



DOSSIER · SUBSTANCE

Stress, Cortisol and Inflammation

Controlled study evidence is limited: A significant portion of research specifically examines interventions. The most notable finding is the **divergence between observational data and controlled studies**—many assumptions about the consequences of stress derive from correlational studies, not causal investigations.

5,124

STUDIES IN
TOTAL

1,994

IN HUMANS

214

OF WHICH
CONTROLLED

561

IN ANIMALS

80

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Stress, Cortisol and Inflammation at a Glance

ORIGIN:
Stress is a biologically ingrained response pattern to perceived threats, mediated via the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. Cortisol, the primary glucocorticoid, exerts systemic effects through glucocorticoid receptors and engages in bidirectional interaction with inflammatory processes driven by pro-inflammatory cytokines such as IL-6, TNF-α, and CRP. The research is predominantly derived from observational studies, foundational work, and controlled intervention trials, though the evidence regarding causal relationships remains limited.

STUDY LANDSCAPE:
5,124 evaluated publications · 214 controlled human studies · 1,780 observational studies · 1,060 review articles · 561 animal studies · 65 cell culture studies

- STRONGEST EVIDENCE:**
- **Cognition and Mental Health** A randomised, double-blind study (2022) showed that an intervention containing sodium benzoate (250–1,500 mg/day) significantly reduced perceived stress (Perceived Stress Scale) in patients with late-onset depression compared to placebo and improved cognitive function, while sertraline lowered the Geriatric Depression Scale. The study did not isolate the effect of sodium benzoate alone.
 - **Inflammatory Processes** A randomised study (2018) involving 60 patients with irritable bowel syndrome showed a significant reduction in faecal calprotectin (~367 µg/g) and CRP (~2.82 mg/l) after six months in the intervention group, providing a preclinical indication of potential anti-inflammatory effects.
 - **Inflammatory Processes** A randomised study (2016) with breast cancer patients (n=51) confirmed that cognitive behavioural stress management (CBSM) attenuated the upregulation of pro-inflammatory genes (CTRA).
 - **Oncology:** A phase-2 study (2020) with 25 myeloma patients revealed that propranolol (a β-blocker) modulated the activity of CD16-negative classical monocytes and pro-inflammatory signalling pathways during stem cell transplantation.
 - **Fatigue and Stress** A randomised study (2015) with 144 employees found that an eight-week mindfulness-based intervention significantly reduced psychological distress, prolonged fatigue, and perceived stress (p < 0.05).

- LIMITATIONS:**
- Most studies rely on observational data, which establish correlations but not causality between stress, cortisol, and inflammation. Controlled trials are methodologically heterogeneous and often employ small or specific samples (e.g., surgeons, cancer patients), limiting generalisability.
 - Long-term studies (>12 months) are lacking, as are investigations combining psychological and biological endpoints (e.g., stress perception + cortisol + gene expression). Evidence for effects on biomarkers or clinical endpoints remains limited.

INTERPRETATION:
Chronic stress amplifies inflammatory processes via the HPA axis and pro-inflammatory signalling pathways, contributing to mental and somatic diseases.

1. The Link Between Stress, Cortisol and Inflammation

Stress is a biologically ingrained response pattern to perceived threats, mediated via the **hypothalamic-pituitary-adrenal (HPA) axis** and the **sympathetic nervous system**. **Cortisol**, the primary human glucocorticoid, is secreted by the adrenal cortex and exerts systemic effects through **glucocorticoid receptors**. **Inflammation** refers to an immunological response to harmful stimuli, regulated by pro-inflammatory **cytokines** such as IL-6, TNF-α, and CRP. The interface between these systems lies in **bidirectional regulation**: chronic stress can exacerbate inflammatory processes, while inflammation, in turn, influences the HPA axis—through **glucocorticoid resistance** or altered receptor sensitivity, for example.

Critical for research is the **measurement of these parameters**. Stress is typically assessed using **subjective scales** (e.g., Perceived Stress Scale) or **biological markers** (cortisol in saliva, blood, or hair), though the latter are subject to significant **diurnal variation**. Inflammatory markers are measured in blood, but their interpretation is complex: **CRP** is a non-specific acute-phase protein, while **cytokines** like IL-6 are short-lived and context-dependent. Controlled studies often employ **experimental stressors** (e.g., Trier Social Stress Test) or **endotoxin challenges** to create standardised conditions. However, the **diverse forms of stress**—acute vs. chronic, psychological vs. physical—complicate the comparability of results.

2. What the Studies Show in Detail

The pivotal human studies and key reviews—by application, population, duration, preparation, outcome measures, and results—as reported in the original publications. Numbers are included only where the studies provide them.

Distribution of **controlled human studies** by field of application — the figures cannot be summed as a single study may be assigned to multiple fields:

FIELD OF APPLICATION	CONTROLLED STUDIES
Fatigue and stress	196
Cognition and mental health	114
Inflammatory processes	111
Safety and tolerability	66
Immune system	56

FIELD OF APPLICATION	CONTROLLED STUDIES
Oncology	45
Cardiovascular system	33
Metabolism	31

Cognition and Mental Health

A randomised, double-blind, placebo-controlled study (2022) investigated the effects of sodium benzoate (250–1500 mg/day) compared with sertraline (25–150 mg/day) and placebo over 8 weeks in 117 patients (≥55 years) with late-life depression. Primary endpoints were the Hamilton Depression Rating Scale (HDRS) and the Perceived Stress Scale (PSS). While all three groups showed similar improvements in HDRS, sodium benzoate significantly reduced PSS scores more than placebo (effect size not quantified) and improved cognitive function. Sertraline, however, reduced the self-reported Geriatric Depression Scale (GDS), which sodium benzoate did not. Limitations included the short intervention duration, and the study did not examine polyphenol-rich extracts or other natural substances ¹¹.

A review article (2010) discussed neurobiological theories of depression, including the role of stress hormones, neurotransmitters (serotonin, noradrenaline, dopamine, glutamate, GABA), neurotrophic factors, and circadian rhythms. Chronic stress and elevated cortisol levels were identified as central mechanisms that, via autonomic dysregulation and vascular changes, exacerbate the pathophysiology of depression and neurodegenerative diseases. The paper broadly addressed these mechanisms but did not focus on interventions targeting stress, cortisol, or inflammation specifically.

HYPOTHESIS The studies suggest that stress-induced increases in cortisol and neuroinflammatory processes impair cognitive function and mental health. The available research focuses on pharmacological or psychotherapeutic approaches, not on natural substances.

Randomised controlled trials explicitly investigating the effect of polyphenol-rich extracts on stress parameters, cortisol levels, or cognitive function in clinical populations (e.g., depression, anxiety disorders) are currently lacking.

Inflammatory Processes

The primary endpoint was faecal calprotectin, a surrogate marker for intestinal inflammation, with secondary endpoints including CRP and hair cortisol. After 6 months, the intervention group showed a reduction in calprotectin by 367 µg/g (95% CI: -705, -29; p = 0.03; ηp² = 0.085) and in CRP by 2.82 mg/l (95% CI: -5.70, 0.08; p = 0.05; ηp² = 0.066) compared to the control group. Cortisol levels remained unchanged. Limitations included the small sample size and the absence of an active control group.

A randomised, placebo-controlled study (2016) examined the effect of cognitive behavioural stress management (CBSM) on the gene expression of the 'Conserved Transcriptional Response to Adversity' (CTRA) in 51 breast cancer patients (stage 0–IIIb). The intervention group (n = 28) received 10 weekly group sessions, while the control group (n = 23) received psychoeducation. After 6–12 months, the CBSM group showed an attenuated upregulation of proinflammatory genes (53 indicator genes) compared to the control group, which exhibited an increase in CTRA expression.

A randomised controlled trial (2019) involving 115 healthy adults assessed the influence of psychosocial factors on the inflammatory response following endotoxin administration (0.8 ng/kg *Escherichia coli*). Participants with higher baseline levels of perceived stress, social disconnection sensitivity, or anxiety symptoms exhibited greater increases in TNF-α and IL-6, as well as upregulation of inflammatory genes (e.g., NF-κB, EGR1). The study demonstrated that psychological stress amplifies the inflammatory response but did not investigate interventions such as polyphenol-rich extracts ⁸.

HYPOTHESIS Preclinical models suggest that psychological stress and inflammatory processes are bidirectionally linked. However, clinical data supporting this hypothesis in humans are yet to be established.

Controlled studies specifically investigating the effect of polyphenol-rich extracts on inflammatory biomarkers (e.g., IL-6, CRP, faecal calprotectin) or the gene expression of inflammation-relevant signalling pathways in clinical populations (e.g., chronic inflammatory diseases, depression) remain limited.

Oncology

A randomised, controlled phase-2 study (2020) examined the effect of the β-blocker propranolol (administered 1 week before to 4 weeks after transplantation) on CTRA gene expression in 25 patients with multiple myeloma undergoing autologous haematopoietic stem cell transplantation (HCT). Bioinformatic analyses indicated reduced activity of CD16-negative classical monocytes.

A review (2023) summarised evidence on stress management interventions in cancer patients, covering various approaches. Among these, randomised studies on cognitive behavioural therapy or mindfulness-based interventions showed reductions in psychological distress and improvements in quality of life. Some studies also reported effects on immunological parameters (e.g., NK cell activity) or inflammatory markers (e.g., IL-6) within the broader context of stress management ³.

HYPOTHESIS The studies suggest that stress reduction via psychological or pharmacological approaches can modulate proinflammatory and immunosuppressive processes in cancer patients.

Fatigue and Stress

A randomised controlled trial (2015) evaluated an 8-week mindfulness-based intervention (MBI) in 144 employees with psychological distress. The intervention group showed significantly greater reductions in psychological distress (measured via the General Health Questionnaire), prolonged fatigue, and perceived stress (p < 0.05) compared to the control group after completion of the intervention. The effects persisted after adjustment for demographic variables. The rates of increase for fatigue and stress declined more steeply in the intervention group. Limitations included the absence of an active control group and the short follow-up period (8 weeks).

Despite improvements in economic indicators (e.g., consumer spending, food security), no significant reduction in perceived stress (measured via the Cohen Perceived Stress Scale) was observed. Only food insecurity correlated with higher stress levels. The study suggests that material improvements alone are insufficient to reduce perceived stress but did not examine biological interventions or physiological stress markers such as cortisol or inflammation⁷.

HYPOTHESIS

The studies suggest that psychological interventions (e.g., MBI) may reduce stress and fatigue, whereas material support alone appears insufficient.

Overall Picture

The available studies consistently demonstrate that chronic stress contributes to mental illnesses (depression, anxiety), neurodegenerative processes (glaucoma, optic neuropathy), and somatic diseases (inflammatory bowel disease, cancer) via elevated cortisol levels, autonomic dysregulation, and proinflammatory pathways (e.g., NF- κ B, CTRA). Psychological interventions (e.g., cognitive behavioural therapy, mindfulness) and pharmacological approaches (e.g., β -blockers, antidepressants) have shown potential to modulate these mechanisms in related endpoints, such as psychometric scales and inflammatory biomarkers.

Additionally, studies investigating the effect of stress-modulating interventions on the gene expression of inflammation-relevant pathways (e.g., CTRA) or their interaction with psychological stressors (e.g., social isolation) are lacking. While existing research on stress and inflammation provides plausible mechanisms, the therapeutic potential of specific interventions remains to be clarified without direct evidence.

Methodology of the evidence base

The key studies include randomised controlled trials (RCTs) with intervention durations ranging from 8 weeks to 12 months, alongside observational studies and reviews. Typical endpoints include psychometric scales (e.g., Perceived Stress Scale, Hamilton Depression Rating Scale), inflammatory biomarkers (IL-6, TNF- α , CRP, faecal calprotectin), gene expression profiles (CTRA), and clinical parameters (e.g., disease-free survival in cancer). Systematic gaps exist in the investigation of natural substances such as polyphenol-rich extracts, long-term effects (>12 months), and generalisability to clinical populations (e.g., patients with depression or chronic inflammatory diseases). Furthermore, studies combining psychological and biological endpoints (e.g., stress perception + cortisol + gene expression) to comprehensively capture mechanisms are lacking.

Stress as cause or consequence? The causality trap

The

MOST CITED STUDIES

derive from **observational research**. These demonstrate **associations**—such as between **elevated cortisol** and **increased inflammatory markers**—but do not prove **causal direction**. For example: Does chronic stress lead to inflammation, or do inflammatory processes cause stress symptoms? **Controlled studies** are rare here: Most research examines targeted interventions, and even these often rely on **surrogate markers** (e.g., CRP) rather than clinical endpoints.

Endotoxin models show that **experimental inflammation** can trigger stress responses—but whether this translates to **chronic everyday stress** remains unclear.

Another issue is the

OVERSIMPLIFICATION OF COMPLEX SYSTEMS

. Stress is often treated as a **uniform stimulus**, even though it is processed **individually**—for example, through **genetics** (e.g., glucocorticoid receptor polymorphisms) or **socioeconomic factors**. The **most cited review** postulates a **social signal transduction** from stress to depression, yet the **mechanistic evidence** predominantly comes from **animal models**. Even in controlled studies, **long-term data** are often lacking: most interventions (e.g., mindfulness) are tested over **weeks to months**, while the **consequences of chronic stress** take **years to decades** to manifest.

3. How Robust the Research Is

Research is divided into **three key areas**: **observational studies** explore associations between stress, cortisol, and inflammatory markers—such as in depression, cardiovascular diseases, or social isolation. **Basic research** clarifies mechanisms, for instance, the role of **β -adrenergic signalling pathways** or **hippocampal atrophy** under chronic stress. **Controlled human studies** focus on **exhaustion**, **cognition**, and **inflammation**, followed by **safety assessments** and **immune modulation**. Oncology, cardiovascular diseases, and metabolic disorders are less frequently investigated. The most cited controlled studies examine **stress management interventions** (e.g., in cancer or surgeons) or **pharmacological approaches** (e.g., propranolol).

The **data** on stress, cortisol, and inflammation are **methodologically heterogeneous**. Observational studies show **correlations** but not causality—for example, between social stress and inflammatory markers. Controlled studies vary in design: some use **experimental stressors** (e.g., endotoxin), while others employ **behavioural interventions** (mindfulness, social support). **Sample sizes** are often small or specific (e.g., surgeons, cancer patients), limiting generalisability. **Review articles** (e.g., on **social signal transduction**) provide theoretical models, but their empirical validation remains incomplete. **Animal and cell studies** demonstrate **molecular pathways** (e.g., **NF- κ B activation**), yet their relevance to humans is not yet established. The **data on long-term consequences** (e.g., chronic inflammation) are particularly sparse.

4. What Is Frequently Claimed—and What the Data Support

STATEMENT	EVIDENCE
Chronic stress always leads to elevated inflammatory markers	Observational studies demonstrate associations , but controlled studies find no consistent pattern . Some research even reports lower inflammation markers in stressed individuals.
Cortisol is a reliable biomarker for stress	Cortisol is subject to significant diurnal variations and is influenced by diet, sleep, and exercise . Even in controlled studies, it does not always correlate with stress levels.
Stress management interventions reduce inflammatory markers	The data situation is contradictory . Some studies show no effects on CRP or cytokines, while others demonstrate effects only in specific groups . The mechanisms of action are unclear.
Anti-inflammatory treatments improve stress-related outcomes	Animal studies demonstrate effects of anti-inflammatory drugs, yet these have been employed in human research to investigate the consequences of stress; their effectiveness for stress-related outcomes is uncertain.

5. Fact Sheet: Molecule and Charge

Stress, cortisol, and inflammation are not a single molecule but a **mixture**—there is no empirical formula or fixed molecular mass. What can be described are functional groups, charge behaviour, and redox properties; this is the focus of the next section.

6. Charge, Electrons, Radicals

Stress, cortisol, and inflammation are associated with the formation of reactive oxygen species (ROS). In humans, increased ROS production has been observed in chronic inflammatory conditions, such as diabetes (NOX2-mediated) ¹⁸, depression ²¹, or skin disorders like vitiligo. Exogenous factors, such as cigarette smoke, also enhance ROS-induced lipid peroxidation and toxic effects ¹⁹. ROS are neutralised by antioxidants like coenzyme Q10, SOD1 ¹⁷, or carotenoids, which directly scavenge free radicals ^{22 22}. From an electrochemical perspective, ROS are highly reactive and can act as electron acceptors or donors, driving redox reactions. In humans, ROS concentrations and their effects on biomarkers such as oxidised mitochondrial DNA ²¹ or inflammatory mediators ²⁰ have been measured.

The role of ROS in signalling pathways and cellular damage is well-documented. In the human body, ROS influence pathways such as NF-κB or PI3K/Akt/mTOR and contribute to neurotransmitter system dysregulation, for instance, through activated glial cells ²⁰. Animal and human studies show that chronic stress promotes ROS production, thereby accelerating ageing processes such as DNA damage or telomere shortening ²³. Electrochemically, cation exchange during ROS formation is relevant, such as via NOX2, which transfers electrons to oxygen ¹⁸. Direct measurements in humans include ROS concentrations in tissues (e.g., skin) or blood, as well as their correlation with inflammatory markers ^{17 21}. Whether **polyphenol-rich extracts** intervene electrochemically—through radical scavenging or redox modulation—would require investigation in controlled studies, particularly regarding ROS-induced cellular damage.

7. Interactions with Other Substances

Substances with which this topic has been **jointly** investigated or discussed in human studies and reviews—whether through combination, comparison, or shared mechanisms. The number indicates studies in which both appear.

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Chronic inflammation	2774	186
Gut microbiome	1078	69
Adaptogens	375	106

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Turmeric and curcumin	278	44
Probiotics	276	115
Melatonin	240	50
Vitamin D	214	34
Anthocyanins (berries)	161	30
Omega-3 fatty acids	157	26
Zinc	151	25

Interactions between stress, cortisol, and inflammation with drugs have been described in controlled studies. Propranolol, a non-selective β -antagonist, was investigated in 25 individuals with multiple myeloma and demonstrated effects on CTRA-associated gene expression ²⁴. The combination with other cancer therapies and the timing of administration are considered crucial for efficacy ²⁵. Propranolol is also attributed a potential role in reducing tumour progression, although results are inconsistent when combined with chemo- or radiotherapy ^{30 25}. Haloperidol influences the hypothalamic-pituitary-adrenal (HPA) axis and the immune system via D2 receptor antagonism ¹².

Glucocorticoid receptor antagonists (GR antagonists), such as mifepristone, are being investigated in the treatment of depression associated with childhood trauma. A study involving 158 participants examines their impact on cortisol, inflammation, and epigenetic regulation ²⁶. Selective GR antagonists show synergistic effects with various cancer drugs, including taxanes and immune checkpoint inhibitors, in preclinical data ²⁷. Electroacupuncture enhances the effect of escitalopram on glucocorticoid-inducible genes, inflammatory markers, and neurotrophins in patients with depression ²⁹. Nutrient-based approaches, such as the MIND diet, are being studied in combination with other factors for cardiovascular and mental health, though no specific interactions with cortisol or inflammation have been established ²⁸.

8. Overdose, Tolerability, and Limitations

In a four-week study with daily supplementation, no adverse effects attributable to the active substance were observed ³¹. Salivary cortisol and plasma TNF- α were significantly reduced ($p = 0.016$ and $p = 0.037$, respectively), with no safety concerns reported ³³. The studies provide no evidence of upper limits or toxic effects at the tested dosages and durations. Animal or tissue studies on overdose or long-term toxicity are not included in the available evidence.

For instance, SGLT2 inhibitors have been associated with sleep disturbances and anxiety as potential side effects ³², while systemic corticosteroids or 5-aminosalicylic acid are contraindicated in certain patient groups. Esketamine reduced postoperative anxiety (OR = 0.38, $p < 0.05$) but has a distinct safety profile ³⁴. Whether interactions with other substances or specific risk groups exist cannot be inferred from the evidence. Further studies would be required to investigate potential dose-response relationships or long-term effects.

9. The Most Robust Studies

Ranked by evidential strength, not by prominence. The full evaluation includes significantly more studies; only the most reliable are listed here.

Controlled Human Studies

- ¹ Mental stress as consequence and cause of vision loss: the dawn of psychosomatic ophthalmology for preventive and personalized medicine (2018)
- The pursuit of euthymia (2020)
- ² Glucocorticoids in Sepsis: To Be or Not to Be (2020)
- ³ Stress Management Interventions to Facilitate Psychological and Physiological Adaptation and Optimal Health Outcomes in Cancer Patients and Survivors (2023)
- Neural response to emotional stimuli during experimental human endotoxemia (2013)
- Kindness in the blood: A randomized controlled trial of the gene regulatory impact of prosocial behavior (2017)
- ⁴ Stress management, leukocyte transcriptional changes and breast cancer recurrence in a randomized trial: An exploratory analysis (2016)
- ⁵ Trait sensitivity to social disconnection enhances pro-inflammatory responses to a randomized controlled trial of endotoxin (2015)
- ⁶ Enhanced Stress Resilience Training in Surgeons: Iterative Adaptation and Biopsychosocial Effects in 2 Small Randomized Trials (2021)
- ⁷ Poverty and perceived stress: Evidence from two unconditional cash transfer programs in Zambia (2017)
- ⁸ Moderators for depressed mood and systemic and transcriptional inflammatory responses: a randomized controlled trial of endotoxin (2019)
- The effect of a mindfulness-based therapy on different biomarkers among patients with inflammatory bowel disease: a randomised controlled trial (2020)
- Propranolol inhibits molecular risk markers in HCT recipients: a phase 2 randomized controlled biomarker trial (2020)
- ⁹ Differential Health Effects on Inflammatory, Immunological and Stress Parameters in Professional Soccer Players and Sedentary Individuals after Consumption (2021)

- ¹⁰ Psychobiotic Supplementation of PS128TM Improves Stress, Anxiety, and Insomnia in Highly Stressed Information Technology Specialists: A Pilot Study (2021)
- ¹¹ Effects of Sodium Benzoate, a D-Amino Acid Oxidase Inhibitor, on Perceived Stress and Cognitive Function Among Patients With Late-Life Depression: A Randomised Controlled Trial (2022)
- The Potential for Mindfulness-Based Intervention in Workplace Mental Health Promotion: Results of a Randomised Controlled Trial (2015)
- ¹² Effects of Antipsychotics on Cortisol, Interleukin-6, and Hippocampal Perfusion in Healthy Volunteers (2016)
- ¹³ Beta-Adrenergic Blockade Blunts Inflammatory and Antiviral/Antibody Gene Expression Responses to Acute Psychosocial Stress (2021)
- ¹⁴ A Short Mindfulness Retreat Can Improve Biological Markers of Stress and Inflammation (2022)
- Repurposing Existing Medications as Cancer Therapy: Design and Feasibility of a Randomised Pilot Investigating Propranolol Administration in Patients (2018)
- ¹⁵ A Randomised Controlled Trial of a Multicomponent Online Stress Reduction Intervention in Inflammatory Bowel Disease (2022)
- ¹⁶ *Lactobacillus rhamnosus* CNCM I-3690 Decreases Subjective Academic Stress in Healthy Adults: A Randomised Placebo-Controlled Trial (2022)
- Patient-Reported Outcomes and Socioeconomic Status as Predictors of Clinical Outcomes After Haematopoietic Stem Cell Transplantation: A Study from the (2016)

10. Summary

The available studies consistently demonstrate that chronic stress, via the HPA axis and the sympathetic nervous system, leads to elevated cortisol levels, autonomic dysregulation, and proinflammatory signalling pathways (e.g., NF- κ B, CTRA). This is associated with mental health disorders such as depression and anxiety, neurodegenerative processes, and somatic conditions like inflammatory bowel disease or cancer. Controlled trials show that psychological interventions (e.g., cognitive behavioural therapy, mindfulness) and pharmacological approaches (e.g., beta-blockers, antidepressants) can modulate these mechanisms and improve surrogate markers such as inflammatory biomarkers (e.g., CRP, IL-6) or perceived stress. However, many of these findings rely on these surrogate markers or specific populations, which limits generalisability. Evidence on the long-term clinical effects of chronic inflammation or stress remains particularly sparse, and the causal direction between stress and inflammation often remains unclear.

A potential mechanism could involve effects on inflammatory biomarkers (e.g., IL-6, CRP) or cognitive functions in stress-associated conditions like depression or chronic inflammatory bowel disease.

To clarify the role of **interventions** in the stress-inflammation axis, randomised controlled trials would be required to investigate the following aspects: 1) effects on specific biomarkers (e.g., IL-6, CRP, faecal calprotectin, cortisol) and clinical endpoints (e.g., cancer recurrence rates, disease flares in chronic inflammatory conditions) in clinical populations; 2) influence on the gene expression of inflammation-relevant pathways (e.g., CTRA, NF- κ B) and their interaction with psychological stressors (e.g., social isolation); 3) long-term effects (>12 months) on stress parameters, cognitive functions, and immunological profiles. Additionally, studies would need to combine psychological and biological endpoints to comprehensively capture the mechanisms. Only such data could determine whether **these interventions** represent an evidence-based complement to existing therapeutic approaches.

11. Broader Context

Chronic stress activates the HPA axis, leading to sustained elevation of cortisol levels, which in controlled studies is associated with increased inflammatory markers such as IL-6 and CRP. Observational data further show that social stress—such as exclusion or occupational overload—is linked to HPA axis dysregulation, manifesting as reduced cortisol reactivity or glucocorticoid resistance. This resistance weakens cortisol's anti-inflammatory effects and promotes subclinical, systemic inflammation. Causality is supported by experimental stressors like the Trier Social Stress Test, which acutely elevates both cortisol and proinflammatory cytokines. However, data interpretation remains complex due to individual differences in stress processing and the context-dependent nature of biomarkers. Nonetheless, the bidirectional link between stress, cortisol, and inflammation is sufficiently established to serve as a foundation for further research.

The mechanisms connecting stress, cortisol, and inflammation are well described in foundational studies and animal models. Chronically elevated cortisol levels lead to downregulation of glucocorticoid receptors, reducing sensitivity to the hormone's anti-inflammatory effects. Concurrently, the sympathetic nervous system activates β -adrenergic pathways, promoting the production of proinflammatory cytokines such as IL-6 and TNF- α . In the gut, this inflammatory burden may impair barrier function, increasing permeability ("leaky gut") and altering the microbiome—a process correlated with stress-induced inflammatory responses in animal studies. Additionally, stress and inflammation reduce BDNF expression, impairing neuroplasticity and negatively affecting cognitive functions like memory and learning.

The available data suggest that the interplay between stress, cortisol, and inflammation is a central node in the pathogenesis of stress-associated diseases—from depression to cardiovascular disorders and metabolic syndromes. The divergence between observational and interventional studies indicates that not all forms of stress have equivalent effects: while acute stress may be adaptive, chronic, uncontrollable stress could dysregulate the HPA axis and trigger an inflammatory cascade. Future research should explore whether natural compounds like **polyphenols or plant extracts** can interrupt this cascade at specific points—such as by modulating glucocorticoid resistance, stabilising the gut barrier, or directly inhibiting proinflammatory cytokines. It would also need to clarify whether such effects are dose-dependent and whether they differ across stress contexts (e.g., social vs. physical stress). Long-term studies should investigate whether a targeted combination of stress management, anti-inflammatory measures, and microbiome modulation acts synergistically.

12. Open Questions

- **Causality:** Is there a **direct pathway** from chronic stress to clinically relevant inflammation, or are both merely **epiphenomena** of other processes (e.g., sleep deprivation, poor diet)?
- **Individuality:** Why do some individuals respond to the same stressor with **hyperinflammation**, while others exhibit **immunosuppression**? What roles do **genetics, epigenetics, and early-life programming** play?
- **Interventions:** Which **non-pharmacological approaches** (e.g., social support, physical activity) have a **causal** effect on the stress-inflammation axis—and in which populations?

13. Further Paths

Topics, mechanisms and chains in which this substance appears — for those who want to look beyond the substance.

- Interaction Network
- From Exclusion to Inflammation: Stress, Cortisol, and the Gut
- Brain Under Current: BDNF, Neuroplasticity, and the Compounds That Target It

Frequently Asked Questions

Can elevated inflammatory markers in stressed patients be interpreted as evidence of a causal role for inflammation?

No. Observational studies demonstrate **associations**, not causality. Elevated markers such as CRP or IL-6 may also be a **consequence** of other stress-related factors (e.g., sleep disturbances, lack of physical activity). Controlled studies involving **anti-inflammatory interventions** show **no consistent effects** on stress symptoms. Even experimental inflammation models (e.g., endotoxin) do not prove that **chronic everyday stress** operates via the same mechanism.

Are there specific forms of stress that are particularly strongly associated with inflammation?

The evidence suggests that **social stressors** (e.g., loneliness, unemployment) are particularly relevant. Observational studies show **stronger associations** with inflammatory markers for these than for **physical stressors** (e.g., noise). Controlled studies involving **social interventions** report **lower inflammatory values**, but the effects are **small and inconsistent**. Whether this reflects **causal mechanisms** remains unclear.

How reliable are cortisol measurements in saliva or hair for stress diagnostics?

Cortisol in **saliva** reflects **acute stress responses** but is subject to significant **diurnal fluctuations** and is influenced by **diet, sleep, and medications**. **Hair cortisol** is considered a marker for **chronic stress**, yet **standardisation** remains inconsistent. Controlled studies show **no consistent correlation** between cortisol and subjective stress or clinical symptoms. Even in **experimental stress tests**, cortisol responses **vary widely between individuals**.

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