Medical Science

To Cite:
Antonina S, Paweł C, Maciej J, Marta G, Jakub G. Inflammation and Depression: Biological Links and Implications for Treatment Response. *Medical Science* 2025; 29: e178ms3706
doi: https://doi.org/10.54905/disssi.v29i163.e178ms3706

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Peer-Review History
Received: 14 June 2025
Reviewed & Revised: 29/June/2025 to 01/September/2025
Accepted: 14 September 2025
Published: 25 September 2025

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

Inflammation and Depression: Biological Links and Implications for Treatment Response

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ABSTRACT

Research from the last two decades indicates that inflammation plays a substantial role in the pathogenesis of depression. Numerous studies have reported elevated levels of pro-inflammatory markers, including C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Tumour Necrosis Factor-alpha (TNF-α), in individuals diagnosed with Major Depressive Disorder (MDD). These findings appear to be more pronounced in cases that are treatment-resistant. Chronic inflammation affects mood through several biological mechanisms. It disrupts the Hypothalamic-Pituitary-Adrenal (HPA) axis stress response, resulting in sustained cortisol secretion and chronic hypercortisolaemia. Ongoing immune activation downregulates the expression of Brain-Derived Neurotrophic Factor (BDNF), a protein essential for neurogenesis and plasticity. Inflammation impairs serotonin synthesis and signalling, which negatively affects mood, appetite, and sleep. Collectively, these biological changes alter the function of synaptic pathways involved in emotional regulation and stress management, particularly the prefrontal cortex and the amygdala. In this narrative review, we aim to emphasise the role of inflammation in depression pathophysiology and explore whether addressing inflammation through pharmacological and lifestyle interventions could alleviate depressive symptoms. We conducted a structured narrative search focusing on adult MDD and examined observational cohorts, longitudinal and Mendelian randomisation studies, neuroimaging, experimental inflammation paradigms, and randomised trials of anti-inflammatory augmentation. Overall, the findings suggest an inflammatory contribution in a subset of patients, with modest and heterogeneous effects. Stratifying potential candidates for anti-inflammatory treatment will require researchers to use standardised biomarker assessments, carefully control confounders, and conduct stratified, adequately powered studies that integrate lifestyle modification with targeted anti-inflammatory approaches while monitoring safety.

Keywords: Inflammation, Depression, Pro-inflammatory cytokines, Treatment-resistant depression

1. INTRODUCTION

In 2017, over 300 million people worldwide were affected by depression (WHO, 2017). MDD is one of the leading contributors to Years Lived With Disability (YLDs) (GBD, 2022). Even with wide access to pharmacological and psychological interventions, approximately one in three patients does not achieve adequate improvement on first-line therapy (Trivedi et al., 2006). Historically, researchers have explained MDD through the monoamine deficiency model, which links depression to imbalances in specific neurotransmitters and has guided the development of most modern antidepressant medications (Coppen, 1967). However, monoamine deficiency does not fully explain the variety of symptoms observed across patients with MDD or explain why conventional antidepressants often fail to provide substantial improvement (Trivedi et al., 2006).

Today, a growing body of research is slowly transforming the psychiatric field by expanding our understanding of the pathophysiology of MDD. The involvement of the immune system in the development and persistence of depressive symptoms has attracted considerable attention, particularly (Miller & Raison, 2016). The inflammatory hypothesis states that psychosocial stress, infections, trauma, and metabolic disturbances activate immune responses, which can lead to aggravation and maintenance of depressive symptoms (Köhler-Forsberg et al., 2019). The proposed framework has the potential to offer novel strategies in the clinical management of MDD. Implementing inflammatory markers could enable physicians to identify patients who are likely to benefit from the adjunctive anti-inflammatory treatment (Uher et al., 2014).

This narrative review presents a comprehensive synthesis of recent studies on the connection between chronic low-grade inflammation and depression, with a focus on integrating biological evidence from the neuroendocrine, neurotransmitter, and neuroimmune systems. It evaluates the clinical utility of inflammatory biomarkers, as well as anti-inflammatory and lifestyle interventions. This review also highlights gaps in the current literature and suggests future directions that could help bring immunopsychiatric insights closer to clinical practice.

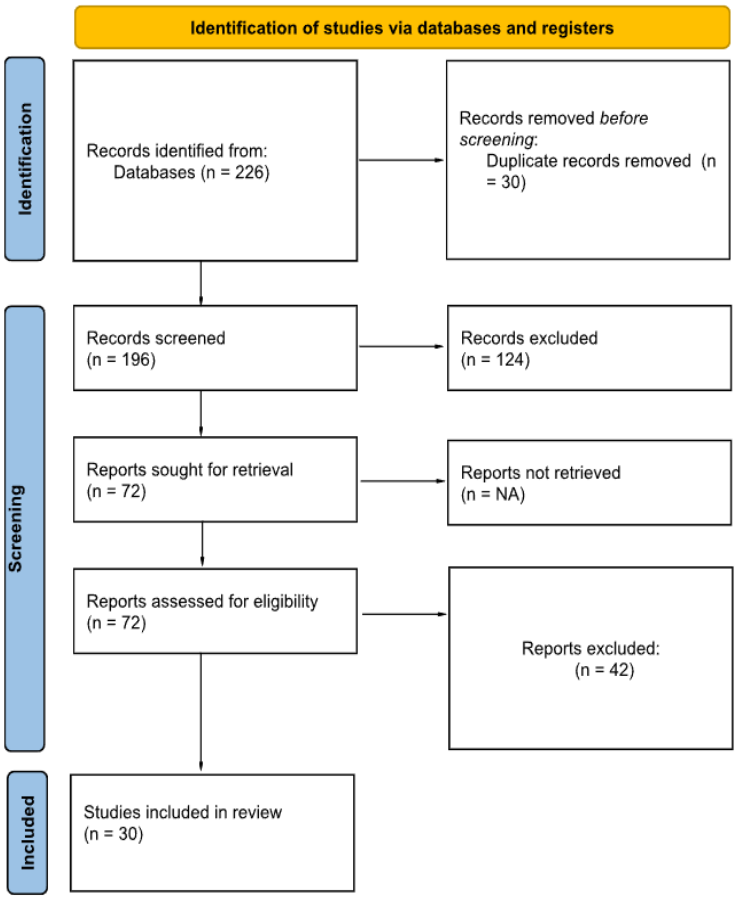

Figure 1. Prisma flow chart

2. REVIEW METHODS

We conducted a structured literature search from January 2004 to May 2025 using PubMed, Scopus, Web of Science, PsycINFO, and the Cochrane Library. For this process, we used combined keywords related to depression and inflammation, including: depression, MDD, inflammation, CRP, IL-6, TNF-alpha, and biomarkers. Following duplicates removal, this search yielded 196 records. We included peer-reviewed studies which focused on inflammatory biomarkers and depression. We excluded studies with insufficient biomarker data or methodological clarity. From these, we extracted data covering study design, sample characteristics, methods, biomarkers, and depression-related outcomes. During the process of selecting studies, we followed structured PRISMA guidelines (Figure 1).

3. RESULTS & DISCUSSION

Evidence for Inflammation in Depression

Several high-quality studies across multiple cohorts have found elevated concentrations of CRP, IL-6, and TNF-α in individuals with depression compared to non-depressed controls (Dowlati et al., 2010; Haapakoski et al., 2015). Similarly, a cohort study from 2021 presents a statistically significant association between increased CRP and the severity of depressive somatic symptoms (Milaneschi et al., 2021). However, interpreting these results is complicated by methodological differences, including the choice of symptom scales and pre-analytical variables such as participant fasting status and venipuncture site (Osimo et al., 2020). Effects are more pronounced in treatment-resistant cases, those with prominent somatic symptoms, or those with medical comorbidity (Miller & Raison, 2016). Nevertheless, it is essential to note that correlation does not imply causation, and residual confounding is possible. In this context, longitudinal cohorts and Mendelian randomisation studies report a minor impact of inflammation on new-onset MDD after accounting for confounding and pleiotropy (Mac Giollabhui et al., 2021; Ye et al., 2021).

Mechanisms Linking Inflammation and Depression

Inflammation can affect the central nervous system through multiple, partly overlapping routes. Pro-inflammatory cytokines signal to the brain via neural, humoral, and endothelial pathways, modulating neurotransmission, neuroendocrine tone, synaptic plasticity, and motivation-related circuits (Dantzer et al., 2008).

HPA-axis dysregulation is one of the most researched mechanisms—cytokine-induced corticotropin-releasing hormone (CRH) release results in increased adrenal cortisol production. Chronic hypercortisolemia impairs negative feedback and sustains activation of the HPA axis (Miller et al., 2009). Disruption of circadian cortisol rhythm compromises sleep, appetite, and energy balance. Such changes lead to worsening of main depressive symptoms: fatigue, anhedonia and cognitive impairment (Pariante et al., 2008). However, causality remains uncertain due to bidirectional stress–immune effects and between-study heterogeneity.

Chronic inflammation downregulates the expression of BDNF, an essential protein for neurogenesis. A 2016 study highlights that the administration of pro-inflammatory cytokines results in reduced BDNF concentrations in both the peripheral and central nervous systems (Zhang et al., 2016). The hippocampus seems to be particularly affected, as meta-analytic MRI evidence reveals volume loss in depressed patients. The same study found that a higher number of depressive episodes is associated with greater reductions in right hippocampal volume (Videbech & Ravnkilde, 2004). Together, these findings are consistent with inflammation-related impairments in neuroplasticity, though they fall short of definitive evidence.

A 2012 review found that individuals diagnosed with MDD have increased levels of kynurenine and its metabolites. Increased kynurenine production is associated with oxidative stress, excitotoxicity, and neuroinflammation. On the molecular level, cytokine-driven activation of indoleamine 2,3-dioxygenase (IDO) modifies tryptophan metabolism by redirecting it from serotonin synthesis to the kynurenine pathway. This metabolic shift leads to an increase in the production of neuroactive metabolites. However, the strength of association between depression and inflammatory metabolites differs across demographic groups and study designs (Schwarcz et al., 2012).

Elevated pro-inflammatory markers are associated with altered activity in the anterior cingulate cortex, amygdala, and other brain regions responsible for emotional regulation (Haroon et al., 2017). Cytokines in peripheral blood can reach the central nervous system through several mechanisms, including crossing the blood-brain barrier at circumventricular organs, active endothelial cell transport, signalling initiated by endothelial activation, and transmission via the vagus nerve (Sun et al., 2022).

Antidepressants and Inflammation

A growing body of research shows that individuals with Treatment-Resistant Depression (TRD) exhibit higher levels of inflammatory markers compared to treatment-responsive patients. This pattern suggests that systemic inflammation could play a role in poor treatment outcomes, potentially by reducing the effectiveness of standard antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs). For instance, patients with high CRP levels appear less likely to benefit from SSRIs but may respond better to noradrenergic agents such as nortriptyline (Uher et al., 2014). Presented evidence suggests that systemic inflammation in patients diagnosed with depression correlates with poor response to the first-line pharmacological treatment.

Anti-Inflammatory Treatment Approaches

The adjunctive use of anti-inflammatory agents, such as COX-2 inhibitors, monoclonal antibodies or compounds like minocycline, pioglitazone, and statins, has demonstrated therapeutic potential in several trials (Köhler et al., 2014; Raison et al., 2013). However, a 2018 meta-analysis examining the antidepressant effect of anti-cytokine treatment found that anti-inflammatory agents do not produce a statistically significant impact on MDD overall. Nevertheless, outcomes differ according to drug type, study design, and patient profile, with minor to moderate effects observed in the TRD subgroup (Kappelmann et al., 2018). Although anti-inflammatory drugs are not a part of standard depression treatment protocols, the presented evidence suggests they might be effective in a biologically distinct subset of patients.

Interaction with Risk Factors

Chronic inflammation typically co-occurs with modifiable and contextual risk factors for major depressive disorder (MDD), which may amplify the impact of these factors.

Poor diet, physical inactivity, smoking, and obesity all promote systemic inflammation, which alters brain regions involved in emotion management (Miller & Raison, 2016; Osimo et al., 2020). Excess adipose tissue and frequent consumption of processed foods stimulate the release of pro-inflammatory cytokines, whereas implementing a diet rich in omega-3 fatty acids reduces inflammation and alleviates depressive symptoms (Calder, 2017; Suneson et al., 2024). Leading a sedentary lifestyle tends to sustain low-grade inflammation. In contrast, maintaining a regular physical activity has been shown to reduce peripheral inflammatory markers and enhance mental well-being (Magni et al., 2025).

Early-life stress and childhood adversity are recognised risk factors for MDD and several autoimmune conditions, including rheumatoid arthritis, multiple sclerosis, and psoriasis (Jesuthasan et al., 2025). Recent evidence helps explain how trauma may cause lasting biological changes and heightened inflammation. A 2023 study found that individuals exposed to early-life stress exhibit substantial demethylation in the intronic regions of the FKBP5 gene. FKBP5 encodes a co-chaperone protein that modulates glucocorticoid receptor sensitivity. Trauma-induced demethylation in the FKBP5 gene leads to reduced sensitivity of the glucocorticoid receptor. Consequently, glucocorticoid receptor resistance disrupts the negative feedback loop of the HPA axis, causing sustained cortisol secretion (Mendonça et al., 2023).

Overall, the presented evidence indicates that inflammation can be an outcome of chronic psychosocial stress and a contributor to the biological vulnerability that underpins MDD (Table 1).

Table 1. Risk Factors for Major Depressive Disorder and Associations with Inflammation

Risk Factor	Findings
Chronic stress	Leads to prolonged inflammatory responses via cytokine release.
Poor diet (e.g., high in processed foods)	Frequent consumption of processed foods increases the concentration of pro-inflammatory cytokines.
Obesity	Excess adipose tissue releases pro-inflammatory cytokines.
Sedentary lifestyle	Sustains low-grade inflammation.
Childhood adversity and early-life stress	Trauma-induced epigenetic modifications in the FKBP5 gene can lead to hypercortisolaemia.

Limitations and Future Directions

Recent research indicates a growing interest in the impact of chronic inflammation on the pathophysiology of MDD. However, several methodological issues obstruct clinical application.

Primarily, predominant reliance on cross-sectional designs in research obscures temporal order, increasing the risk of reversed causation (Miller & Raison, 2016). Heterogeneity in study populations, biomarker assessment methods, and diagnostic criteria complicates comparison across studies and diminishes reproducibility (Kappelmann et al., 2018).

Non-specific factors, such as age, sex, body mass index (BMI), medical comorbidities, and lifestyle behaviours, can influence inflammatory marker levels and act as confounders in studies examining the association with depression (Kiecolt-Glaser et al., 2015). Global generalizability is limited because most studies have been conducted on Western populations (Dantzer et al., 2008).

Although anti-inflammatory treatments have demonstrated benefit in a subset of depressed patients with elevated inflammatory markers, concerns remain regarding their long-term safety, tolerability and developing criteria for selecting responsive individuals (Raison et al., 2013; Köhler et al., 2014).

Progress will require longitudinal, multicenter research built on standardised biomarker assays and diagnostic tools. Integrating genetic, epigenetic, and immune profiling could facilitate the identification of depression subtypes defined by biology rather than symptoms alone. In addition, the inclusion of underrepresented populations and the careful evaluation of social, behavioural, and environmental factors will be essential for effective implementation.

4. CONCLUSION

Studies repeatedly tie inflammation to depression, suggesting a role in both the onset and persistence of depressive symptoms. Many patients with depression show increased inflammatory markers, particularly those with TRD. Inflammation perturbs the HPA axis, inhibits BDNF transcription, and redirects tryptophan from serotonin synthesis toward the kynurenine pathway. Cytokines can also directly affect brain areas involved in stress and emotion control. Inflammation does not act in isolation. Interacting with chronic stress, early trauma, and lifestyle risk (obesity, poor diet, inactivity) leads to amplification of depressive symptoms. Anti-inflammatory treatment appears beneficial in depressed patients with elevated inflammation, but we still need data to fine-tune protocols and identify potential candidates. To proceed responsibly, clinical application will require prospective, standardised studies across diverse cohorts. From there, pairing lifestyle measures with anti-inflammatory treatment could genuinely widen available treatment options, especially in TRD.

Abbreviations

CRP - C-Reactive Protein
IL-6 - Interleukin-6
TNF-α - Tumour Necrosis Factor-alpha
MDD - Major Depressive Disorder
HPA axis - Hypothalamic-Pituitary-Adrenal axis
YLD - Years Lived with Disability
BDNF - Brain-Derived Neurotrophic Factor
TRD - Treatment-Resistant Depression
CRH - Corticotropin-Releasing Hormone
SSRIs - Selective Serotonin Reuptake Inhibitors

Acknowledgments

The authors have no acknowledgments to disclose.

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Informed consent
Not applicable.

Ethical approval
Not applicable.

Funding
This study has not received any external funding.

Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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