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Post-Traumatic Stress Disorder as a Systemic Cascade: A Psychoneuroimmunological Systematic Review

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ABSTRACT: Post-Traumatic Stress Disorder (PTSD) has traditionally been viewed as a psychiatric condition; however, emerging evidence from psychoneuroimmunology (PNI) demonstrates that PTSD involves systemic physiological dysregulation extending across neural, endocrine, cardiovascular, gastrointestinal, and immune domains. This systematic review synthesizes recent findings from studies published between 2004 and 2025 to conceptualize PTSD as a psychoneuroimmunological cascade. Literature retrieved from PubMed, Scopus, and Web of Science was analyzed thematically to identify converging mechanisms of neuroendocrine, immune, and metabolic alterations associated with PTSD. The review reveals consistent patterns of hypothalamic pituitary adrenal (HPA) axis dysfunction, autonomic overactivation, chronic inflammation, gut–microbiota imbalance, and endocrine–immune cross-talk. These interconnected processes form self-perpetuating feedback loops that translate psychological trauma into systemic disease. PTSD should therefore be reframed as a multisystem disorder sustained by psychoneuroimmunological dysregulation rather than as a purely psychological condition. Integrative, multidisciplinary interventions—combining pharmacotherapy, mind–body therapies, and lifestyle modulation—are essential to restore systemic homeostasis and improve long-term outcomes. This reconceptualization expands theoretical understanding of PTSD, bridges psychiatry with internal medicine, and informs trauma-informed clinical and policy practices.

Keywords: Post Traumatic Stress Disorder, Psychoneuroimmunol ogy, Systemic Disorder, Inflammation, HPA Axis, Gut–Brain Axis, Allostatic Load.

INTRODUCTION

Post-Traumatic Stress Disorder (PTSD) is a debilitating psychiatric condition that develops following exposure to traumatic events and is characterized by intrusive recollections, hyperarousal, and persistent avoidance of trauma-related cues (Yehuda, 2002). Traditionally, PTSD

has been viewed as a mental disorder rooted in maladaptive fear conditioning and dysfunctional memory processing. However, recent advances in neurobiological research demonstrate that PTSD extends far beyond the psychological realm, manifesting as a system-wide disorder that profoundly affects multiple physiological systems (Arenson & Cohen, 2017). This conceptual transition—from a purely psychiatric diagnosis to a multisystem disorder—reflects the growing recognition that psychological trauma interacts with neuroendocrine and immune networks, creating lasting biological imprints that increase vulnerability to chronic diseases.

Globally, PTSD affects approximately 4–6% of the population, with significantly higher rates among trauma-exposed groups such as combat veterans, refugees, survivors of natural disasters, and healthcare professionals (Goldstein et al., 2020; Koenen et al., 2017). Epidemiological studies reveal that individuals with PTSD are at a 1.5- to 2-fold higher risk of developing cardiovascular disease, diabetes, thyroid dysfunction, and autoimmune disorders compared to those without PTSD (Edmondson et al., 2013; Mandagere et al., 2025; Vaccarino et al., 2013). The disorder therefore constitutes not only a major mental health challenge but also a pressing public health concern that contributes substantially to global morbidity and mortality.

Mounting evidence suggests that PTSD is underpinned by systemic physiological alterations—particularly chronic sympathetic activation, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, neuroinflammatory responses, and gut–microbiome imbalance (Malpas, 2010; Sumner et al., 2020; Zhang et al., 2025). These mechanisms mediate the interface between psychological stress and somatic health, explaining why PTSD frequently co-occurs with hypertension, metabolic syndrome, gastrointestinal disorders, and autoimmune diseases. Such findings lend empirical support to the field of psychoneuroimmunology (PNI), which posits that mental and physical health are interconnected through dynamic feedback loops involving the brain, endocrine glands, and immune cells (Pace & Heim, 2011).

From a theoretical standpoint, PTSD may represent a chronic state of allostatic overload—a condition in which repeated activation of the stress response leads to cumulative wear and tear across bodily systems (McEwen, 2023). This concept bridges psychiatry and physiology by suggesting that unresolved trauma can dysregulate systemic homeostasis through persistent alterations in cortisol secretion, autonomic tone, and inflammatory signaling. Over time, this biological dysregulation fosters a cascade of adverse outcomes that span from endothelial dysfunction to altered immune tolerance.

Despite these advances, much of the literature on PTSD's physical comorbidities remains fragmented across specialties. Cardiologists, endocrinologists, gastroenterologists, and immunologists have independently reported trauma-related alterations within their respective systems, yet few studies integrate these findings within a unified theoretical model. Moreover, conventional psychiatric frameworks often overlook these peripheral pathophysiological processes, limiting the effectiveness of existing treatment paradigms. Recognizing PTSD as a psychoneuroimmunological disorder rather than a purely psychological one is essential for developing holistic, interdisciplinary approaches to both prevention and treatment.

The present review therefore aims to consolidate recent empirical evidence linking PTSD with multisystem physiological dysfunction. By systematically synthesizing data across cardiovascular, endocrine, gastrointestinal, and immune domains, this paper advances a comprehensive model of PTSD as a systemic cascade disorder. The review also discusses emerging mechanistic insights from psychoneuroimmunology and proposes integrated clinical strategies that bridge psychiatry with internal medicine. Such a synthesis is expected to inform future research directions and guide clinicians toward more comprehensive, trauma-informed care for individuals affected by PTSD.

Theoretical Framework and Hypothesis

The psychoneuroimmunological (PNI) framework provides a comprehensive model for understanding how psychological trauma exerts systemic physiological effects. Rooted in the integration of neuroscience, endocrinology, and immunology, PNI emphasizes that mental processes are biologically embodied and reciprocally linked with physical health outcomes (Pace & Heim, 2011). Within this framework, PTSD can be conceptualized as a chronic condition of systemic dysregulation, where persistent stress responses disrupt the body's capacity to maintain homeostasis across multiple physiological systems.

When a traumatic event occurs, the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic–adrenal–medullary (SAM) system are activated to mobilize stress responses. In acute situations, this activation is adaptive. However, when prolonged, as in chronic PTSD, it induces allostatic overload—a cumulative physiological wear and tear caused by repeated neuroendocrine activation. Elevated cortisol and catecholamines initially serve to regulate energy and inflammation, but chronic exposure results in desensitization of glucocorticoid receptors, leading to paradoxical cortisol resistance and sustained inflammatory signaling (Dhabhar, 2018). This imbalance between stress hormones and immune regulation forms the biological core of PTSD as a systemic condition.

The neuroinflammation theory further extends the PNI model by emphasizing the role of microglia activation and pro-inflammatory cytokines in altering neural circuitry (Slavich, 2020). Chronic inflammation influences amygdala hyperreactivity, hippocampal atrophy, and prefrontal cortex dysfunction—neural signatures consistently observed in PTSD imaging studies (Gill et al., 2022). These central changes, in turn, reinforce peripheral inflammation through a bidirectional brain–body feedback loop, establishing a self-sustaining cycle of physiological dysregulation.

At the organ-system level, this framework predicts multilevel physiological consequences spanning cardiovascular, endocrine, gastrointestinal, and immune domains. Cardiovascular disturbances emerge through sympathetic overactivity and endothelial inflammation (Akosile et al., 2018; Malpas, 2010). Endocrine disruption manifests as altered cortisol rhythms and thyroid autoimmunity (Toloza et al., 2020). The gut–brain axis becomes dysregulated through stress-induced microbial imbalance, which further modulates systemic inflammation (Cryan et al., 2019). Finally, immune dysfunction promotes autoantibody production and impaired tissue repair

(Mandagere et al., 2025). These interconnected mechanisms highlight that PTSD does not affect isolated systems but propagates through an integrated physiological network.

This theoretical framework positions PTSD within a biopsychosocial systems paradigm, where trauma-induced neural dysregulation triggers downstream endocrine and immune alterations, thereby linking mental distress with physical morbidity. Conceptually, PTSD can thus be understood as a multi-organ cascade disorder—a state of disrupted systemic coherence maintained by chronic psychoneuroimmunological feedback. This model provides the theoretical foundation for the analyses and interpretations presented in the following discussion.

METHOD

1. Design of the Study: This study employed a systematic review design, synthesizing peer-reviewed evidence on the association between PTSD and physical health outcomes.
2. Data Sources: Electronic databases including PubMed, PsycINFO, Scopus, and Web of Science were systematically searched using keywords such as post-traumatic stress disorder, PTSD, cardiovascular disease, endocrine dysfunction, gastrointestinal disorders, autoimmunity, and psychoneuroimmunology.
3. Inclusion and Exclusion Criteria: Articles were included if they (a) were published in English; (b) involved human participants; and (c) reported associations between PTSD and at least one physical health outcome. Studies were excluded if they (a) were case reports or conference abstracts; (b) lacked methodological rigor; or (c) were not peer-reviewed.
4. Screening and Data Extraction: Two reviewers independently screened titles, abstracts, and full texts. Discrepancies were resolved through consensus. Data extracted included author(s), publication year, study population, design, measures of PTSD, physical health outcomes, and key findings (Edmondson et al., 2013).
5. Quality Assessment: Methodological quality was appraised using standardized tools appropriate for observational and meta-analytic studies.
6. Data Synthesis: A narrative synthesis was conducted to summarize associations across cardiovascular, endocrine, gastrointestinal, and autoimmune outcomes. Where available, pooled effect sizes from meta-analyses were highlighted to strengthen the evidence base (Akosile et al., 2018; Mandagere et al., 2025).

RESULT AND DISCUSSION

The findings from this systematic review converge on a clear conclusion: PTSD exerts pervasive effects across multiple physiological systems through chronic dysregulation of psychoneuroimmunological pathways. Rather than functioning as an isolated psychiatric condition, PTSD operates as a multisystem disorder sustained by continuous cross-talk between neural, endocrine, immune, and metabolic circuits. This section integrates evidence from the

cardiovascular, endocrine, gastrointestinal, and immune domains to illustrate the cascading nature of this systemic dysregulation.

Cardiovascular Dysregulation and Autonomic Overload

Consistent evidence indicates that PTSD is associated with increased incidence of hypertension, coronary artery disease, and cardiac mortality (Akosile et al., 2018; Edmondson & Känel, 2017). The primary driver of this relationship lies in chronic sympathetic overactivity—manifested through persistent elevations in catecholamines and reduced vagal tone. This autonomic imbalance promotes endothelial injury, platelet aggregation, and systemic inflammation (Edmondson & Cohen, 2021; Wirtz & Känel, 2017). Over time, these alterations produce a hyper-reactive cardiovascular system, where stress-related physiological arousal becomes pathogenic rather than adaptive. This phenomenon represents the archetype of allostatic overload (McEwen, 2023), where compensatory mechanisms that once promoted survival ultimately degrade vascular and metabolic integrity.

Endocrine Disruptions and HPA Axis Dysregulation

PTSD-related endocrine disturbances reflect maladaptive regulation of the HPA axis and thyroid function. Studies report inconsistent cortisol patterns—both hypo- and hypercortisolism—indicating loss of rhythmic control and receptor sensitivity (Tsatsoulis, 2006). This dysregulation alters energy metabolism, contributes to insulin resistance, and may facilitate the onset of type 2 diabetes and obesity (Winning et al., 2015). Simultaneously, autoimmune thyroiditis and altered sex hormone profiles have been documented, underscoring the link between chronic psychological stress and endocrine autoimmunity (Mizokami et al., 2004). These hormonal alterations feed back into central nervous system processes, amplifying anxiety and hyperarousal, thereby creating a bidirectional loop between mental and endocrine health.

Gut–Brain Axis and Microbiota-Inflammation Feedback

Emerging evidence underscores the role of the gut microbiota as a pivotal mediator of the brain–immune interface in PTSD. Stress-induced dysbiosis alters intestinal permeability, facilitating translocation of bacterial endotoxins that activate systemic inflammatory cascades (Bastiaanssen et al., 2023). Experimental and clinical studies show that PTSD patients exhibit reduced microbial diversity, particularly decreased levels of Lactobacillus and Bifidobacterium, which are associated with regulation of the HPA axis (Foster et al., 2024). The resulting inflammatory milieu disrupts serotonin synthesis and vagal signaling, contributing to both gastrointestinal distress and mood instability. Thus, the gut–brain axis represents a central hub where psychological trauma translates into physiological dysregulation.

Immune Dysregulation and Autoimmunity

A substantial body of research demonstrates heightened systemic inflammation and autoimmunity among PTSD populations. Elevated cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) are consistently reported (Sumner et al., 2020). Longitudinal studies reveal that this chronic low-grade inflammation precedes the onset of autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (Mandagere et al., 2025). The persistence of these markers, even years after trauma exposure, suggests that immune system recalibration following PTSD is incomplete—indicating long-term psychoneuroimmunological scarring. This state of inflammatory memory may partly explain why PTSD is linked to premature aging and increased all-cause mortality.

Cross-System Integration: The Psychoneuroimmunological Cascade

Synthesizing across these domains, PTSD can be viewed as a self-perpetuating cascade of dysregulation. Chronic stress activates the HPA axis and sympathetic nervous system, elevating cortisol and catecholamines. These hormones modulate immune cell function, triggering inflammatory signaling that feeds back to the brain through cytokine-mediated neural sensitization (Slavich, 2020). Meanwhile, gut dysbiosis amplifies immune reactivity, and immune activation sustains endothelial dysfunction—linking gut, vascular, and neural inflammation within a closed-loop feedback system.

In this context, the hypothalamus serves as the central integrator, coordinating neuroendocrine and immune responses (Yang & Liu, 2023). The breakdown of its regulatory capacity under chronic stress results in parallel dysfunction across organ systems—a hallmark of systemic cascade pathology. This framework explains why PTSD's physical comorbidities rarely occur in isolation and often co-cluster in patients as complex multimorbidity syndromes.

Conceptual Implications

The integrative evidence presented here reframes PTSD as a disorder of biological network dysregulation rather than isolated organ pathology. It extends the PNI model by incorporating concepts of allostatic load, neuroinflammation, and gut–microbiome signaling into a unified mechanistic synthesis. This theoretical refinement provides a robust foundation for future research exploring systemic biomarkers, cross-system interventions, and longitudinal pathways of recovery. It also underscores the need for clinical paradigms that treat PTSD through an integrative lens—addressing both neural trauma and its physiological echoes throughout the body.

Integrative Treatment Implications

Recognizing PTSD as a psychoneuroimmunological disorder necessitates a paradigm shift in treatment—from symptom management to systemic restoration. Conventional approaches that target only psychiatric manifestations are insufficient to reverse the chronic physiological dysregulation underlying PTSD. Instead, an integrative care model that bridges psychiatry, internal

medicine, and behavioral health is essential for long-term recovery and prevention of comorbid diseases.

Pharmacological and Neurobiological Interventions

Pharmacotherapy remains foundational for alleviating the psychiatric symptoms of PTSD. Selective serotonin reuptake inhibitors (SSRIs) such as sertraline and paroxetine demonstrate efficacy in reducing hyperarousal and intrusive symptoms while partially normalizing autonomic tone (Williams et al., 2022). However, the modest physiological effect sizes of SSRIs suggest that pharmacological intervention alone cannot fully restore homeostatic balance. Novel treatments targeting neuroinflammatory mechanisms, such as anti-cytokine agents or neurosteroids, are under investigation and may offer adjunctive benefits. These emerging therapies highlight the need for biologically informed approaches that address PTSD's systemic substrates rather than its surface symptoms.

Mind–Body and Psychophysiological Regulation Therapies

Mind–body therapies have demonstrated measurable effects on stress physiology. Mindfulness-based stress reduction (MBSR) and yoga interventions significantly lower cortisol levels, reduce systemic inflammation, and improve heart rate variability—indicators of restored autonomic regulation (Hoge et al., 2021; Regehr & Leblanc, 2017). Biofeedback and neurofeedback techniques similarly help patients gain conscious control over physiological arousal, improving both mental resilience and immune balance. These interventions act directly on the PNI loop, fostering re-regulation of the brain–body interface.

Lifestyle and Nutritional Modulation

Lifestyle modification represents another vital pillar of systemic healing. Regular physical activity enhances vagal tone, reduces inflammatory cytokines, and mitigates metabolic dysregulation commonly observed in PTSD (Winning et al., 2015). Sleep hygiene programs restore circadian alignment, counteracting endocrine imbalances linked to HPA axis dysfunction. Nutritional interventions, particularly anti-inflammatory diets and probiotic supplementation, show promise in modulating the gut–brain–immune axis. Probiotics such as Lactobacillus rhamnosus have been found to reduce anxiety-like behavior and normalize gut microbial diversity in stress-related conditions (Foster et al., 2024). Collectively, these findings underscore that treating PTSD requires attention not only to neural pathways but also to metabolic and microbiological balance.

Integrative and Multidisciplinary Care Models

At the clinical systems level, effective management of PTSD demands collaborative care pathways involving psychiatrists, cardiologists, endocrinologists, and immunologists. Integrating routine physiological monitoring—such as cortisol levels, blood pressure, inflammatory markers, and microbiota profiles—into mental health practice can facilitate early detection of systemic risk

(Edmondson & von Känel, 2017). Trauma-informed primary care frameworks are particularly beneficial for addressing the medical sequelae of chronic stress while reducing fragmentation between mental and physical health services. Yehuda et al., (2023) emphasize that multidisciplinary care not only improves symptom remission but also lowers long-term mortality and healthcare burden among trauma-exposed individuals.

Public Health and Policy Implications

From a public health perspective, reconceptualizing PTSD as a systemic disorder has significant implications for prevention and policy. Screening for PTSD should be integrated into cardiometabolic and endocrine clinics, where physical comorbidities often first manifest. Public health campaigns that promote trauma awareness, resilience-building, and community-based interventions can mitigate the chronic inflammation and metabolic risks associated with PTSD. Moreover, insurance systems and national mental health policies should support integrative treatment frameworks that combine psychotherapy, pharmacology, and physiological rehabilitation as part of comprehensive trauma care.

CONCLUSION

This systematic review consolidates multidisciplinary evidence demonstrating that Post-Traumatic Stress Disorder (PTSD) is not merely a psychiatric condition but a multisystem disorder characterized by chronic psychoneuroimmunological dysregulation. Across the reviewed literature, consistent associations were found between PTSD and dysfunctions in cardiovascular, endocrine, gastrointestinal, and immune systems. These findings collectively substantiate the psychoneuroimmunological cascade model, wherein sustained stress activation, neuroendocrine imbalance, and immune dysregulation create self-perpetuating feedback loops of physiological disturbance.

At the theoretical level, this synthesis extends the psychoneuroimmunology (PNI) framework by integrating emerging concepts such as allostatic overload, neuroinflammation, and gut–brain–immune signaling. PTSD thus represents a paradigmatic example of how psychological trauma becomes biologically embodied—translating mental distress into systemic pathology through complex feedback among the brain, endocrine glands, and immune networks. This reconceptualization supports a biopsychosocial systems model of mental illness that transcends the traditional mind–body dichotomy.

Clinical and Practical Implications

The recognition of PTSD as a systemic disorder has profound implications for clinical practice. Integrating physical health screening—such as cardiovascular, metabolic, and inflammatory assessments—into routine psychiatric evaluation should become standard care. Clinicians should

collaborate across disciplines, linking psychiatric treatment with cardiology, endocrinology, and immunology to address the full spectrum of PTSD's physiological consequences. Furthermore, implementing trauma-informed primary care and integrative health frameworks can improve early detection, reduce long-term morbidity, and enhance patient outcomes. Mind–body interventions, lifestyle modulation, and nutritional therapies, when combined with pharmacotherapy, hold promise for restoring systemic homeostasis and preventing recurrent dysregulation.

Research Implications

Future studies should adopt longitudinal and multimodal designs to elucidate causal relationships between chronic stress exposure and systemic disease development. Biomarker-based research integrating neuroimaging, hormonal profiling, microbiota sequencing, and immune phenotyping is needed to map the precise biological pathways linking trauma and physiology. Comparative intervention studies should evaluate the efficacy of integrative approaches—such as combining psychotherapeutic, pharmacological, and physiological rehabilitation—in normalizing psychoneuroimmunological markers.

Policy and Public Health Implications

At the population level, recognizing PTSD as a systemic disorder calls for policy reform. National mental health programs should collaborate with cardiovascular, metabolic, and endocrine health initiatives to create trauma-informed preventive strategies. Insurance systems and funding bodies must support multidisciplinary treatment models and translational research bridging psychiatry and internal medicine. Public education campaigns emphasizing the bodily consequences of psychological trauma could also reduce stigma and encourage timely intervention.

Limitations of This Review

This review is limited by the heterogeneity of included studies and potential publication bias favoring positive associations. The cross-sectional nature of most studies restricts causal inference. In addition, differences in measurement tools and diagnostic criteria across studies may have introduced variability in reported effect sizes. Nonetheless, the consistency of findings across diverse samples and methodologies strengthens the overall conclusion that PTSD produces systemic physiological consequences.

Concluding Remarks

In summary, the evidence supports reframing PTSD as a psychoneuroimmunological cascade disorder—a dynamic state of chronic dysregulation affecting the brain, body, and immune system in concert. This conceptualization not only advances theoretical understanding but also transforms

clinical and public health approaches to trauma. By integrating mind–body medicine, systemic screening, and interdisciplinary care, it becomes possible to move from symptom control toward holistic recovery and long-term resilience. Ultimately, addressing PTSD as both a psychological and biological condition may redefine the future of trauma-informed healthcare.

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