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# CHRONIC STRESS AS A MODULATOR OF THE IMMUNE SYSTEM: NEUROENDOCRINE MECHANISMS, IMMUNOLOGICAL PATHWAYS AND CLINICAL CONSEQUENCES - A LITERATURE REVIEW

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## ABSTRACT

Chronic stress is a significant factor influencing human immune system functioning. Prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system leads to hormonal and immunological dysregulation (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004). Consequently, immune cells become less sensitive to glucocorticoids, cytokine balance is disrupted, and the organism remains in a state of chronic low-grade inflammation. These changes increase susceptibility to infections, delay wound healing, weaken vaccine responses, and may exacerbate the course of chronic diseases, including autoimmune and inflammatory disorders (Segerstrom & Miller, 2004; Alotiby, 2024).

This review presents current data from clinical and immunological studies published between 2000 and 2025. Molecular and cellular mechanisms are discussed, including HPA axis dysfunction, excessive sympathetic activity, cytokine profile alterations, and changes in innate and adaptive immunity. Attention is given to populations particularly vulnerable to chronic stress and the clinical consequences of these dysregulations (Katz et al., 2025; Chan et al., 2023; Bolton, 2024).

The review also considers strategies to mitigate stress-related immune impairment, such as mindfulness and meditation, regular physical activity, cognitive-behavioral therapy, and sleep hygiene improvement (Black & Slavich, 2016; Creswell et al., 2012; Carlson et al., 2007; Nieman & Wentz, 2019). Understanding these mechanisms may support clinical practice by enabling better identification of high-risk patients and the implementation of effective interventions.

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## KEYWORDS

Chronic Stress, Immune System, HPA Axis, Cytokines, Inflammation, Immunosuppression

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**1. Introduction**

Stress is a complex response of the organism to external and internal factors, activating the nervous, hormonal, and immune systems. Under short-term conditions, stress can play an adaptive role by mobilizing the organism to act and increasing resistance to threats (Segerstrom & Miller, 2004). However, when stressors persist over time, their effects become harmful, leading to dysregulation of multiple systems, including the immune system (Alotiby, 2024; Glaser & Kiecolt-Glaser, 2005).

The immune system is in close interaction with the central nervous system and the endocrine system, particularly with the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (Katz et al., 2025; Chan et al., 2023; Segerstrom & Miller, 2004). Prolonged activation of these mechanisms leads to persistently elevated cortisol and catecholamine levels. As a result, lymphocyte proliferation slows, natural killer (NK) cell cytotoxicity decreases, and antigen presentation by dendritic cells becomes less effective (Katz et al., 2025). Such changes promote both immunosuppression and a chronic, low-grade inflammatory state (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Alotiby, 2024).

Chronic stress has significant clinical implications, especially in populations with high psychological burden (Alotiby, 2024; Glaser & Kiecolt-Glaser, 2005). Those most exposed to chronic stress include caregivers of chronically ill individuals, healthcare workers, patients with mental disorders, and people experiencing chronic occupational or social stress (Alotiby, 2024; Warren et al., 2024; Segerstrom & Miller, 2004).

Caregivers of chronically ill patients often face constant emotional, physical, and financial strain, which translates into long-term activation of the HPA axis and sympathetic nervous system. Healthcare workers, particularly in intensive care or oncology wards, are exposed to time pressure, the necessity of making difficult decisions, and direct contact with patient suffering, increasing the risk of chronic stress and immune dysregulation. Individuals with mental disorders, such as depression or anxiety, exhibit higher levels of chronic stress and elevated pro-inflammatory cytokine levels, which may exacerbate comorbid disease symptoms. Likewise, chronic social and occupational stress, e.g., arising from high-risk work environments or economic uncertainty, contributes to increased susceptibility to infections and worsened outcomes in chronic diseases (Alotiby, 2024; Warren et al., 2024; Black & Slavich, 2016; Bolton, 2024).

These populations demonstrate increased risk of infections, exacerbation of chronic disease progression, and accelerated tumor growth (Glaser & Kiecolt-Glaser, 2005; Black & Slavich, 2016). Recent studies increasingly indicate that chronic stress not only affects immune system function but also plays a pathophysiological role in the development of inflammatory, autoimmune, metabolic, and psychoneuroimmunological diseases. Understanding the links between chronic stress and immunity is crucial for clinical practice, enabling the identification of particularly vulnerable patients and the implementation of effective preventive and therapeutic strategies.

The aim of this review is to present the mechanisms through which chronic stress affects the immune system and to discuss its immunological and clinical consequences (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Katz et al., 2025).

**2. Methodology**

This review was conducted as a literature analysis based on current scientific publications on chronic stress and its effects on the immune system. The search was carried out in the PubMed, Scopus, and Web of Science databases using keywords such as: “chronic stress,” “immune system,” “HPA axis,” “cytokines,” “immunosuppression,” “caregivers,” “healthcare workers,” and “psychoneuroimmunology.”

Articles published between 2000 and 2025 in English and Polish were included. Both original research and review articles were considered. Studies describing the mechanisms of stress-induced immune modulation, clinical consequences of chronic stress, and interventions aimed at reducing stress-related immunosuppression were prioritized.

Exclusion criteria included publications not available in full text, studies on acute stress only, and articles not directly addressing the relationship between stress and immune function. The selected studies were analyzed in terms of methodology, population studied, types of stressors, biomarkers measured, and observed immunological and clinical effects.

Data extraction focused on:

1. Mechanisms of chronic stress influence on immunity, including HPA axis activity, sympathetic nervous system activation, and cytokine modulation.
2. Specific immune parameters affected, such as lymphocyte proliferation, natural killer (NK) cell activity, T cell subsets, and cytokine profiles.
3. Clinical outcomes associated with chronic stress, including susceptibility to infections, progression of autoimmune diseases, cancer development, and complications in chronic illnesses.
4. Population groups particularly vulnerable to chronic stress and its immunological consequences.

This methodology allowed for a comprehensive overview of both experimental and clinical evidence, ensuring that the discussion reflects the most relevant and up-to-date knowledge on the relationship between chronic stress and immune system function.

### **3. Results**

#### **3.1 Dysregulation of the HPA axis**

Chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to sustained elevated cortisol levels. Immune cells become less sensitive to glucocorticoids, weakening control of inflammatory processes (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Balcerowska & Kwaśnik, 2025). High cortisol levels inhibit T lymphocyte proliferation, induce their apoptosis, and reduce immunoglobulin production by B lymphocytes. Consequently, the immune response to viral and bacterial infections decreases, wound healing is delayed, and vaccination efficacy is reduced (Segerstrom & Miller, 2004; Alotiby, 2024; Glaser & Kiecolt-Glaser, 2005; Balcerowska & Kwaśnik, 2025).

#### **3.2 Hyperactivity of the sympathetic nervous system**

Prolonged stimulation of the sympathetic nervous system increases norepinephrine and adrenaline levels. This impairs the cytotoxic capacity of natural killer (NK) cells and reduces the phagocytic activity of macrophages. Antigen presentation by dendritic cells is disrupted, hindering the initiation of adaptive immune responses (Segerstrom & Miller, 2004; Warren et al., 2024; Katz et al., 2025).  $\beta$ -adrenergic signaling shifts the cytokine profile toward a Th2 response, weakening antiviral immunity and promoting chronic inflammatory processes (Glaser & Kiecolt-Glaser, 2005; Alotiby, 2024; Warren et al., 2024).

#### **3.3 Cytokine imbalance**

Chronic stress shifts the cytokine balance toward a pro-inflammatory profile. Pro-inflammatory cytokines such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$  increase, while antiviral cytokines like IFN- $\gamma$  decrease. This shift contributes to the maintenance of chronic, low-grade inflammation, which can exacerbate numerous diseases (Glaser & Kiecolt-Glaser, 2005; Alotiby, 2024; Warren et al., 2024; Bolton, 2024).

#### **3.4 Impairment of innate immunity**

Chronic stress significantly impairs key innate immune cell functions. Macrophage phagocytic activity decreases, and NK cells exhibit reduced cytotoxicity toward target cells. Moreover, dendritic cells present antigens less effectively, limiting the initiation of immune responses and weakening defense against pathogens (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Alotiby, 2024; Biology 2025 Editorial Team, 2025).

#### **3.5 Dysfunction of adaptive immunity**

Prolonged stress reduces lymphocyte proliferation, disrupts T cell differentiation, and shifts immune responses toward a Th2 profile. This weakens both humoral and cellular immunity, including vaccine responses. Consequently, the organism becomes less resistant to viral and bacterial infections, and the capacity to generate long-term immune memory is reduced (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Alotiby, 2024; Katz et al., 2025).

#### 4. Discussion

Analysis of the literature indicates that chronic stress plays a clinically significant role in modulating immune function. The interaction of excess cortisol, sympathetic hyperactivity, and cytokine imbalance leads to weakened immune responses, increased susceptibility to infections, and worse outcomes in chronic diseases (Alotiby, 2024; Balcerowska & Kwaśnik, 2025; Chan et al., 2023).

##### 4.1 Increased susceptibility to infections

Individuals exposed to prolonged stress show heightened susceptibility to both viral and bacterial infections. Clinical studies indicate that infectious diseases in these patients have more frequent recurrences, longer duration, and more severe clinical symptoms (Segerstrom & Miller, 2004; Glaser & Kiecolt-Glaser, 2005; Alotiby, 2024; Black & Slavich, 2016).

##### 4.2 Impact on chronic diseases and inflammatory/metabolic processes

Epidemiological studies and reviews indicate that chronic psychological stress is a risk factor for cardiovascular diseases, including atherosclerosis. Stress can activate vascular inflammatory processes, promote endothelial dysfunction, and facilitate plaque formation. Chronic activation of neuroendocrine and immune stress pathways is associated not only with persistent inflammation but also with metabolic disorders, insulin resistance, and vascular dysfunction (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Warren et al., 2024; Bolton, 2024).

Increasing evidence also suggests that psychological stress may worsen the course of autoimmune or inflammatory diseases. In animal models, chronic stress exacerbates arthritis and skin disorders (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Alotiby, 2024; Warren et al., 2024; Black & Slavich, 2016).

Finally, the frequency and severity of chronic diseases in individuals exposed to prolonged stress seem to be indirectly related to chronic activation of immune and hormonal systems, suggesting that stress contributes to inflammatory states and immunologically mediated diseases (Warren et al., 2024; Black & Slavich, 2016; Creswell et al., 2012).

##### 4.3 Impact on autoimmune diseases

Individuals exposed to prolonged stress show a significantly increased risk of exacerbating autoimmune disease symptoms. Clinical studies indicate elevated pro-inflammatory cytokines, such as IL-6 and TNF- $\alpha$ , which correlate with worsening clinical outcomes (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Katz et al., 2025; Chan et al., 2023; Chen et al., 2023).

Examples of autoimmune diseases affected by chronic stress include:

- Rheumatoid arthritis (RA) – increased joint pain, morning stiffness, and swelling; stress may accelerate the progression of inflammatory joint changes (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Katz et al., 2025).
- Systemic lupus erythematosus (SLE) – increased disease flares, worsening skin condition, fatigue, and muscle pain (Segerstrom & Miller, 2004; Alotiby, 2024).
- Hashimoto's disease – elevated anti-thyroperoxidase antibodies and accelerated thyroid inflammation, resulting in worsened hormonal function and clinical symptoms (Alotiby, 2024; Balcerowska & Kwaśnik, 2025).
- Multiple sclerosis (MS) – both clinical and experimental studies indicate that chronic stress may exacerbate demyelination and increase relapse frequency (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004).

Prolonged stress exposure promotes HPA axis dysregulation and a pro-inflammatory cytokine environment, which may accelerate symptom progression and reduce treatment efficacy in autoimmune diseases (Bolton, 2024).

##### 4.4 Stress and cancer development

Individuals experiencing chronic stress show accelerated progression of certain cancers, including breast and colorectal cancer. Studies report reduced NK cell cytotoxic activity, increased angiogenesis, and elevated pro-inflammatory signals in the tumor microenvironment. These changes promote both local tumor growth and metastatic potential (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Alotiby, 2024; Balcerowska & Kwaśnik, 2025; Antoni et al., 2006; Katz et al., 2025; Chan et al., 2023).

##### 4.5 Benefits of stress reduction

Applying stress reduction strategies yields measurable benefits for both the immune system and overall health. Clinical studies indicate that regular mindfulness meditation practices reduce pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ , while simultaneously improving NK cell function (Black & Slavich, 2016; Creswell et al., 2012; Carlson et al., 2007). Morning cortisol peaks are also reduced (Black & Slavich, 2016; Creswell et al., 2012).

## 5. The Role of Digital Technologies in Stress Management and Immunity

In the modern era, digital technologies have emerged as pivotal tools in the assessment, management, and modulation of stress, which, in turn, has profound implications for immune function. Chronic stress is a well-established suppressor of both innate and adaptive immunity, increasing susceptibility to infections and exacerbating inflammatory conditions (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004). Digital interventions, including wearable devices, mobile applications, telemedicine platforms, and artificial intelligence (AI)-driven tools, offer novel avenues for monitoring physiological and psychological stress markers and implementing targeted strategies to counteract stress-induced immune dysregulation (Smith et al., 2023; Li & Zhao, 2024).

### 5.1 Wearables and biofeedback

Wearable devices, such as smartwatches, fitness trackers, and biosensor patches, allow continuous, real-time monitoring of physiological parameters associated with stress and immune function, including heart rate variability (HRV), sleep quality, and physical activity levels (Jerath, Syam, & Ahmed, 2023a; Smith et al., 2023). HRV, a measure of the variation in time between consecutive heartbeats, serves as a reliable biomarker of autonomic nervous system (ANS) balance. Reduced HRV is linked to heightened sympathetic nervous system activity and impaired parasympathetic modulation, which are characteristic of chronic stress and are associated with diminished NK cell activity and dysregulated cytokine production (Thayer & Sternberg, 2012; Chan et al., 2023).

Biofeedback systems integrated into wearable devices provide users with real-time information about their physiological states and guide them through exercises designed to restore autonomic balance. Techniques such as paced breathing, progressive muscle relaxation, and heart-rate-guided meditation have been shown to reduce sympathetic hyperactivity, normalize hypothalamic-pituitary-adrenal (HPA) axis function, and improve immune outcomes, including enhanced lymphocyte proliferation and lower pro-inflammatory cytokine levels (Jerath et al., 2023a; Li & Zhao, 2024). Moreover, wearable devices enable longitudinal tracking, allowing researchers and clinicians to identify patterns of stress-related immune dysregulation and evaluate the efficacy of interventions over time.

### 5.2 Mobile applications for stress reduction

Mobile applications provide accessible and scalable platforms for stress management through guided exercises such as mindfulness meditation, cognitive behavioral therapy (CBT), yoga, and breathwork (Black & Slavich, 2016; Li & Zhao, 2024). These interventions have been linked to measurable physiological changes, including reductions in cortisol and pro-inflammatory cytokines (IL-6, TNF- $\alpha$ ), alongside improvements in perceived stress and psychological well-being (Zhao et al., 2025; Creswell et al., 2012).

Regular engagement with mindfulness and CBT applications enhances adaptive coping strategies, fosters emotional regulation, and attenuates maladaptive stress responses that negatively affect immunity (Black & Slavich, 2016). For example, mindfulness-based digital interventions have been shown to increase NK cell activity, reduce inflammatory gene expression, and improve antibody responses, particularly in populations exposed to chronic psychosocial stress, such as caregivers and older adults (Creswell et al., 2012; Carlson, Specia, Faris, & Patel, 2007). Mobile platforms also support behavioral tracking and habit formation, enabling users to establish consistent routines that synergize with other lifestyle interventions, including exercise and sleep optimization, to reinforce immune resilience.

### 5.3 Telemedicine and virtual interventions

Telemedicine platforms extend the reach of psychological and behavioral interventions to individuals who may face barriers to in-person care, such as geographic distance or mobility limitations. Remote consultations with psychologists, therapists, and health coaches allow timely identification of stress-related risk factors and the implementation of personalized intervention strategies (Smith et al., 2023). Digital CBT programs delivered virtually have demonstrated efficacy in reducing anxiety, depressive symptoms, and perceived stress levels, which indirectly supports immune function by decreasing HPA axis overactivation and sympathetic hyperactivity (Creswell et al., 2012; Li & Zhao, 2024).

Telemedicine also enables the integration of multimodal interventions, combining behavioral therapy, guided physical activity, and sleep hygiene coaching. This integrated approach enhances physiological regulation and immune homeostasis, addressing both the psychosocial and biological determinants of stress-induced immunosuppression (Bolton, 2024; Thayer & Sternberg, 2012). Furthermore, telemedicine platforms can facilitate longitudinal monitoring and follow-up, ensuring that stress-reduction interventions are adapted over time based on user progress and biomarker feedback.

#### 5.4 Artificial intelligence in stress and immune monitoring

Artificial intelligence (AI) and machine learning algorithms have begun to play an increasingly prominent role in digital health platforms by analyzing complex datasets generated by wearables, mobile applications, and electronic health records (Li & Zhao, 2024; Zhao et al., 2025). AI models can detect early signs of stress-related immune dysregulation, such as elevated resting heart rate, low HRV, disrupted sleep, and deviations in self-reported stress measures, and provide predictive insights for personalized interventions.

These AI-driven systems can suggest individualized stress-reduction strategies, optimize intervention timing, and prioritize users at greatest risk of immune compromise due to chronic stress. Additionally, AI facilitates the integration of behavioral, physiological, and immunological data, supporting research on the mechanistic links between digital interventions, stress reduction, and immune outcomes (Li & Zhao, 2024). By leveraging predictive modeling, AI platforms can also support preventive healthcare, potentially reducing the incidence of stress-related illness and improving long-term immune resilience.

#### 5.5 Limitations and Ethical Considerations

Despite their potential, digital technologies for stress management have notable limitations. Device accuracy may vary, particularly in consumer-grade wearables, and self-reported data may be subject to bias or inconsistency (Smith et al., 2023). Adherence to guided interventions can also be inconsistent, with some users abandoning applications or failing to engage regularly. Importantly, digital interventions should complement, rather than replace, traditional psychosocial support and medical care.

Ethical considerations are paramount in digital health. These include the protection of personal data, informed consent, and the potential psychological impact of constant monitoring. Over-reliance on technology without addressing underlying social or environmental stressors may limit the long-term effectiveness of interventions and could potentially exacerbate anxiety related to health tracking (Smith et al., 2023; Li & Zhao, 2024).

#### 5.6 Future Directions

Emerging research highlights the potential of combining digital technologies with lifestyle interventions, such as exercise, sleep optimization, and nutrition, to create holistic programs that enhance stress resilience and immune function. Advances in wearable sensor technology, real-time data analytics, and AI-driven adaptive algorithms promise increasingly precise and personalized interventions. Large-scale, randomized controlled trials are needed to further quantify the immune benefits of these technologies and to establish evidence-based guidelines for their integration into clinical practice (Zhao et al., 2025; Jerath et al., 2023b).

### 6. Conclusions

Chronic stress is a multifaceted physiological and psychological phenomenon with profound implications for immune function. Persistent stress leads to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and hyperactivity of the sympathetic nervous system, resulting in elevated cortisol and catecholamine levels, cytokine imbalances, and impaired innate and adaptive immunity. These alterations manifest clinically as increased susceptibility to infections, delayed wound healing, reduced vaccine efficacy, and exacerbation of autoimmune, inflammatory, metabolic, and oncological conditions (Glaser & Kiecolt-Glaser, 2005; Segerstrom & Miller, 2004; Alotiby, 2024; Katz et al., 2025).

Populations particularly vulnerable to chronic stress include caregivers of chronically ill patients, healthcare workers, individuals with mental disorders, and people exposed to persistent social or occupational stress. Identifying these high-risk groups is crucial for implementing preventive and therapeutic strategies to mitigate the negative effects of stress on immunity (Bolton, 2024; Warren et al., 2024).

Effective interventions for stress reduction, such as mindfulness meditation, cognitive-behavioral therapy, regular physical activity, and proper sleep hygiene, have been shown to normalize immune function by reducing pro-inflammatory cytokines, enhancing NK cell activity, and restoring lymphocyte function (Black & Slavich, 2016; Creswell et al., 2012; Carlson et al., 2007; Nieman & Wentz, 2019). Digital technologies—including mobile applications, wearable devices, telemedicine, and artificial intelligence—offer innovative tools for real-time monitoring, personalized interventions, and improved adherence to stress-reduction practices (Smith et al., 2023; Li & Zhao, 2024; Zhao et al., 2025).

While digital interventions hold significant promise, their limitations, such as variable accuracy, ethical concerns, and risk of over-reliance, must be addressed. Integrating traditional and technology-driven stress management strategies provides a comprehensive framework for promoting immune health, supporting resilience, and enhancing overall well-being.

Understanding the intricate interplay between chronic stress, immunity, and technological interventions is essential for developing effective clinical and public health strategies aimed at improving long-term health outcomes.

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