whether excessively high or low, can lead to specific diseases and disorders that significantly affect the body's physiological and psychological functions. Diseases related to abnoemal coertisol levels are shown in Table 5.

Table 5. Disease related to abnormal cortisol levels

| Condition | Cortisol Level | Symptoms |
|---|---|---|
| Cushing’s Syndrome | Increased | Obesity, hypertension, hyperglycemia, depression [44]. |
| Metabolic Syndrome | Increased | Obesity, insulin resistance, dyslipidemia, hypertension [45]. |
| Anxiety/Depression | Increased | Mood disturbances, cognitive decline, sleep issues[46]. |
| Addison’s Disease | Decreased | Fatigue, hypotension, hyperpigmentation, weight loss [47]. |
| Secondary Adrenal Insufficiency | Decreased | Similar to Addison's disease without pigmentation or severe electrolyte imbalance [48]. |
| Adrenal Crisis | Decreased | Severe hypotension, abdominal pain, confusion, life-threatening shock [49]. |

## 4. Conclusion

Cortisol is crucial in how the body reacts to stress, serving as a key element in the hypothalamic-pituitary-adrenal (HPA) axis. When the body detects a threat, the HPA axis is triggered, leading to a rise in cortisol levels. This hormone helps release energy reserves, slows down non-essential functions like digestion and immune activity, and primes the body for quick action, often known as the "fight or flight" response. Cortisol is typically elevated during stressful situations, aiding the body in dealing with short-term stress. However, when stress becomes chronic or long-lasting, it can disrupt cortisol production, potentially leading to negative health effects such as immune suppression, memory issues, and an increased risk of conditions like heart disease and depression. The body’s cortisol levels fluctuate, rising sharply during acute stress and gradually decreasing once the stressor is gone or resolved. While normal cortisol responses are beneficial and adaptive, prolonged or excessive cortisol exposure due to ongoing stress can be harmful, highlighting the importance of managing stress for overall well-being.

## 5. Recommendation

Based on the results of this study to better manage stress and its impact on cortisol levels, individuals should adopt stress reduction techniques such as mindfulness, regular physical activity, and adequate sleep. Psychological interventions, like cognitive-behavioral therapy, can help reduce chronic stress and regulate cortisol production. Additionally, healthcare professionals should consider monitoring cortisol levels in patients with chronic stress, as early intervention may help prevent long-term health issues. Further research is also needed to explore the most effective strategies for cortisol regulation in stress-related conditions.


## 6. Acknowledgements

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## 7. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper. All research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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