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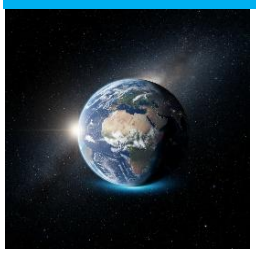

**Journal of Education, Health and Sport. eISSN 2391-8306.**

**Journal Home Page**
**https://apcz.umk.pl/JEHS/index**

**MAJEWSKA, Melania, PIASECKA, Natalia, MIARA, Natalia, KADŁUBAŃSKA, Martyna, STRZYŻ, Joanna, SZYDŁOWSKA, Dorota, BARANIECKA, Aleksandra and SZPILCZYŃSKA, Karolina. The role of lifestyle-related inflammation in linking depression and metabolic disorders. Journal of Education, Health and Sport. 2026;89:70298. eISSN 2391-8306. https://doi.org/10.12775/JEHS.2026.89.70298**

**The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).**
**Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).** 
**The authors declare that there is no conflict of interests regarding the publication of this paper.**
**Received: 26.03.2026. Revised: 30.03.2026. Accepted: 30.03.2026. Published: 10.04.2026.**

# The role of lifestyle-related inflammation in linking depression and metabolic disorders

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## Abstract

### Introduction and purpose

Depressive disorders and metabolic diseases, including obesity, type 2 diabetes mellitus, and metabolic syndrome, frequently co-occur and constitute a major public health burden. Epidemiological and clinical evidence indicates that this association is bidirectional rather than coincidental. Increasing attention has been directed toward chronic low-grade inflammation as a potential shared biological mechanism linking these conditions. This narrative review summarizes current evidence regarding the role of chronic low-grade inflammation in the interaction between depression and metabolic disorders, with particular emphasis on modifiable lifestyle-related factors.

**State of knowledge**

Metabolic disorders are characterized by persistent, low-intensity immune activation and elevated inflammatory mediators that interfere with insulin signaling, lipid metabolism, and vascular function. Parallel evidence suggests that a substantial subset of individuals with depressive disorders exhibits low-grade systemic inflammation. Integrative studies describe an immunometabolic profile of depression, in which inflammatory and metabolic dysregulation coexist with specific symptom patterns and unfavorable clinical outcomes. Experimental, longitudinal, and clinical data support bidirectional interactions between immune, metabolic, neurobiological, and behavioral pathways influencing disease development and treatment response. Increasing evidence also highlights the role of lifestyle-related factors, including diet, physical inactivity, sleep disturbances, and chronic stress, as important contributors to sustained low-grade inflammation.

**Summary**

Chronic low-grade inflammation may represent a common biological pathway linking depressive disorders and metabolic diseases. Recognition of shared immunometabolic mechanisms, together with the identification of modifiable lifestyle-related risk factors, may support an integrated approach to prevention, early identification, and health promotion, as well as more personalized management of comorbid psychiatric and metabolic conditions.

**Keywords:** depression; inflammation; metabolic syndrome; obesity; insulin resistance; immunometabolism; lifestyle; health promotion

## Introduction

Chronic non-communicable diseases are the leading causes of disability and mortality worldwide and constitute a major global public health burden (1). Depressive disorders and metabolic diseases, including obesity, type 2 diabetes mellitus, and metabolic syndrome, are

highly prevalent and frequently coexist in both clinical and population-based studies (2). The high prevalence and frequent comorbidity of these disorders suggest shared biological mechanisms that extend beyond traditional disease-specific pathophysiological models (3). Accumulating evidence indicates that inflammatory and metabolic dysregulation contribute to the pathophysiology and clinical course of depressive disorders **(4).** In parallel, chronic low-grade inflammation has been increasingly recognized as a key contributor to the development and progression of metabolic diseases, particularly obesity and type 2 diabetes mellitus. Together, these observations have led to growing interest in chronic low-grade inflammation as a potential common biological pathway linking depression and metabolic disorders.

Chronic low-grade inflammation differs fundamentally from acute inflammation, as it is characterized by persistent, systemic immune activation without overt clinical symptoms. This inflammatory state is associated with mildly but chronically elevated circulating inflammatory markers, including C-reactive protein, interleukin-6 and tumor necrosis factor-alpha, reflecting sustained activation of innate immune pathways (1,5). Unlike acute inflammatory responses, which are time-limited and protective, low-grade inflammation may persist for years and exert deleterious effects on metabolic, vascular and neural systems. Such prolonged inflammatory signaling has been implicated in the development of insulin resistance, endothelial dysfunction and alterations in neurobiological processes involved in mood regulation (1). Consequently, chronic low-grade inflammation is increasingly viewed not merely as a consequence, but as an active contributor to the pathogenesis of both metabolic and psychiatric disorders.

In addition to biological mechanisms, increasing attention has been directed toward modifiable lifestyle-related factors that may contribute to chronic low-grade inflammation. Dietary patterns, physical inactivity, sleep disturbances, and chronic psychological stress have been identified as important determinants of sustained inflammatory activation. Understanding these factors may be crucial for developing effective prevention and health promotion strategies targeting both metabolic and depressive disorders.

The aim of this narrative review is to summarize and discuss current evidence on chronic low-grade inflammation as a shared pathophysiological mechanism linking depressive disorders with selected metabolic diseases, including obesity, type 2 diabetes mellitus, and metabolic

syndrome, with particular emphasis on lifestyle-related determinants and their implications for prevention and health promotion.

## Materials and Methods

This narrative review was based on a targeted search of PubMed and Google Scholar using combinations of keywords related to chronic low-grade inflammation, depression, obesity, type 2 diabetes mellitus, metabolic syndrome, and lifestyle-related factors. Priority was given to systematic reviews, meta-analyses, large observational cohorts, and mechanistic studies relevant to immunometabolic pathways. Particular attention was also given to studies examining behavioral and lifestyle determinants of low-grade inflammation. Additional records were identified through screening of reference lists of key articles.

## Inflammatory mechanisms linking depression and metabolic disorders

Chronic low-grade inflammation (CLGI) is increasingly recognized as a plausible biological bridge between depressive disorders and metabolic conditions, including obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS). In both clinical and population-based research, these disorders share a pattern of mildly but persistently elevated inflammatory markers—most consistently C-reactive protein (CRP) and pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)—suggesting sustained activation of innate immune signaling rather than an acute, self-limited inflammatory response (1,5,6).

A key mechanistic intersection is the adipose tissue–immune axis. In obesity, adipose tissue undergoes immune cell infiltration and functional remodeling, characterized by increased macrophage accumulation and a shift toward a pro-inflammatory secretory profile, including elevated production of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). This adipose tissue–derived inflammatory state contributes to systemic low-grade inflammation and plays a central role in the development of insulin resistance, thereby linking obesity with type 2 diabetes mellitus (7,8). More broadly, chronic low-grade inflammation driven by immunometabolic interactions is increasingly recognized as a shared underlying mechanism across multiple chronic diseases (6).

Inflammation may contribute to metabolic dysfunction through multiple interrelated pathways. Pro-inflammatory cytokines interfere with insulin signaling and glucose homeostasis, promote systemic insulin resistance, and impair vascular function, thereby facilitating key metabolic abnormalities characteristic of MetS. Persistent low-grade inflammatory signaling can therefore be conceptualized as an active driver of metabolic risk rather than merely a downstream marker of disease severity (1,5–8).

Conversely, inflammatory activation is increasingly recognized as clinically relevant in a subset of patients with depressive disorders. Elevated inflammatory markers have been associated with specific symptom profiles and worse clinical outcomes, including chronicity and reduced response to standard antidepressant treatment. Prospective cohort evidence indicates that higher baseline inflammatory and metabolic dysregulation—particularly elevated IL-6 levels and adverse lipid or glucose parameters—predict a more persistent or recurrent course of depression among antidepressant users, supporting the concept of an inflammation-associated or "metabolic" subtype of depression (4,9).

Several interconnected neurobiological mechanisms have been proposed to explain how peripheral inflammation may contribute to depressive symptomatology. Elevated circulating levels of pro-inflammatory cytokines, particularly IL-6 and TNF-α, have been consistently reported in patients with depressive disorders, supporting the presence of systemic immune activation in this population (10). Experimental and clinical evidence indicates that inflammatory signaling can influence monoaminergic neurotransmission, dysregulate hypothalamic–pituitary–adrenal (HPA) axis activity, and impair neuroplasticity-related pathways, thereby contributing to the development and persistence of depressive symptoms (11,12). In addition, inflammation-associated metabolic alterations, including insulin resistance and disturbances in energy homeostasis, may further increase vulnerability to mood dysregulation (10,12). Importantly, accumulating evidence suggests that these interactions form a bidirectional and self-reinforcing network: depression-related behavioral and neuroendocrine changes—such as sleep disturbances, reduced physical activity, and chronic activation of stress-response systems—may in turn perpetuate low-grade inflammation, creating a vicious cycle that links metabolic deterioration with increasing depressive burden over time (11,12).

**Low-grade inflammation in depressive disorders**

Accumulating **evidence** indicates that depressive disorders are biologically heterogeneous, with chronic low-grade inflammation characterizing a distinct subset of patients. This inflammation-associated phenotype of depression is marked by persistent activation of innate immune pathways and modest but sustained elevations of circulating inflammatory markers, particularly interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), rather than features of acute inflammatory responses **(10,11).** Importantly, inflammatory activation in depression appears to have clear clinical relevance. Elevated inflammatory markers have been associated with specific symptom dimensions, including anhedonia, fatigue, psychomotor slowing, and somatic symptoms, as well as with a more chronic and treatment-resistant course of illness **(11,12).**

Prospective cohort studies further indicate that a higher baseline inflammatory burden—particularly elevated IL-6 and C-reactive protein (CRP)—is associated with an increased risk of persistent or recurrent depressive episodes. Moreover, longitudinal evidence from antidepressant-treated cohorts suggests that combined inflammatory and metabolic dysregulation predicts poorer treatment response and a more chronic disease course, supporting the concept of an inflammation-associated or "metabolic" subtype of depression **(4,9).**

Several neurobiological mechanisms have been proposed to explain how peripheral inflammation may influence depressive symptomatology. Pro-inflammatory cytokines can interfere with monoaminergic neurotransmission, including serotonergic and dopaminergic signaling, may alter glutamatergic balance, and simultaneously affect neuroendocrine stress regulation through sustained activation of the hypothalamic–pituitary–adrenal (HPA) axis **(11,12).** In addition, inflammatory signaling has been shown to negatively impact neuroplasticity and neurogenesis—processes that are central to mood regulation and antidepressant response **(11).**

Metabolic disturbances frequently accompanying chronic low-grade inflammation, such as insulin resistance, may further amplify vulnerability to depressive symptoms through combined central and peripheral mechanisms, linking immunological and metabolic dysregulation with altered brain function **(11).** Notably, the relationship between depression and inflammation appears to be bidirectional. Behavioral and neuroendocrine features commonly observed in depressive disorders—including sleep disturbance, reduced physical activity, altered dietary patterns, and chronic activation of stress-response systems—may themselves promote or

sustain low-grade inflammatory states, creating a self-reinforcing cycle that links metabolic deterioration with depressive burden over time **(11,12).**

**Low-grade inflammation in metabolic diseases**

Chronic low-grade inflammation is a central feature of metabolic disorders, including obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS). Unlike classical acute inflammation, this inflammatory state is characterized by persistent, low-intensity activation of the immune system and chronically elevated circulating inflammatory mediators, most consistently C-reactive protein, interleukin-6, and tumor necrosis factor-α, reflecting sustained activation of innate immune pathways (1,6). Increasing evidence indicates that this inflammatory milieu is not merely a consequence of metabolic dysregulation but represents a broader disturbance of immunometabolic homeostasis that actively contributes to the initiation and progression of chronic metabolic diseases (13).

Adipose tissue plays a pivotal role in this process. In obesity, excess adiposity—particularly visceral fat—is associated with immune cell infiltration, including increased accumulation of pro-inflammatory macrophages and other innate immune cells. These changes result in functional remodeling of adipose tissue toward a pro-inflammatory endocrine phenotype, characterized by enhanced secretion of cytokines, chemokines, and adipokines that promote systemic inflammation and insulin resistance (7,8). This obesity-related inflammatory state, often referred to as metaflammation, represents a distinct form of chronic inflammation driven by nutrient excess and energy surplus rather than infection and is a key mechanistic link between obesity, insulin resistance, and T2DM (14).

As a result, adipose tissue functions as a key immunometabolic organ linking excess energy storage with chronic inflammation.

Inflammatory signaling interferes with multiple metabolic pathways relevant to type 2 diabetes mellitus and metabolic syndrome. Pro-inflammatory cytokines impair insulin signaling, promote insulin resistance, alter lipid metabolism, and contribute to endothelial dysfunction, thereby facilitating hyperglycemia, dyslipidemia, hypertension, and accelerated atherosclerosis (5,6,15).

These observations support the concept that chronic low-grade inflammation actively contributes to metabolic disease pathogenesis rather than representing a mere downstream consequence of metabolic dysfunction (6,13).

Persistent low-grade inflammation therefore acts as an active driver of metabolic risk rather than a passive biomarker of disease severity.

Importantly, metabolic inflammation exerts systemic effects that extend beyond peripheral tissues. Circulating inflammatory mediators have been shown to influence central nervous system function, modulate neuroendocrine regulation, and interact with neural pathways involved in appetite control, energy balance, and stress responsiveness. Through these mechanisms, chronic metabolic inflammation may increase vulnerability to psychiatric conditions, particularly depressive disorders, and provide a biological framework for the high prevalence of comorbidity observed between metabolic and mood disorders (6,8,16).

Bidirectional relationship between depression and metabolic dysregulation

Growing evidence indicates that the relationship between depressive disorders and metabolic diseases is bidirectional rather than unidirectional. Large population-based and longitudinal studies demonstrate that individuals with obesity, type 2 diabetes mellitus, or metabolic syndrome are at increased risk of developing depressive symptoms over time, while depression itself predicts subsequent metabolic deterioration and incident cardiometabolic disease (17–19).

Prospective cohort studies indicate that metabolic dysregulation, including adverse glucose and lipid profiles, may precede the clinical onset of depressive and other stress-related disorders over long-term follow-up periods (20). These associations remain significant after adjustment for key sociodemographic factors, although the independent contributions of lifestyle behaviors and adiposity are difficult to fully disentangle in long-term observational studies (20). Such findings are consistent with the concept of an immunometabolic subtype of depression, characterized by the clustering of metabolic disturbances with specific atypical symptom profiles, such as hyperphagia and weight gain (21).

Conversely, metabolic and inflammatory dysregulation appears to shape the clinical expression of depressive disorders. Cross-sectional evidence indicates that obesity, metabolic syndrome components, and elevated inflammatory markers are preferentially associated with atypical

depressive symptoms, supporting the concept of an immunometabolic subtype of depression (22).

Several mechanisms have been proposed to underlie this bidirectional association. Behavioral factors commonly observed in depressive disorders, including reduced physical activity, sleep disturbance, and altered dietary patterns, may contribute to increased metabolic vulnerability. In parallel, neuroendocrine alterations—particularly dysregulation of the hypothalamic–pituitary–adrenal axis—have been consistently documented in depression and are thought to link depressive pathology with elevated cardiometabolic risk (23,24).

At the same time, metabolic inflammation and insulin resistance may adversely affect brain function through inflammatory, neuroendocrine, and metabolic pathways, leading to impaired brain energy metabolism and neurobiological changes that increase vulnerability to depressive symptoms (25). Experimental and human studies further indicate that disturbances in central insulin signaling influence neural circuits involved in behavior, energy regulation, and cognition, providing additional mechanistic links between metabolic dysregulation and altered brain function (26).

Importantly, accumulating evidence suggests that chronic low-grade inflammation may represent a shared biological substrate underlying the bidirectional relationship between depressive disorders and metabolic diseases. Integrative studies combining inflammatory, metabolic, and psychiatric phenotyping provide support for the existence of a biologically distinct subgroup of individuals in whom immunometabolic dysregulation links depressive symptom burden with progressive metabolic impairment. In this subgroup, low-grade inflammatory activation and metabolic abnormalities appear to mutually reinforce one another, contributing to greater disease chronicity and poorer clinical outcomes across both psychiatric and metabolic domains (27–29).

**Lifestyle-related determinants of chronic low-grade inflammation**

Chronic low-grade inflammation is strongly influenced by modifiable lifestyle-related factors that contribute to sustained immune activation. Among these, dietary patterns play a central role. Diets rich in ultra-processed foods, refined sugars, and saturated fats have been associated with increased levels of inflammatory markers, whereas anti-inflammatory dietary patterns,

such as the Mediterranean diet, may reduce systemic inflammation (5,35). Physical inactivity represents another important contributor to low-grade inflammation. Sedentary behavior is associated with increased adiposity, impaired metabolic regulation, and elevated inflammatory mediators. In contrast, regular physical activity has been shown to exert anti-inflammatory effects and improve both metabolic and mental health outcomes (35). Sleep disturbances and chronic psychological stress are also recognized as important determinants of inflammatory activation. Poor sleep quality and duration have been linked to increased inflammatory markers, while chronic stress may promote sustained activation of neuroendocrine pathways, including the hypothalamic–pituitary–adrenal axis, contributing to immune dysregulation (11). Moreover, low-grade inflammation is consistently observed in patients with depressive disorders, as reflected by elevated levels of inflammatory markers such as C-reactive protein (12). Importantly, these lifestyle-related factors often coexist and interact, creating a cumulative effect on inflammatory burden. Their modification may represent an effective strategy for reducing chronic low-grade inflammation and mitigating the risk of both metabolic and depressive disorders (6,35).

**Clinical implications and future directions**

The recognition of chronic low-grade inflammation as a pathophysiological mechanism contributing to depressive disorders—and linking central nervous system processes with peripheral biological systems—has important clinical and translational implications. It challenges traditional disease-specific diagnostic frameworks and supports a more integrated, systems-based approach to patient assessment, in which inflammatory and neurobiological dimensions are considered alongside clinical symptoms **(30,31).**

From a clinical perspective, accumulating evidence suggests that inflammatory biomarkers may help identify subgroups of patients with depression who are at increased risk of poor clinical outcomes. Elevated levels of C-reactive protein, interleukin-6, and tumor necrosis factor-α have been consistently associated with reduced response to conventional antidepressant therapies, highlighting the potential utility of biomarker-informed stratification to guide treatment selection **(32).** Such stratification may be particularly relevant for patients presenting with atypical depressive features, obesity, or metabolic syndrome, in whom immunometabolic dysregulation appears most pronounced.

These observations have stimulated growing interest in adjunctive interventions targeting inflammatory pathways. Meta-analytic evidence from randomized controlled trials suggests that anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs and cytokine inhibitors, can reduce depressive symptoms. However, substantial heterogeneity and methodological limitations warrant cautious interpretation and underscore the need to identify patient subgroups most likely to benefit from such approaches **(33,34).**

Lifestyle-based strategies that improve metabolic and inflammatory profiles—such as weight reduction, dietary modification, and structured physical activity—are also being explored as complementary interventions. Preliminary evidence supports potential benefits for depressive symptoms, particularly among patients with cardiometabolic comorbidity **(35).** Importantly, these interventions may confer dual benefits by simultaneously improving metabolic health and reducing systemic inflammation, thereby addressing both psychiatric and cardiometabolic risk factors.

Beyond treatment implications, an immunometabolic framework is also relevant for prevention and early risk stratification. Longitudinal cohort data indicate that elevated or increasing levels of low-grade systemic inflammation, commonly indexed by C-reactive protein, may precede the onset of clinically significant depressive symptoms, supporting inflammation as a measurable antecedent of depression risk (36). Integrating mental health screening into metabolic care settings, and conversely incorporating metabolic risk assessment into psychiatric practice, may therefore represent a pragmatic strategy to mitigate long-term disease burden.

Finally, these findings highlight the need for future research adopting integrative and multidimensional approaches that combine immune, metabolic, neuroendocrine, neurobiological, and behavioral measures. Such strategies are essential to improve the characterization of shared biological mechanisms, identify clinically relevant subgroups, and inform the development of targeted interventions addressing the comorbidity between depression and metabolic disease (37).

Taken together, the available evidence supports the concept that chronic low-grade inflammation represents a unifying biological framework linking depressive disorders and metabolic diseases. Rather than acting in isolation, immune, metabolic, and neurobiological pathways appear to interact dynamically across the life course, shaping both disease

vulnerability and clinical outcomes. Recognizing these shared mechanisms provides a foundation for more integrated models of research and care.

**Conclusions**

Chronic low-grade inflammation emerges from the available evidence as a key shared pathophysiological mechanism linking depressive disorders with metabolic diseases, including obesity, type 2 diabetes mellitus, and metabolic syndrome. Rather than representing independent disease entities, these conditions appear to be interconnected through complex interactions between immune activation, metabolic dysregulation, neuroendocrine signaling, and brain function. This immunometabolic framework helps explain the high prevalence of comorbidity, the heterogeneity of clinical presentations, and the tendency toward chronicity observed across both psychiatric and metabolic domains.

Recognition of these shared mechanisms has important implications for research and clinical practice. Integrative approaches that simultaneously consider inflammatory, metabolic, and psychological dimensions may improve risk stratification, facilitate identification of biologically meaningful subtypes, and support the development of more personalized preventive and therapeutic strategies. Future longitudinal and interventional studies incorporating multidimensional biological and behavioral assessments are needed to clarify causal pathways and to translate immunometabolic insights into effective interventions addressing the growing burden of depression–metabolic disease comorbidity.

**Disclosure**

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All authors have read and agreed to the published version of the manuscript.

Funding statement: The study did not receive special funding.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process.

During the preparation of this work, the authors used ChatGPT (OpenAI) for the purpose of language editing and stylistic improvement only. The authors reviewed and approved the final version of the manuscript and take full responsibility for its content.

**References**

Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25(12):1822–1832. https://doi.org/10.1038/s41591-019-0675-0

1. Al-Khatib Y, Akhtar MA, Kanawati MA, Mucheke R, Mahfouz M, Al-Nufoury M. Depression and Metabolic Syndrome: A Narrative Review. Cureus. 2022;14(2):e22153. https://doi.org/10.7759/cureus.22153
2. Penninx BWJH, Lange SMM. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. Dialogues Clin Neurosci. 2018;20(1):63–73. https://doi.org/10.31887/DCNS.2018.20.1/bpenninx
3. Vogelzangs N, Beekman ATF, Van Reedt Dortland AKB, Schoevers RA, Giltay EJ, De Jonge P, et al. Inflammatory and Metabolic Dysregulation and the 2-Year Course of Depressive Disorders in Antidepressant Users. Neuropsychopharmacology. 2014;39(7):1624–1634. https://doi.org/10.1038/npp.2014.9

4. Calder PC, Albers R, Antoine JM, Blum S, Bourdet-Sicard R, Ferns GA, et al. Inflammatory Disease Processes and Interactions with Nutrition. Br J Nutr. 2009;101(Suppl 1):S1–S45.
https://doi.org/10.1017/S0007114509377867
5. van de Vyver M. Immunology of chronic low-grade inflammation: relationship with metabolic function. J Endocrinol. 2023;257(1):e220271.
https://doi.org/10.1530/JOE-22-0271
6. Burhans MS, Hagman DK, Kuzma JN, Schmidt KA, Kratz M. Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus. Compr Physiol. 2019;9(1):1–58.
https://doi.org/10.1002/cphy.c170040
7. Wernstedt Asterholm I, Tao C, Morley TS, Wang QA, Delgado-Lopez F, Wang ZV, et al. Adipocyte Inflammation is Essential for Healthy Adipose Tissue Expansion and Remodeling. Cell Metab. 2014;20(1):103–118.
https://doi.org/10.1016/j.cmet.2014.05.005
8. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of Serum Interleukin 6 and C-Reactive Protein in Childhood With Depression and Psychosis in Young Adult Life. JAMA Psychiatry. 2014;71(10):1121–1128.
https://doi.org/10.1001/jamapsychiatry.2014.1332
9. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A Meta-Analysis of Cytokines in Major Depression. Biol Psychiatry. 2010;67(5):446–457.
https://doi.org/10.1016/j.biopsych.2009.09.033
10. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016;16(1):22–34.
https://doi.org/10.1038/nri.2015.5
11. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychol Med. 2019;49(12):1958–1970.
https://doi.org/10.1017/S0033291719001454
12. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–867.
https://doi.org/10.1038/nature05485
13. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 2011;29:415–445.
https://doi.org/10.1146/annurev-immunol-031210-101322
14. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011;11(2):98–107.
https://doi.org/10.1038/nri2925
15. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest. 2011;121(6):2111–2117.
https://doi.org/10.1172/JCI57132
16. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, et al. Bidirectional association between depression and metabolic syndrome. Diabetes Care. 2012;35(5):1171–1180.
https://doi.org/10.2337/dc11-2055
17. Frank P, Batty GD, Pentti J, Jokela M, Poole L, Ervasti J, et al. Association Between Depression and Physical Conditions Requiring Hospitalization. JAMA Psychiatry.

2023;80(7):690–699.
https://doi.org/10.1001/jamapsychiatry.2023.0777
18. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and Type 2 Diabetes Over the Lifespan. Diabetes Care. 2008;31(12):2383–2390.
https://doi.org/10.2337/dc08-0985
19. Chourpiliadis C, Zeng Y, Lovik A, Wei D, Valdimarsdóttir U, Song H, et al. Metabolic Profile and Long-Term Risk of Depression. JAMA Netw Open. 2024;7(4):e244525.
https://doi.org/10.1001/jamanetworkopen.2024.4525
20. Milaneschi Y, Lamers F, Berk M, Penninx BWJH. Depression Heterogeneity and Its Biological Underpinnings. Biol Psychiatry. 2020;88(5):369–380.
https://doi.org/10.1016/j.biopsych.2020.01.014
21. Lamers F, Milaneschi Y, De Jonge P, Giltay EJ, Penninx BWJH. Metabolic and inflammatory markers. Psychol Med. 2018;48(7):1102–1110.
https://doi.org/10.1017/S0033291717002483
22. Stetler C, Miller GE. Depression and HPA activation. Psychosom Med. 2011;73(2):114–126.
https://doi.org/10.1097/PSY.0b013e31820ad12b
23. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. Nat Rev Dis Primers. 2016;2:16065.
https://doi.org/10.1038/nrdp.2016.65
24. Leonard BE, Wegener G. Inflammation, insulin resistance and neuroprogression in depression. Acta Neuropsychiatr. 2020;32(1):1–9.
https://doi.org/10.1017/neu.2019.17
25. Kullmann S, Kleinridders A, Small DM, Fritsche A, Häring HU, Preissl H, et al. Central nervous pathways of insulin action. Lancet Diabetes Endocrinol. 2020;8(6):524–534.
https://doi.org/10.1016/S2213-8587(20)30113-3
26. Lamers F, Milaneschi Y, Vinkers CH, Schoevers RA, Giltay EJ, Penninx BWJH. Depression profilers. Brain Behav Immun. 2020;88:174–183.
https://doi.org/10.1016/j.bbi.2020.04.002
27. Milaneschi Y, Lamers F, Peyrot WJ, Baune BT, Breen G, Dehghan A, et al. Genetic Association of Major Depression. JAMA Psychiatry. 2017;74(12):1214–1225.
https://doi.org/10.1001/jamapsychiatry.2017.3016
28. de Kluiver H, Jansen R, Penninx BWJH, Giltay EJ, Schoevers RA, Milaneschi Y. Metabolomics signatures of depression. Transl Psychiatry. 2023;13(1):198.
https://doi.org/10.1038/s41398-023-02484-5
29. Raison CL, Miller AH. Role of inflammation in depression. Mod Trends Pharmacopsychiatry. 2013;28:33–48.
https://doi.org/10.1159/000343966
30. Kivimäki M, Steptoe A. Effects of stress on cardiovascular disease. Nat Rev Cardiol. 2018;15(4):215–229.
https://doi.org/10.1038/nrcardio.2017.189
31. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and response to treatment. Eur Neuropsychopharmacol. 2015;25(10):1532–1543.
https://doi.org/10.1016/j.euroneuro.2015.06.007
32. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A Randomized Controlled Trial of Infliximab. JAMA Psychiatry. 2013;70(1):31–41.
https://doi.org/10.1001/2013.jamapsychiatry.4

33. Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, et al. Effect of Anti-inflammatory Treatment on Depression. JAMA Psychiatry. 2014;71(12):1381–1391. https://doi.org/10.1001/jamapsychiatry.2014.1611
34. Lopresti AL, Hood SD, Drummond PD. Lifestyle factors in depression. J Affect Disord. 2013;148(1):12–27. https://doi.org/10.1016/j.jad.2013.01.014
35. Osimo EF, Stochl J, Zammit S, Lewis G, Jones PB, Khandaker GM. CRP and depression. Compr Psychiatry. 2020;96:152143. https://doi.org/10.1016/j.comppsych.2019.152143
36. Milaneschi Y, Simmons WK, van Rossum EFC, Penninx BW. Depression and obesity. Mol Psychiatry. 2019;24(1):18–33. https://doi.org/10.1038/s41380-018-0017-5