

Current Developments in the Physiological Effects of Stress: Mechanisms and Health Consequences - Structured Narrative Review

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Abstract

Background: Stress is an essential adaptive process that links neuroendocrine, autonomic, immunological, metabolic, and behavioural reactions to a perceived or real challenge. Generally, acute activation is protective, while chronic activation or insufficient recovery could lead to multisystem dysregulation and allostatic load over time.

Objectives: To integrate current literature regarding the physiological pathways involved in the relationship between acute and chronic psychological stress and health outcomes, with a particular focus on neuroendocrine, autonomic, immune, metabolic, neural, cardiovascular, mitochondrial and cellular-aging pathways.

Method: A structured narrative review was conducted on PubMed/MEDLINE, ScienceDirect/Elsevier LeapSpace and Google Scholar citation searching. We prioritized all human systematic reviews, meta-analyses, prospective cohorts, and experimental studies published from 2019 to September 2026, and included earlier seminal studies as needed to provide conceptual or mechanistic background. We did not quantitatively pool evidence; instead, we synthesized it thematically.

Results: The literature suggests a dynamic, context-dependent stress response leading to coordinated activation of the HPA axis and the

autonomic nervous system. Persistent dysregulation is linked to disrupted cortisol function, decreased autonomic recovery, inflammation, metabolic dysfunction, cardiovascular risk, cognitive risk factors, and biological ageing. Few studies have directly tested human mitochondrial evidence, though cell-free mitochondrial DNA and related markers are promising biomarker candidates. Across domains, the best evidence supports multisystem associations, and causal inference and biomarker standardization remain key limitations.

Conclusions: stress results in a biological phenotype that is not homogeneous. Its effects are stressor-specific, time-dependent, recovery-dependent, adversity-history-dependent, and susceptibility- and measurement-dependent. Future studies should focus on longitudinal multimodal phenotyping, standardized biomarkers, and causal designs to elucidate the time window during which adaptive stress responses become biologically deleterious.

1. Introduction

Stress should be viewed as a dynamic process involving the body and not just a pathological state. In response to physical, psychological, or social challenges, the central nervous system assesses the stimulus's controllability and salience and activates actions that help to adapt quickly. Two main effector systems are involved: the sympathetic-adrenomedullary system and the hypothalamic-pituitary-adrenal (HPA) axis. They activate to mobilize energy, increase cardiovascular output, and heighten vigilance and behavioral readiness. This is usually time-limited and succeeded by recovery. However, prospective data suggest that both hyper- and hypo-responsiveness to stress can be linked to later health outcomes, indicating a more complex, context-specific relationship rather than a straightforward “more cortisol is more stress” explanation [1].

Allostasis is a useful model for understanding this complexity. Allostasis is defined as the ability to maintain stability through physiological change, and allostatic load as the cumulative biological load resulting from repeated adaptation or failure to recover. Modern research has focused on the multidimensionality of allostatic load, as it can include neuroendocrine, cardiovascular, metabolic and inflammatory markers. Studies have linked higher allostatic load to mortality and cardiovascular disease, but definitions vary widely [4,5,31].

Stress affects more than the HPA axis. Autonomic regulation, immune-inflammatory signaling, glucose metabolism, mitochondrial function and neural plasticity/epigenetic processes are interdependent. Such an integrated model can help to rationalize the correlation of stress exposure with a variety of outcomes, such as hypertension, metabolic dysfunction, cognitive impairment and accelerated biological aging. Concurrently, the evidence is not conclusive; increased cortisol levels do not necessarily characterize stress responses, decreased heart-rate variability (HRV) is not exclusive to increased sympathetic activity, and links between perceived stress and metabolic and/or epigenetic outcomes are inconsistent across populations [2,7,20,32].

Thus, this review focuses on recent advances in the physiological effects of stress, highlighting the relative stability of these effects in humans, the ongoing emergence of new findings, and areas of uncertainty or confounding in causal interpretation.

2. Methodology

This article was not a systematic review or meta-analysis, but rather a structured narrative review. The aim was to compile current, up-to-date human scientific data on the physiological mechanisms and health effects of psychological stress, with a specific focus on identifying relatively well-established data and distinguishing them from more heterogeneous or emerging evidence. The main literature sources were PubMed/MEDLINE and ScienceDirect/Elsevier LeapSpace, with additional citation chasing and identification of relevant related studies through Google Scholar.

The search spanned 2019: Jan. – 2026: Sep. The following concepts were used to organize the search: psychological stress, chronic stress, psychosocial stress, occupational stress, life stress, adversity, HPA axis, cortisol, corticotropin-releasing hormone, autonomic nervous system, sympathetic, parasympathetic, heart rate variability, inflammation, cytokines, oxidative stress, mitochondria, mitochondrial DNA, metabolic dysfunction, insulin resistance, cognition, cardiovascular disease, epigenetic aging, DNA methylation, allostatic load. If a combined query is not specific enough, we use domain-specific searches. We also explored reference lists and citation links from key reviews and highly relevant studies to find earlier or more recent evidence. For reproducibility, the core Boolean search strategy was: ("psychological stress" OR "psychosocial stress" OR "chronic stress" OR "occupational stress" OR adversity OR "life stress") AND ("HPA axis" OR cortisol OR "autonomic nervous system" OR sympathetic OR parasympathetic OR "heart rate variability" OR inflammation OR cytokine* OR "oxidative stress" OR mitochondria* OR "mitochondrial DNA" OR "metabolic dysfunction" OR "insulin resistance" OR cognition OR "cardiovascular disease" OR "DNA methylation" OR "epigenetic aging" OR "allostatic load"). We adapted database-specific syntax as needed and used domain-specific searches when the combined query was insufficiently specific.

Criteria for eligibility: relevance to human stress and a clinically relevant health outcome with a physiological, molecular, or clinically meaningful basis. We prioritized human systematic reviews, meta-analyses, and prospective cohort and experimental studies. We retained studies from earlier studies that provided conceptual or mechanistic information not adequately covered in newer literature. We included animal and cellular studies only for mechanistic context and did not give them the same weight as direct human evidence. We did not remove studies with null or inconsistent findings but included them in the narrative synthesis when findings were inconsistent.

We selected studies through an iterative process of title/abstract screening, followed by full-text review and reference list checks. We did not conduct duplicate independent screening or a formal adjudication process, as this was a single-reviewer structured narrative synthesis. The review therefore cannot claim to have systematically reviewed all records, and we did not attempt to produce a numerical estimate of all records retrieved or excluded. Take this limitation into account when considering the extent of the evidence base.

In synthesis, we included studies based on study design, population, method of stress exposure or measurement, biological endpoint, main finding, consistency with other studies in the field, and major study limitations. We presented evidence in the following domains: neuroendocrine system, autonomic system, immune-inflammatory system, oxidative/mitochondrial system, metabolic system, neural/cognitive system, cardiovascular system, and cellular/epigenetic system. We interpreted the findings by considering acute and chronic exposures, reactivity and recovery, timing of measurement, biological compartment, population characteristics, and potential confounding. We distinguished between associative and causal relationships, and between direct human evidence and mechanistic evidence based primarily on model experiments.

Because literature varies in its definition of exposure, populations, biomarkers, sampling conditions, and outcomes, we did not perform a quantitative meta-analysis. The synthesis instead focused on convergence, disagreement and the maturity of evidence for each physiological domain. The final interpretation thus uses three broad categories of evidence: relatively established human evidence, moderate or heterogeneous evidence, and emerging evidence that needs further validation.

3. Results

3.1 Stress physiology and allostasis

Acute stress triggers coordinated changes that are typically adaptive. The sympathetic-adrenomedullary response is rapid, increasing catecholamine availability, heart rate, vascular tone, and energy mobilization, whereas the HPA-axis response is slower and produces a glucocorticoid response. These systems work in conjunction with immune and metabolic systems and then need to recover effectively. Emerging evidence suggests that overreactivity or underreactivity to contexts can have negative consequences, so that there may be better adaptations at intermediate or appropriately regulated levels of reactivity than at either extreme [1].

Allostatic load attempts to quantify the sum of biomarkers across systems of repeated adaptation. Methodological consensus is lacking regarding the biomarkers and thresholds used to assess allostatic load in multi-cohort studies. However, a meta-analysis shows an association between allostatic load and death and cardiovascular disease. The results demonstrate the need for a physiological framework and caution when interpreting any single biomarker as an indicator of chronic stress. [4,5,31]

3.2 Neuroendocrine mechanisms

Psychological stress and systemic physiology are linked through the HPA axis. Neural signaling in response to stress activates corticotropin-releasing hormone and arginine vasopressin in the hypothalamus, which triggers adrenocorticotrophic hormone and cortisol secretion in the adrenal. Cortisol then acts via glucocorticoid receptors to affect metabolism, immune activity, and nervous system function. Importantly, chronic stress is associated with changes in HPA regulation, not sustained high cortisol levels. Responses may be magnified or diminished depending on the nature of the stressor, the amount and length of exposure, and individual adaptation and timing of measurement [1-3].

Recent syntheses of Trier Social Stress Test reviews show significant differences between biological systems, underscoring the need to consider response kinetics and sampling conditions. The direction and magnitude of cortisol changes depend on intervention and population and may be influenced by stress-management interventions. Therefore, cortisol is best viewed as part of a stress phenotype, not a single diagnostic test for stress [2,6].

3.3 Autonomic mechanisms

Stress quickly affects cardiovascular physiology and behavior via the ANS. The parasympathetic system is active during recovery, while the sympathetic system increases cardiac output and vascular tone. HRV, particularly vagally modulated parameters, such as RMSSD, may provide important data regarding autonomic regulation and recovery from stress. However, several factors affect HRV, including respiration, posture, age, medication, fitness, comorbidity, and measurement conditions, and HRV should not be used directly or solely as a measure of sympathetic activity [7].

Recent evidence increasingly focuses on recovery, rather than peak reactivity. In a large scoping review of studies on acute psychological stress, greater cardiac vagal recovery was typically linked to resilience-related outcomes. In comparison, poorer cardiac vagal recovery was linked with adverse psychological or cardiovascular outcomes. Small to moderate effects also emerge for emotional and physical outcomes

with HRV biofeedback, which highlights the potential clinical significance of autonomic regulation and the inter-protocol and inter-population variability [8,9].

3.4 Immune and inflammatory mechanisms

Stress affects immune function via glucocorticoid signaling, catecholamines, immune-cell trafficking, and cytokines. Stress can acutely trigger immune redistribution and changes in inflammatory signaling that may be adaptive. Alterations in glucocorticoid sensitivity and β 2-adrenergic signaling may, however, lead to a more pro-inflammatory state with persistent psychological stress [10].

Childhood and adolescent adversity may be related to inflammatory burden throughout life and be biologically embedded. Meta-analyses of psychological interventions also suggest potential to alter inflammatory markers, with some interventions and markers showing a beneficial effect while others show no effect. There is greater consistency of inflammatory changes in clinical populations with depression, compared to anxiety and PTSD alone, highlighting the role of phenotype and/or comorbidity. In addition, salivary immunoglobulin responses to acute stress are highly time-dependent, so sampling time can significantly affect interpretation [11-14].

3.5 Oxidative and mitochondrial mechanisms

Oxidative and mitochondrial pathways are an important but less developed area of human stress research. Psychological stress may influence mitochondrial energetics, reactive oxygen species signaling, mitochondrial DNA integrity, and the release of mitochondrial components into circulation. Studies report significant variability in circulating cell-free mitochondrial DNA (cf-mtDNA) levels and inconsistent associations with inflammation. Still, it may be a promising candidate biomarker because it can change dynamically with stress [15].

Direct mechanistic studies in humans are far less extensive than those in animal literature and cellular studies. A 2026 experimental human study reported emerging evidence that psychological stress is associated with measurable mitochondrial responses in humans, including stress-related changes in circulating mitochondrial material and metabolic correlates in the medial prefrontal cortex. Yet, because of small sample sizes, indirect tissue measures, and limited standardization, mitochondrial biomarkers are currently used as exploratory rather than clinical markers [16,17].

3.6 Metabolic mechanisms

Stress hormones affect glucose availability, hepatic metabolism, appetite, adipose biology and insulin signaling. Cortisol and catecholamines help mobilise acute energy, but prolonged activation of the neuroendocrine system can lead to metabolic dysfunction in vulnerable people. There is strong evidence for associations between psychological/occupational stressors and metabolic syndrome and between insulin resistance and incident type 2 diabetes, but results for associations with individual measures, like obesity or HOMA-IR, are more variable [18-21].

A prospective cohort study found a relationship between occupational stress and insulin resistance and incident type 2 diabetes, with several cardiometabolic variables involved in the overall relationship. A more recent (2026) systematic review of perceived stress and metabolic parameters found high heterogeneity and many null relationships, but also some exploratory associations with insulin resistance. The results highlight the importance of taking into account the type of stressor, population, type of behaviour, and measure of outcome when studying the metabolic consequences of stress [19,20].

3.7 Neural and cognitive effects

Stress affects cognition through interactions among glucocorticoids, catecholamines, inflammatory mediators, and neural networks that regulate attention, memory, and executive function. Acute stress doesn't uniformly impair cognition. Evidence for episodic memory effects may be less robust than anticipated, and effects on executive functions may vary with task characteristics and timing. Stress can also alter memory processing to focus on more current, threat- or adaptation-relevant information [23,25].

Longitudinal evidence is more supportive of a link between ongoing psychological stress or distress and subsequent cognitive vulnerability. A systematic review and meta-analysis showed that stress was associated with the risk of mild cognitive impairment or dementia, and another systematic review found that self-reported stress was associated with cognitive decline. A large multi-cohort (2026) study further reported that a higher baseline Psychological Distress score was associated with lower cognitive function and dementia at follow-up. Still, the authors noted that the role of causality and the possibility of preclinical disease and confounding were not fully addressed [22,24,26].

3.8 Cardiovascular effects

Some of the most reliable and consistent physiological reactions to acute stress are cardiovascular. These include increased HR, contractility, vascular tone, and increased catecholamine release by sympathetic activation, as well as the effects of the HPA axis and inflammatory pathways on vascular and metabolic function. A systematic review and meta-analysis showed that stress hormones were associated with cardiovascular disease risk, and current cardiovascular reviews have combined autonomic, vascular, inflammatory, and neural mechanisms into a holistic stress-CVD model [27,28].

In a prospective, observational cohort study of 2215 patients with stable CHD, high perceived stress was shown to be a risk factor for cardiovascular events over 24 months (adjusted HR 1.369; 95% CI 1.037–1.807). But the link was less obvious after 24 months. Experimental evidence also shows that acute psychological stress increases pulse-wave velocity, an indicator of arterial stiffness, and systematic evidence indicate that higher allostatic load is associated with cardiovascular disease. [29-32]

3.9 Cellular, epigenetic and biological-aging effects

Stress can be embedded at epigenetic and molecular levels of biological aging. Observational and heterogeneous evidence from a systematic review and meta-analysis linked psychological adversity to epigenetic aging. Human longitudinal data have also linked psychological adversity to other indices of cumulative life stress, such as GrimAge and DunedinPACE, the former of which showed a dampened association after adjustment for health behaviors [32,33].

This is supported by other literature, as epigenome-wide studies have found DNA methylation differences associated with psychosocial stress, including studies suggesting an association with cardiometabolic risk factors. In particular, experimental evidence is compelling: a 2026 study showed acute, epigenome-wide changes in DNA methylation during stress. Acute methylation changes may not reflect chronic methylation changes, but it is unclear whether they last longer, are tissue-specific, or have clinical implications. [34,35]

3.10 Emerging biomarkers and monitoring approaches

No single biomarker reflects the body's full “stress load.” Cortisol reflects HPA axis regulation, HRV reflects autonomic nervous system regulation, inflammatory markers indicate immune activity, and cf-mtDNA or epigenetic measures indicate cellular responses. Timing, behavior, medication, comorbidity and technical factors affect each. The new trend is therefore not to rely on one “stress biomarker” but to use multimodal monitoring.

Wearable technologies may enable repeated assessment of heart rate, HRV, and sleep, and they may complement information from salivary, blood, and molecular measures. To implement this in the clinic, however, standardized protocols, validated thresholds, and future evidence are needed to show that biomarker-based intervention improves outcomes. It should therefore be considered a new idea in stress medicine that is being researched.

3.11 Evidence maturity across physiological domains

Evidence is inconsistent across the material searched. Growing human evidence suggests activation of the HPA axis and sympathetic-adrenomedullary systems during acute stress, cardiovascular reactions to acute stress, the importance of autonomic recovery, and links between increased allostatic load and poor health outcomes. Immune-inflammatory findings are significant and sensitive to phenotype, timing and biomarker selection. Metabolic and cognitive effects are supportive but variable, depending on exposure definitions and populations. In contrast, circulating cell-free mitochondrial DNA, direct mitochondrial measures, epigenetic aging, and multimodal or precision stress monitoring are emerging areas. This hierarchy matters because a statistically significant association does not necessarily equal a clinically validated biomarker or proven causal pathway, but rather biological plausibility.

Table 1. Major physiological mechanisms through which stress influences human health

Physiological system/ mechanism	Principal mediators	Acute response	Potential consequences of persistent dysregulation	Evidence
HPA axis	CRH, ACTH, cortisol, glucocorticoid receptors	Glucocorticoid mobilization	Altered cortisol regulation/feedback	Strong
Autonomic nervous system	Sympathetic/parasympathetic activity, catecholamines	Increased cardiovascular output and vigilance	Autonomic imbalance/impaired recovery	Strong
Immune/inflammatory signaling	Cytokines, immune-cell trafficking, glucocorticoid signaling	Transient immune modulation	Low-grade inflammation/altered cortisol-immune coupling	Moderate–strong
Oxidative/redox pathways	ROS, antioxidant systems, mitochondrial signaling	Controlled ROS signaling with metabolic activation	Oxidative damage/mitochondrial dysfunction	Moderate/emerging
Mitochondrial function	mtDNA, mitochondrial energetics, cellular respiration	Increased energy production	Altered bioenergetics and cellular stress	Emerging
Metabolic regulation	Cortisol, catecholamines, insulin/glucose pathways	Increased glucose/energy availability	Insulin resistance/metabolic syndrome	Moderate; heterogeneous

Neural/cognitive regulation	Glucocorticoids, catecholamines, inflammatory mediators	Attention/memory modulation	Cognitive vulnerability	Moderate
Cardiovascular regulation	Catecholamines, cortisol, autonomic and vascular signaling	Increased HR/BP/vascular tone	Hypertension/vascular dysfunction/CV risk	Strong
Cellular/epigenetic regulation	DNA methylation, epigenetic clocks, telomeres	Short-term molecular adaptation	Associations with biological aging	Emerging/moderate
Integrated allostatic load	Multisystem neuroendocrine, CV, metabolic and inflammatory biomarkers	Coordinated adaptation	Cumulative multisystem burden	Strong for association

Table 2. Selected contemporary human evidence linking stress-related physiology with health outcomes

Reference	Study type/population	Stress-related exposure or measure	Principal finding	Interpretation/limitation
Turner et al., 2020 [1]	Systematic review of prospective evidence	Psychological stress reactivity/HPA/SAM	Both exaggerated and blunted responses may predict different outcomes	Context and heterogeneity
McCrory et al., 2023 [4]	Multi-cohort IPD meta-analysis	Allostatic-load biomarkers	Supports multidimensional AL construct	Operational definitions vary
Roddick et al., 2025 [8]	Scoping review; 294 studies, n=23,533	Vagal HRV recovery	Better recovery is generally linked to resilience; blunted recovery is linked to adverse outcomes.	Recovery methods heterogeneous
Walsh et al., 2021 [10]	Systematic review across species	GR/ β 2-adrenergic signaling	Mechanistic link to pro-inflammatory conditions	Some evidence non-human
Ballesio et al., 2023 [12]	Systematic review/network meta-analysis; 104 RCTs	Psychological interventions/inflammation	Interventions can reduce inflammatory markers	Heterogeneity
Trumpff et al., 2021 [15]	Systematic review of human studies	Stress/cf-mtDNA	cf-mtDNA changes dynamically but is variable	Assay/standardization issues
Ankeeta et al., 2026 [16]	Experimental human; n=35	Acute stress/mitochondrial markers	Circulating mitochondrial material and prefrontal metabolic correlates changed.	Small, emerging evidence
Kuo et al., 2019 [18]	Systematic review/meta-analysis	Psychological/occupational stress	Association with metabolic syndrome	Longitudinal limitations
Chen et al., 2023 [19]	Prospective cohort	Occupational stress/metabolic dysfunction	Associated with insulin resistance and incident T2D	Residual confounding
Franks et al., 2021 [22]	Systematic review/meta-analysis	Stress/life events	Higher stress associated with MCI/dementia	Observational evidence
McManus et al., 2022 [23]	Meta-analysis; 51 studies	Acute psychosocial stress/cognition	Episodic-memory effects weaker than	Laboratory heterogeneity

			expected; executive effects task-dependent	
Tsai et al., 2024 [27]	Systematic review/meta-analysis; 33 studies, n=43,641	Stress hormones/CVD	Stress hormones associated with CVD risk	Associative evidence
Zieff et al., 2025 [30]	Meta-analysis; 7 studies, n=162	Acute stress/pulse-wave velocity	Acute stress increased arterial stiffness	Very small evidence base
Guo et al., 2026 [32]	Systematic review/meta-analysis; 22 studies	Psychological adversity/epigenetic aging	Greater epigenetic age acceleration	Observational
Zillich et al., 2026 [35]	Within-subject experimental; n=122	Acute stress/DNA methylation	Acute epigenome-wide methylation changes	Acute change $\neq$ long-term aging

4. Discussion

4.1 Integrated interpretation of the evidence

Overall, the evidence examined supports an integrated model that centers on the non-biologically uniform and non-intrinsic harmful nature of stress. Acute activation of the HPA axis and the autonomic nervous system is crucial for adaptation, while repeated activation, suboptimal recuperation, or maladaptive calibration may increase cumulative biological burden. This is the difference between reactivity and recovery, especially: an effective stress system should be allowed to turn on when necessary and then return to normal. This is why both overactive and underactive reactions can lead to poor outcomes [1,8].

Therefore, it is important to think of the HPA axis and autonomic nervous system as a set, rather than two separate pathways. Cortisol regulates immune, metabolic and neural functions, and catecholamines regulate cardiovascular and immune signaling. These changes in inflammation, mitochondrial responses, and metabolic regulation could then alter neural and cardiovascular responses and physiology. Allostatic load offers a valuable integrative model because multiple dysregulated systems likely give rise to clinically relevant outcomes that a single abnormal biomarker would miss [4,5,10,28].

One general observation across domains is that apparent contradictions between studies often stem from definitions of stress and/or the methods used to measure physiology. Some exposures are related and not equivalent to acute laboratory stress, such as occupational strain and perceived stress, childhood adversity and psychiatric distress. Likewise, a single cortisol level, an HRV or an inflammatory marker reflects only one aspect of a time-dependent physiological response. Observed associations may be further modified by differences in age, sex, prior adversity, sleep, physical activity, socioeconomic conditions, medication use, and sampling conditions due to comorbidity. These differences are sources of heterogeneity that should be considered explanatory factors, not just statistical noise.

The clinical importance of the evidence gradient is also significant. Human evidence is relatively well established for autonomic and cardiovascular response associations and allostatic load associations. The immune-inflammatory findings are significant, but both phenotype- and time-dependent. Overall metabolic and cognitive results are confirmed, but less consistent across populations and measurement approaches. Promising but less clinically validated are mitochondrial and epigenetic data. This gradient should guide biomarker interpretation in research and practice and prevent new molecular signals from being claimed as valid diagnostic tools.

4.2 Critical analysis of the evidence

Although the overall literature supports a multisystem relationship between psychological stress and physiological function, the strength of evidence is not uniform across domains. The most reproducible findings concern acute neuroendocrine and autonomic responses and cardiovascular reactivity, whereas evidence linking stress to chronic inflammatory, metabolic, cognitive, mitochondrial, and epigenetic outcomes is more dependent on the population, exposure definition, biological measure, and timing of assessment.

An important limitation across literature is that stress is operationalized in substantially different ways. Acute laboratory stress, occupational strain, perceived stress, childhood adversity, and psychiatric distress should not be treated as interchangeable exposures. Similarly, single measurements of cortisol, HRV, inflammatory markers, or molecular signals cannot fully characterize a dynamic stress response. Much of the evidence remains observational, so reverse causation, residual confounding, health behaviours, comorbidity, and shared vulnerability may contribute to reported associations. Consequently, biological plausibility and statistical association should not be interpreted as proof of causality or clinical significance.

The emerging molecular literature is promising but remains less clinically mature. Findings involving cf-mtDNA, mitochondrial responses, DNA methylation, and epigenetic-aging measures provide biologically plausible signals, but issues of tissue specificity, assay standardization, temporal persistence, and clinical validity remain unresolved. Future studies should therefore prioritize longitudinal multimodal designs, standardized measurement protocols, repeated sampling, and causal or experimental approaches before these markers are considered validated clinical indicators of stress-related disease risk.

5. Limitations and evidence gaps

5.1 Limitations of the evidence base

The evidence base has limitations that make it difficult to interpret. First, in addition to the large spectrum of operationalizations of stress (from acute stressors in the laboratory to occupational strain to childhood adversity to perceived stress and psychiatric symptoms), there are several largely unexplored distinctions between them. These exposures are connected but not mutually exclusive. Second, they differ in timing and the biological compartment of physiological measurements. A single measurement of cortisol does not reflect the diurnal regulation, and a single HRV measure does not reflect an individual's recovery profile. The same issues apply to inflammatory and molecular markers.

Many publications remain descriptive. There may be reverse causation, residual confounding, health behaviours or shared vulnerability, or sociodemographic factors, and there is a risk of association between stress and disease. Prospective associations do not prove that a biological stress pathway causes disease. Experimental studies offer stronger mechanistic inference but may involve fewer subjects and shorter follow-up.

Evidence varies across biological systems. Experimental evidence in the mitochondrial literature is fairly substantial mechanistically, but evidence from human tissue is much less certain. Epigenetic studies show associations and clear molecular changes, but whether these changes persist and what their

functional implications have remains unclear. Therefore, claims of accelerated aging or cellular damage shouldn't be taken at face value.

5.2 Evidence gaps and priorities

Future studies should follow up with longitudinal, multi-modal characterization of stress physiology. Repeated measures can help identify trajectories of HPA-axis activity, autonomic recovery, inflammatory and metabolic parameters and molecular endpoints rather than relying on isolated measurements. Standardizing HRV, cortisol sampling, cf-mtDNA, and epigenetic measures is needed for greater reproducibility. Causal inference is another high priority. Longitudinal mediation analyses, a carefully designed randomized intervention, and genetically informed approaches could help disentangle stress pathways from confounding. Other sources of heterogeneity also need explanation: prior adversity, physical activity and comorbidity, sex and age, socioeconomic factors, and sleep. For mitochondrial studies, tissue specificity and biological source must be considered; for epigenetic-aging studies, follow-up must be extended to evaluate whether stress-related molecular changes relate to clinically relevant aging pathways. Finally, prospective validation is needed before routine clinical use of multimodal monitoring and precision stress medicine.

5.3 Limitations of this review

The structured narrative design of this review has limitations. It did not employ a systematic-review protocol, two independent screeners, a formal risk-of-bias evaluation or quantitative meta-analysis. Literature searches focused primarily on PubMed/MEDLINE and Elsevier LeapSpace, and Google Scholar was used as supplementary search assistance; some relevant literature may not have been found. We did not keep a formal record count or a comprehensive screening log, so this review should not be viewed as a systematic and exhaustive evidence map.

6. Conclusion

Stress triggers a coordinated adaptive physiological response of neuroendocrine and autonomic systems that affect immunity, metabolism, cardiovascular function, cognition, mitochondrial biology, and cell regulation. The strongest evidence is for dynamic acute stress responses, autonomic/cardiovascular effects, and multisystem associations captured by allostatic-load constructs. Evidence for inflammatory, metabolic, and cognitive consequences is extensive but variable, while mitochondrial, cf-mtDNA, and epigenetic-aging biomarkers are emerging.

The current evidence indicates that stress cannot be measured by a single biomarker or even a single high-cortisol model. Physiological reactions are multidimensional, dynamic, and dependent on the nature of the stressor, its duration, and its recovery, as well as prior stress and individual susceptibility. Future longitudinal and experimental studies are needed to establish which sets of physiological signals reliably mark clinically significant risk and whether specific modification of these pathways improves long-term health. In the meantime, researchers must use novel molecular markers as experimental diagnostic tools, not clinical diagnostics.

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