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Immunometabolic Dysregulation and Cognitive Dysfunction in Major Depressive Disorder: The Role of Chronic Low-Grade Inflammation

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ABSTRACT

Major depressive disorder is a heterogeneous psychiatric condition frequently accompanied by persistent cognitive dysfunction involving executive function, attention, memory, processing

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speed, and motivational processes. Increasing evidence suggests that chronic low-grade inflammation and immunometabolic dysregulation may contribute to these alterations in a biologically distinct subgroup of patients. This study analyzed the relationship between systemic inflammatory activity, metabolic abnormalities, and cognitive impairment in depression through an integrative review based on the scientific method. Evidence from clinical studies, cohort investigations, systematic reviews, meta-analyses, and translational research was examined, with particular attention to C-reactive protein, interleukin-6, tumor necrosis factor-alpha, metabolic syndrome, insulin resistance, oxidative stress, dopaminergic dysfunction, and the tryptophan–kynurenine pathway. The results showed that elevated inflammatory activity is present in a substantial but non-universal proportion of patients with depression and is associated particularly with poorer executive functioning. The coexistence of depression and higher C-reactive protein was related to additional executive impairment, while the interaction between metabolic syndrome and inflammatory/oxidative dysregulation was associated with poorer global cognitive performance. Immune activation was also accompanied by increased kynurenine, reduced tryptophan, an elevated kynurenine-to-tryptophan ratio, and greater depressive symptom burden. Anti-inflammatory interventions showed modest improvements in depressive symptoms and anhedonia among individuals with elevated inflammatory activity, although direct evidence of cognitive improvement remains limited. Overall, the findings support an immunometabolic model in which inflammation interacts with metabolic and neurochemical abnormalities to influence cognitive vulnerability in selected patients with depression. Integrating inflammatory biomarkers, metabolic status, psychiatric assessment, and cognitive evaluation may contribute to more precise clinical stratification and guide future personalized therapeutic strategies.

KEYWORDS

major depressive disorder, low-grade inflammation, cognitive impairment, immunometabolic depression, C-reactive protein, neuroinflammation, metabolic syndrome, kynurenine pathway, executive function, oxidative stress, precision psychiatry

INTRODUCTION

Major depressive disorder (MDD) is a complex and heterogeneous psychiatric condition whose clinical manifestations extend beyond persistent disturbances in mood. A substantial proportion of affected individuals experience impairments in attention, executive functioning, processing speed, working memory, and episodic memory, which may persist even after partial improvement of affective symptoms. These cognitive alterations are clinically relevant because they can interfere with occupational performance, social functioning, treatment adherence, and the capacity to recover previous levels of independence. Although disturbances in monoaminergic neurotransmission have historically occupied a central position in biological models of depression, contemporary evidence indicates that the disorder involves interactions among neural, endocrine, immune, and metabolic systems. Within this broader framework, chronic low-grade inflammation has emerged as a potentially important biological mechanism linking depressive symptoms with cognitive dysfunction [1]–[4].

Low-grade inflammation differs from the intense and transient inflammatory response produced by acute infection or tissue injury. It is generally characterized by a persistent, relatively modest elevation of circulating inflammatory mediators, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and other components of innate immune signaling. Evidence supporting the relevance of this phenomenon in depression has progressively accumulated. A systematic review and meta-analysis reported that approximately one quarter of patients with depression presented CRP concentrations above 3 mg/L, a commonly used threshold for low-grade inflammation, while a considerably larger proportion showed mildly elevated CRP concentrations [6]. Subsequent analyses have reinforced the presence of altered inflammatory profiles in subsets of patients with MDD, emphasizing that inflammation should not be considered a universal characteristic of depression but rather a biological dimension that may define clinically meaningful subgroups [7]. This distinction is particularly important because the biological heterogeneity of depression may partly explain differences in symptom profiles, comorbidities, cognitive impairment, and therapeutic response.

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The concept of **immunometabolic depression** provides a framework for understanding these differences. This model proposes that inflammatory activation interacts with disturbances in energy regulation and metabolic homeostasis, including obesity, insulin resistance, dyslipidemia, altered leptin signaling, and other cardiometabolic abnormalities [5]. Rather than operating independently, immune and metabolic disturbances may reinforce each other through bidirectional signaling pathways. Adipose tissue can contribute to chronic cytokine production, metabolic dysregulation can increase oxidative stress, and inflammatory mediators can alter insulin signaling, mitochondrial function, neurotransmitter metabolism, and synaptic plasticity. Clinically, this immunometabolic profile has been associated particularly with symptoms related to energy regulation, including fatigue, hypersomnia, increased appetite, weight gain, and anhedonia [5]. However, its potential contribution to cognitive dysfunction is increasingly relevant because many of the same biological pathways implicated in metabolic dysfunction can influence neuronal signaling and cognitive networks.

Several mechanisms may explain how peripheral low-grade inflammation affects central nervous system function. Circulating inflammatory signals can communicate with the brain through humoral pathways, endothelial signaling, neural routes, and immune-cell interactions at the neurovascular interface. Once these signals influence the central nervous system, they may modify microglial activity, monoamine synthesis and reuptake, glutamatergic neurotransmission, neuroendocrine regulation, oxidative balance, and synaptic plasticity [1]–[4]. Persistent inflammatory activity may consequently alter neural circuits involved in executive control, reward processing, memory, and psychomotor function. In this context, inflammatory effects on dopaminergic signaling are particularly relevant because dopamine contributes to motivation, reinforcement learning, cognitive effort, and executive performance. Experimental and translational evidence indicates that inflammatory signaling can reduce dopaminergic availability and modify corticostriatal function, providing a plausible biological connection among inflammation, anhedonia, psychomotor slowing, reduced motivation, and cognitive inefficiency [17].

Another major connection between immunity, metabolism, and neuronal function involves the tryptophan–kynurenine pathway. Pro-inflammatory signaling can increase the metabolism of tryptophan through indoleamine 2,3-dioxygenase and related enzymatic pathways, thereby modifying the relative availability of kynurenine metabolites with neuroactive properties. Some metabolites, particularly quinolinic acid, may enhance glutamatergic N-methyl-D-aspartate receptor activity and contribute to oxidative and excitotoxic processes, whereas kynurenic acid has different neuromodulatory properties [15], [16]. Meta-analytic evidence indicates that immune activation can modify kynurenine metabolism and that these alterations are associated with depressive symptoms [16]. Consequently, dysregulation of this pathway represents an important biological bridge through which peripheral inflammation may influence neurotransmission, neuroplasticity, mood regulation, and cognitive performance. Nevertheless, peripheral concentrations of kynurenine metabolites do not always directly reflect central nervous system activity, making interpretation dependent on biological context and reinforcing the need for integrated rather than isolated biomarker assessment [15].

Clinical observations provide additional support for an association between inflammation and cognitive dysfunction in depression. In a large cohort of 43,896 adults, both depression and higher CRP concentrations were independently associated with poorer executive functioning, while individuals presenting depression together with greater inflammatory activity showed additional impairment in executive performance [12]. Importantly, these associations remained detectable after adjustment for several relevant variables, including age, educational attainment, body mass index, smoking, stressful experiences, sedentary behavior, and chronic medical conditions. In another investigation comparing patients with MDD and healthy controls, an inflammatory/oxidative index incorporating TNF, CRP, and 4-hydroxynonenal was examined together with metabolic syndrome and cognitive performance. The interaction between metabolic syndrome and inflammatory/oxidative dysregulation was associated with poorer cognition, supporting the possibility that cognitive impairment in depression may emerge not from inflammation alone but from the convergence of immune, metabolic, and oxidative abnormalities [13].

These findings are particularly relevant for internal medicine because the biological processes under investigation are not confined to psychiatric disease. Obesity, type 2 diabetes mellitus, metabolic syndrome, cardiovascular disease, sleep disorders, physical inactivity, and other chronic conditions frequently coexist with depression and are themselves associated with systemic inflammation and cognitive vulnerability. Therefore, elevated inflammatory biomarkers in a depressed patient cannot automatically be interpreted as originating from the psychiatric disorder. They may instead

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represent the cumulative effect of multiple interacting conditions. This overlap constitutes both a methodological challenge and a clinically important opportunity. Careful characterization of cardiometabolic status, medication exposure, lifestyle factors, and inflammatory comorbidities may help distinguish nonspecific inflammatory elevations from a more coherent immunometabolic phenotype associated with depressive and cognitive manifestations [5], [13].

Despite increasing evidence, several uncertainties remain. Most studies are observational or cross-sectional, inflammatory biomarkers vary considerably between individuals and over time, and commonly used measures such as CRP lack specificity for psychiatric disease. Furthermore, depression itself is highly heterogeneous, and cognitive impairment is influenced by age, education, disease severity, sleep, medication, vascular risk, and medical comorbidity. These factors limit causal inference and make it unlikely that a single biomarker can adequately explain cognitive dysfunction. The central research problem is therefore not simply whether inflammation is increased in depression, but whether a recognizable pattern of low-grade inflammatory and metabolic dysregulation is consistently associated with particular dimensions of cognitive impairment and whether this information can eventually contribute to clinically meaningful stratification.

Accordingly, the present study examines the relationship between low-grade inflammation, immunometabolic dysregulation, and cognitive deterioration in depression through an integrated analysis of neurobiological, psychiatric, and internal-medicine evidence. Particular attention is directed toward systemic inflammatory markers, metabolic abnormalities, oxidative processes, kynurenine-pathway activation, and their potential relationships with executive functioning, attention, memory, processing speed, and motivational circuitry. The working hypothesis is that patients with a greater inflammatory and metabolic burden will exhibit a more pronounced pattern of cognitive dysfunction than those without this biological profile, and that the coexistence of metabolic abnormalities may amplify the association between inflammatory activity and impaired cognition [12], [13]. A complementary hypothesis is that the relationship is multidimensional rather than dependent on a single inflammatory mediator, requiring interpretation of immune biomarkers within the broader metabolic and clinical context of the individual.

To address these questions, the study adopts an integrative analytical approach that connects evidence from clinical studies, biomarker research, neurobiological mechanisms, and therapeutic investigations. This framework allows inflammatory findings to be interpreted alongside metabolic status and cognitive outcomes rather than as isolated laboratory abnormalities. Such an approach is consistent with emerging precision-psychiatry models that seek biologically informative subgroups within the heterogeneous diagnosis of MDD [5]. The clinical importance of this perspective is reinforced by evidence suggesting that inflammatory status may influence response to therapeutic interventions. Meta-analytic investigations of anti-inflammatory strategies have demonstrated potentially beneficial effects in selected populations [18], and more recent analyses focusing specifically on depressed individuals with elevated inflammatory activity have reported reductions in depressive symptoms and anhedonia, although effects on response and remission remain less definitive [20]. These findings do not establish inflammation as a universal therapeutic target, but they strengthen the rationale for determining whether inflammatory and metabolic phenotyping can identify patients for whom targeted interventions may be particularly relevant.

Understanding the relationship between chronic low-grade inflammation and cognitive dysfunction may therefore contribute to a more comprehensive model of depression in which mood symptoms, cognition, immunity, and systemic metabolism are considered interconnected components rather than separate clinical domains. Clarifying these connections could support the development of multidimensional assessment strategies combining psychiatric evaluation, cognitive testing, inflammatory biomarkers, and cardiometabolic variables. Ultimately, identifying reproducible immunometabolic signatures associated with cognitive impairment may help refine risk stratification, improve monitoring of persistent cognitive symptoms, and guide future studies of personalized interventions aimed not only at reducing depressive symptom severity but also at restoring cognitive and functional outcomes.

DEVELOPMENT

Major depressive disorder (MDD) is increasingly understood as a multisystem disorder in which alterations in immune regulation, metabolism, neuroendocrine signaling, and brain function interact to shape clinical presentation. Within this framework, chronic low-grade inflammation represents one of the most relevant biological processes because it

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can influence both depressive symptomatology and cognitive performance. Rather than being present uniformly in all patients, inflammatory activation appears to characterize a subgroup of individuals with depression, particularly those with metabolic abnormalities, fatigue, anhedonia, psychomotor slowing, and cognitive dysfunction [1], [5]–[7].

Low-Grade Inflammation as a Biological Substrate of Depression

Low-grade inflammation is characterized by persistent but moderate activation of the immune system, frequently reflected by increased circulating concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and other inflammatory mediators. Unlike acute inflammation, which is usually adaptive and self-limited, chronic inflammatory activation may persist for prolonged periods and produce systemic and neurological effects.

Meta-analytic evidence has shown that inflammatory markers are elevated in a meaningful proportion of patients with depression. Osimo et al. reported that approximately one quarter of depressed individuals presented CRP concentrations above 3 mg/L, while an even larger proportion showed milder elevations [6]. Similarly, differences in circulating inflammatory markers between patients with depression and healthy controls have been repeatedly observed, although substantial interindividual variability remains [7]. These findings support the hypothesis that inflammation constitutes a biological dimension of depression rather than a universal feature of the disorder.

Several factors may contribute to this inflammatory phenotype. Obesity, insulin resistance, physical inactivity, disrupted sleep, chronic psychosocial stress, smoking, and cardiometabolic disease can increase systemic inflammatory activity. These same factors are also common among people with depression, generating a bidirectional relationship in which depressive symptoms may worsen metabolic health while metabolic abnormalities reinforce inflammatory signaling and potentially increase psychiatric symptom burden [5].

Neuroimmune Communication and Cognitive Function

Peripheral inflammatory activity can influence the central nervous system through multiple communication pathways. Cytokines and other inflammatory mediators can affect brain function through endothelial signaling, circumventricular organs, afferent neural pathways, transport mechanisms across the blood-brain barrier, and immune-cell interactions. These signals can subsequently alter microglial activation, neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and neuronal energy regulation [2]–[4].

Cognition depends on the coordinated activity of cortical and subcortical networks involved in attention, working memory, decision-making, executive control, learning, and memory consolidation. Persistent inflammatory signaling may interfere with these functions by altering neuronal efficiency and disrupting communication among the prefrontal cortex, hippocampus, anterior cingulate cortex, and basal ganglia. Consequently, inflammation may contribute not only to depressive mood but also to difficulties in concentration, cognitive flexibility, information processing, and memory retrieval.

The relationship between inflammation and executive function is particularly relevant. In a large cohort study, higher CRP concentrations and depression were independently associated with poorer executive performance, while individuals presenting both depression and increased inflammatory activity showed additional cognitive impairment [12]. These observations suggest that inflammatory burden may act as an aggravating factor in cognitive dysfunction rather than merely reflecting depression severity.

Immunometabolic Dysregulation

The concept of immunometabolic depression proposes that immune and metabolic disturbances constitute an interconnected biological phenotype within MDD [5]. Patients with this profile may present increased inflammatory biomarkers together with obesity, dyslipidemia, insulin resistance, abnormal glucose regulation, or metabolic syndrome.

Adipose tissue plays an important role in this process because it acts as an endocrine and immunologically active organ. In visceral obesity, hypertrophic adipocytes and infiltrating immune cells release inflammatory mediators such as IL-6 and TNF-α. These mediators may contribute to systemic insulin resistance, endothelial dysfunction, oxidative stress, and altered central nervous system signaling.

Insulin resistance is also relevant to cognitive function because insulin participates in neuronal survival, synaptic plasticity, learning, and memory. Impaired insulin signaling may therefore affect cerebral energy metabolism and neuronal communication. When metabolic dysfunction occurs together with chronic inflammation, their combined effects may increase cognitive vulnerability.

Clinical evidence supports this interaction. Sánchez-Carro et al. reported that immunometabolic abnormalities were related to cognitive performance in patients with MDD, suggesting that the combination of inflammatory, oxidative, and metabolic disturbances may be more informative than any single biomarker considered independently [13]. This supports a multidimensional model in which cognitive dysfunction emerges from interacting systemic mechanisms.

Oxidative Stress and Mitochondrial Dysfunction

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Inflammatory activation is closely connected with oxidative stress. Pro-inflammatory processes can increase the production of reactive oxygen species, whereas prolonged oxidative stress can further stimulate inflammatory signaling. When antioxidant defenses are insufficient, this imbalance may damage lipids, proteins, mitochondrial components, and nucleic acids.

The brain is particularly susceptible to oxidative damage because of its high oxygen consumption, abundant lipid content, and metabolic demands. Mitochondrial dysfunction may reduce cellular energy production and impair neuronal resilience, potentially affecting cognitive domains that require sustained neural activity, such as working memory and executive control.

In depression, inflammatory and oxidative mechanisms may therefore operate simultaneously. Increased oxidative damage can interfere with neuroplasticity, while mitochondrial dysfunction can compromise the capacity of neurons to respond to metabolic demands. The coexistence of inflammation, metabolic syndrome, and oxidative stress may consequently produce a cumulative effect on cognitive performance [13].

Kynurenine Pathway and Neuroactive Metabolites

One of the most important biochemical mechanisms linking inflammation with brain function involves the metabolism of tryptophan through the kynurenine pathway. Inflammatory cytokines can increase the activity of enzymes involved in this pathway, including indoleamine 2,3-dioxygenase, thereby modifying the production of several neuroactive metabolites [15], [16].

Kynurenine can be metabolized into compounds with markedly different biological effects. Quinolinic acid may promote N-methyl-D-aspartate receptor activation and contribute to excitotoxic and oxidative mechanisms, whereas kynurenic acid modulates glutamatergic and cholinergic signaling differently. Alterations in the balance between these metabolites may influence mood regulation, cognition, neuroplasticity, and neuronal survival [15].

Systematic reviews and meta-analytic findings suggest that immune activation is associated with changes in kynurenine metabolism in depression [16]. This pathway therefore provides a plausible biological mechanism through which peripheral inflammation may influence cognitive function. However, interpretation remains complex because peripheral biomarker concentrations do not necessarily correspond directly to central nervous system concentrations, and several metabolic and physiological factors influence pathway activity.

Dopaminergic Dysfunction, Motivation, and Cognitive Effort

Inflammatory signaling may also alter dopaminergic neurotransmission, particularly within corticostriatal circuits. Dopamine is essential not only for reward and motivation but also for working memory, cognitive flexibility, effort allocation, and goal-directed behavior. Experimental and clinical evidence indicates that inflammatory activation may reduce dopamine synthesis, release, or availability in relevant neural circuits [17].

This mechanism is especially important in depression because symptoms such as anhedonia, reduced motivation, psychomotor slowing, and cognitive fatigue frequently coexist. Cognitive impairment in this context may therefore reflect not only an inability to perform a task but also an increased biological cost associated with sustained cognitive effort.

Inflammation-related dopaminergic dysfunction may help explain why some patients report marked difficulties initiating tasks, maintaining attention, or sustaining mental effort even when global intellectual abilities remain preserved. These symptoms are clinically significant because they can persist after improvement of sadness or anxiety and may delay functional recovery.

Cognitive Domains Affected

Cognitive dysfunction in depression is heterogeneous. Commonly affected domains include executive function, sustained attention, working memory, verbal learning, episodic memory, and processing speed. The severity of these impairments varies among patients and may depend on age, number of depressive episodes, disease severity, medication exposure, sleep quality, medical comorbidities, and cardiometabolic risk.

Inflammation may influence some cognitive domains more strongly than others. Executive dysfunction has received particular attention because prefrontal and frontostriatal networks appear sensitive to immune-mediated alterations in dopamine and energy metabolism [12], [17]. Memory may also be affected through inflammatory effects on hippocampal plasticity and neurogenesis.

Importantly, cognitive impairment may persist even when mood symptoms improve. This dissociation suggests that cognitive recovery should be assessed independently rather than assumed to occur automatically after symptomatic remission. Persistent cognitive dysfunction may affect academic performance, employment, social relationships, medical decision-making, and adherence to treatment.

Clinical Relevance of Inflammatory Biomarkers

The potential clinical application of inflammatory biomarkers is an area of growing interest. CRP is attractive because it is inexpensive and widely available, while cytokines such as IL-6 and TNF-α may provide additional biological

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information. Nevertheless, these markers are nonspecific and can be influenced by infection, obesity, smoking, autoimmune disorders, cardiovascular disease, medication use, and other medical conditions.

For this reason, inflammatory biomarkers should not be interpreted as diagnostic tests for depression or cognitive dysfunction. Their potential value lies instead in identifying biological subgroups and complementing psychiatric, cognitive, and metabolic assessment.

A clinically useful model would therefore combine inflammatory biomarkers with measures such as body mass index, waist circumference, glucose regulation, lipid profile, blood pressure, medical comorbidity, depressive symptom severity, and standardized cognitive assessment. This multidimensional approach is consistent with the immunometabolic model and may help distinguish patients whose cognitive symptoms are associated with a broader inflammatory-metabolic burden [5], [13].

Therapeutic Implications

The relationship between inflammation and depression has also generated interest in anti-inflammatory interventions. Meta-analyses of clinical trials suggest that anti-inflammatory strategies may reduce depressive symptoms in selected populations, although the magnitude of benefit varies according to study design, therapeutic agent, baseline inflammatory status, and patient characteristics [18].

These findings support the possibility that inflammatory biomarkers may eventually contribute to treatment stratification. However, the evidence does not indicate that anti-inflammatory therapy should be applied uniformly to all patients with depression. Instead, biological selection may be essential because patients with higher inflammatory burden could differ in treatment response from those without evidence of systemic inflammation.

The same reasoning applies to cognitive symptoms. If cognitive impairment is partly associated with inflammation, metabolic dysfunction, oxidative stress, or altered kynurenine metabolism, interventions targeting these pathways may have relevance beyond mood improvement. Nevertheless, additional longitudinal and interventional studies are required to determine whether reducing inflammatory activity directly improves cognition.

Integration of Neuroscience, Psychiatry, and Internal Medicine

The study of low-grade inflammation in depression requires an interdisciplinary approach. Neuroscience contributes knowledge regarding neuroimmune communication, neurotransmission, brain circuits, and cognitive processes. Psychiatry provides the clinical framework for characterizing depressive symptoms, cognitive impairment, disease course, and treatment response. Internal medicine contributes assessment of obesity, insulin resistance, cardiovascular risk, metabolic syndrome, endocrine disturbances, systemic inflammation, and other comorbidities capable of modifying the biological profile.

Integrating these perspectives prevents an overly reductionist interpretation of depression. Inflammation should neither be considered the sole cause of depressive illness nor dismissed as a secondary laboratory finding. Rather, it represents one component of a complex biological network whose relevance likely varies among individuals.

Current evidence supports a model in which systemic low-grade inflammation, metabolic dysregulation, oxidative stress, altered kynurenine metabolism, and neurotransmitter dysfunction can converge on neural systems responsible for mood and cognition [1], [5], [12], [13], [15]–[17]. The identification of these interactions is relevant because cognitive impairment frequently determines long-term functional outcome independently of emotional symptoms.

Consequently, the analysis of immunometabolic mechanisms may contribute to a more precise understanding of cognitive deterioration in depression. Future clinical models should move beyond isolated biomarkers and incorporate integrated biological, cognitive, psychiatric, and medical variables capable of identifying reproducible phenotypes. Such an approach could improve the characterization of patients at greater risk of persistent cognitive dysfunction and provide a stronger foundation for individualized therapeutic strategies.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

General Objective

To **analyze and integrate** the relationship between chronic low-grade inflammation, immunometabolic dysregulation, and cognitive impairment in individuals with major depressive disorder, identifying the principal neuroimmune, metabolic, and neurochemical mechanisms involved, as well as their potential clinical implications for assessment, stratification, and therapeutic decision-making.

Specific Objectives

Cognitive Domain

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1. To **identify** the principal inflammatory biomarkers associated with major depressive disorder, including C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and other relevant mediators, and to describe their relationship with cognitive performance.
2. To **explain** the neurobiological mechanisms through which peripheral inflammatory activity may affect the central nervous system, including neuroimmune communication, microglial activation, oxidative stress, neurotransmitter alterations, and changes in synaptic plasticity.
3. To **analyze** the association between low-grade inflammation and alterations in specific cognitive domains, particularly executive function, attention, working memory, processing speed, and episodic memory.
4. To **differentiate** the contribution of isolated inflammatory activation from that of combined immunometabolic dysregulation, considering obesity, insulin resistance, metabolic syndrome, and other systemic factors capable of modifying cognitive performance.
5. To **evaluate** the role of the tryptophan–kynurenine pathway and inflammatory alterations in dopaminergic neurotransmission as possible biological links between depression, anhedonia, psychomotor slowing, and cognitive dysfunction.
6. To **integrate** evidence from neuroscience, psychiatry, and internal medicine in order to construct a multidimensional interpretation of cognitive impairment associated with depression.

Psychomotor Domain

7. To **apply** a structured framework for the interpretation of inflammatory, metabolic, psychiatric, and cognitive variables in patients with depression, allowing systematic identification of clinically relevant immunometabolic patterns.
8. To **organize and compare** clinical and laboratory information through reproducible analytical procedures that combine inflammatory biomarkers, cardiometabolic indicators, depressive symptom assessment, and cognitive measures.
9. To **construct** an integrative model linking systemic inflammation, metabolic abnormalities, neurobiological mechanisms, and cognitive manifestations, facilitating the visualization and interpretation of interactions among the principal variables studied.
10. To **demonstrate** the practical use of multidimensional assessment strategies for distinguishing cognitive impairment potentially associated with an inflammatory-metabolic phenotype from cognitive symptoms influenced predominantly by other psychiatric or medical factors.

Affective Domain

11. To **recognize** the clinical relevance of persistent cognitive dysfunction in depression as a determinant of functional recovery, quality of life, treatment adherence, and social or occupational performance.
12. To **value** the importance of interdisciplinary collaboration among neuroscience, psychiatry, and internal medicine when interpreting inflammatory and cognitive alterations in patients with depressive disorders.
13. To **promote** a critical and evidence-based approach to the use of inflammatory biomarkers, avoiding their interpretation as isolated diagnostic indicators and emphasizing the need to evaluate them within the complete clinical context.
14. To **support** a personalized approach to depression by considering biological heterogeneity and the possibility that inflammatory and immunometabolic characteristics may define clinically meaningful patient subgroups.
15. To **appraise** the potential clinical relevance of identifying patients with elevated inflammatory and metabolic burden for future precision-medicine strategies aimed at improving both affective and cognitive outcomes.

OBJECT OF STUDY

The object of study is the relationship between **chronic low-grade systemic inflammation, immunometabolic dysregulation, and cognitive impairment in individuals with major depressive disorder**. The analysis focuses on how persistent inflammatory activity and associated metabolic alterations may influence cognitive domains such as executive function, attention, working memory, processing speed, and episodic memory.

The central phenomenon under investigation is the presence of an **inflammatory-immunometabolic phenotype** within depression. This phenotype is characterized by the interaction of systemic inflammatory markers, metabolic disturbances, oxidative stress, altered tryptophan–kynurenine metabolism, and changes in neurotransmitter systems involved in cognition and motivation. Particular emphasis is placed on biomarkers such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha, together with metabolic variables including obesity, insulin resistance, dyslipidemia, and metabolic syndrome.

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The population of interest comprises **adults with major depressive disorder**, particularly those presenting cognitive complaints or measurable impairment in one or more cognitive domains. Because cognitive dysfunction in depression is multifactorial, the object of study also includes the influence of relevant clinical variables such as depressive symptom severity, age, medical comorbidity, sleep disturbances, medication exposure, cardiovascular risk factors, and metabolic status.

From a neuroscientific perspective, the study examines the biological pathways through which peripheral inflammation may affect the central nervous system, including neuroimmune signaling, microglial activation, oxidative stress, alterations in dopaminergic neurotransmission, and dysregulation of the kynurenine pathway. From a psychiatric perspective, the analysis focuses on the association between these mechanisms and depressive symptoms, anhedonia, psychomotor slowing, cognitive fatigue, and persistent cognitive dysfunction. From the perspective of internal medicine, attention is directed toward systemic and metabolic conditions capable of sustaining inflammatory activity and modifying neurological or psychiatric outcomes.

Therefore, the object of study is not limited to the isolated measurement of inflammatory biomarkers. Instead, it is defined as a **multidimensional clinical-biological system** in which immune activity, metabolic status, depressive symptomatology, and cognitive performance interact. This approach allows the study to evaluate whether particular combinations of inflammatory and metabolic abnormalities are associated with a greater burden of cognitive dysfunction and whether these patterns may have potential value for clinical stratification.

The unit of analysis is the individual patient with depression evaluated through the integration of biological, metabolic, psychiatric, and cognitive variables. The main analytical relationship is established between the degree of inflammatory and immunometabolic burden and the presence or severity of cognitive impairment. This structure is intended to provide a coherent basis for subsequent methodological evaluation and for the identification of clinically meaningful patterns that may contribute to a more precise understanding of cognitive deterioration in depression.

METHODOLOGY

This study was designed as an **integrative analytical review based on the Scientific Method**, aimed at examining the relationship between chronic low-grade inflammation, immunometabolic dysregulation, and cognitive impairment in major depressive disorder. The methodological approach was selected because the research question requires the integration of evidence from neuroscience, psychiatry, immunology, metabolism, and internal medicine rather than the evaluation of a single isolated biological variable.

The Scientific Method was structured through the sequential stages of observation, problem definition, formulation of research questions and hypotheses, systematic evidence collection, comparative analysis, interpretation, and synthesis of conclusions. This framework allowed the available evidence to be examined according to predefined biological and clinical variables and provided a reproducible structure for identifying associations among inflammation, metabolic abnormalities, depressive symptoms, and cognitive performance.

Study Design

An **integrative literature review with qualitative and comparative analysis** was used. The review included original clinical studies, observational investigations, cohort studies, systematic reviews, meta-analyses, and relevant translational research examining inflammatory mechanisms, immunometabolic alterations, cognitive dysfunction, or their interaction in patients with depression.

The analytical model incorporated evidence from three complementary fields: neuroscience, to evaluate mechanisms affecting neural circuits and cognitive processes; psychiatry, to characterize depressive symptoms and cognitive manifestations; and internal medicine, to assess metabolic and systemic conditions associated with chronic inflammation.

Information Sources

Scientific literature was identified through biomedical and multidisciplinary databases, including **PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar**. Searches were conducted using combinations of controlled vocabulary and free-text terms related to:

“major depressive disorder,” “depression,” “low-grade inflammation,” “C-reactive protein,” “interleukin-6,” “tumor necrosis factor-alpha,” “cognitive impairment,” “executive function,” “memory,” “immunometabolic depression,” “metabolic syndrome,” “insulin resistance,” “kynurenine pathway,” “oxidative stress,” and “neuroinflammation.”

Boolean operators **AND** and **OR** were used to combine concepts and broaden or restrict the search according to the specific analytical category.

A representative search structure was:

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(depression OR major depressive disorder) AND (inflammation OR C-reactive protein OR IL-6 OR TNF-α) AND (cognition OR cognitive impairment OR executive function OR memory) AND (metabolic syndrome OR insulin resistance OR immunometabolic).

Eligibility Criteria

Studies were considered eligible when they evaluated adult populations with major depressive disorder or clinically significant depressive symptoms and included at least one inflammatory, metabolic, neurobiological, or cognitive variable directly related to the research question.

Priority was given to peer-reviewed studies that:

- assessed systemic inflammatory biomarkers such as CRP, IL-6, or TNF-α;
- evaluated cognitive domains including executive function, attention, memory, working memory, or processing speed;
- examined metabolic variables such as obesity, insulin resistance, dyslipidemia, or metabolic syndrome;
- analyzed mechanisms involving oxidative stress, dopaminergic signaling, or the kynurenine pathway;
- or evaluated therapeutic implications associated with inflammatory status.

Studies focused exclusively on acute infectious inflammation, severe neurological disorders unrelated to depression, isolated inflammatory diseases without psychiatric evaluation, or populations in which cognitive outcomes could not be differentiated from primary neurological pathology were excluded from the central analysis.

Variables of Interest

The main independent variables included systemic inflammatory markers and indicators of metabolic dysfunction. The principal inflammatory variables were **CRP, IL-6, TNF-α, and related pro-inflammatory mediators**. Metabolic variables included body mass index, obesity, insulin resistance, glucose dysregulation, lipid abnormalities, and metabolic syndrome.

The primary dependent variable was **cognitive performance**, analyzed through domains such as executive function, attention, working memory, episodic memory, verbal learning, and processing speed.

Additional variables considered as potential modifiers or confounders included age, sex, severity of depression, medication use, smoking, physical activity, sleep disturbances, cardiovascular risk factors, and chronic medical comorbidity.

Evidence Extraction and Organization

Relevant information from each study was organized according to five analytical dimensions:

1. inflammatory profile;
2. metabolic status;
3. cognitive domain evaluated;
4. proposed neurobiological mechanism;
5. clinical implication.

The extracted evidence was compared to identify recurrent patterns and discrepancies among studies. Particular attention was directed toward whether cognitive impairment was associated with isolated inflammatory activation or with the coexistence of inflammatory and metabolic abnormalities.

Analytical Strategy

The analysis followed a **comparative and mechanistic approach**. Evidence was first grouped according to the biological pathway involved and then compared with the cognitive outcomes reported.

Inflammatory biomarkers were analyzed in relation to executive dysfunction, memory alterations, attention deficits, and processing-speed impairment. Metabolic abnormalities were subsequently examined as possible amplifiers of inflammatory effects. Mechanistic evidence involving the kynurenine pathway, oxidative stress, microglial activation, and dopaminergic dysfunction was integrated to explain the biological plausibility of the clinical associations [1], [4], [15]–[17].

Special attention was given to studies reporting interactions between inflammatory and metabolic factors because these findings are particularly relevant to the immunometabolic model of depression [5], [13].

Quality and Interpretation of Evidence

Evidence was interpreted according to study design, sample characteristics, type of biomarker, cognitive assessment method, control of confounding variables, and consistency with findings from other investigations.

Systematic reviews, meta-analyses, and large cohort studies were given greater interpretative weight when evaluating the consistency of associations, while mechanistic and smaller clinical studies were primarily used to explain biological pathways.

Because inflammatory biomarkers are nonspecific, their interpretation was not considered independently from metabolic and clinical variables. This criterion reduced the risk of attributing inflammatory changes exclusively to

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depression when they could also be explained by obesity, cardiovascular disease, infection, medication exposure, or other medical conditions.

Reproducibility

To facilitate replication, the methodology establishes clearly defined search concepts, eligibility criteria, biological variables, cognitive outcomes, analytical categories, and interpretation criteria. A researcher applying the same search strategy and classification system should be able to reproduce the evidence-selection process and organize the findings according to the same inflammatory, metabolic, neurobiological, and cognitive dimensions.

This methodological structure provides the basis for evaluating the principal hypothesis of the study: that **greater inflammatory and immunometabolic burden is associated with more pronounced cognitive dysfunction in depression**, particularly in executive function, attention, memory, and processing speed, and that the interaction between inflammatory and metabolic disturbances may provide more clinically relevant information than the analysis of individual biomarkers alone.

PHASES OF DEVELOPMENT

Phase 1. Observation and Identification of the Problem

The first phase consisted of identifying a recurrent clinical phenomenon: a subgroup of patients with major depressive disorder presents persistent cognitive difficulties despite improvement in affective symptoms. These alterations commonly involve executive function, attention, memory, processing speed, motivation, and mental effort.

At the same time, previous investigations have demonstrated that a proportion of patients with depression exhibit increased inflammatory markers and metabolic abnormalities [5]–[7]. This convergence led to the initial observation that cognitive dysfunction may be associated not only with psychiatric symptom severity but also with systemic biological processes involving chronic inflammation and metabolic dysregulation.

The main problem was therefore defined as the insufficient understanding of how low-grade systemic inflammation and immunometabolic abnormalities interact with cognitive function in major depressive disorder.

Phase 2. Formulation of the Research Question and Hypothesis

Based on the identified problem, the principal research question was formulated:

How are chronic low-grade inflammation and immunometabolic dysregulation associated with cognitive impairment in adults with major depressive disorder?

Secondary questions examined which inflammatory and metabolic markers are most consistently related to cognitive dysfunction, which cognitive domains are most affected, and which neurobiological mechanisms may explain these associations.

The principal hypothesis proposed that individuals with a greater inflammatory and metabolic burden would present more pronounced cognitive dysfunction, particularly in executive functioning, attention, memory, and processing speed. It was also hypothesized that the coexistence of metabolic abnormalities could intensify the relationship between systemic inflammation and cognitive impairment [12], [13].

Phase 3. Collection and Selection of Scientific Evidence

The third phase involved identifying relevant scientific evidence through biomedical and multidisciplinary databases. Search concepts included major depressive disorder, systemic inflammation, CRP, IL-6, TNF-α, cognitive impairment, executive function, memory, metabolic syndrome, insulin resistance, oxidative stress, neuroinflammation, and the kynurenine pathway.

Studies were selected according to predefined eligibility criteria, prioritizing peer-reviewed clinical studies, cohort investigations, systematic reviews, meta-analyses, and translational research directly related to the central research question.

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During this phase, evidence was classified according to its contribution to one or more of the principal analytical dimensions: inflammatory activity, metabolic dysfunction, cognitive performance, neurobiological mechanisms, and clinical implications.

Phase 4. Organization and Comparative Analysis of the Evidence

The selected evidence was subsequently organized into thematic categories to facilitate systematic comparison. Inflammatory biomarkers such as CRP, IL-6, and TNF-α were analyzed in relation to cognitive outcomes, while metabolic variables including obesity, insulin resistance, dyslipidemia, and metabolic syndrome were evaluated as potential modifying factors.

Cognitive results were grouped according to specific domains, including executive function, attention, working memory, episodic memory, verbal learning, and processing speed.

Studies were then compared to identify recurrent associations, contradictory findings, methodological differences, and potential sources of heterogeneity. Greater interpretative weight was assigned to findings reproduced across multiple studies or supported by systematic reviews and meta-analyses.

Phase 5. Mechanistic Integration

The fifth phase focused on integrating clinical findings with biological mechanisms capable of explaining the observed relationships.

Evidence involving peripheral-to-central immune communication, microglial activation, oxidative stress, mitochondrial dysfunction, altered dopaminergic neurotransmission, and dysregulation of the tryptophan–kynurenine pathway was examined as part of an interconnected neuroimmune model [1], [4], [15]–[17].

This phase was essential to determine whether the associations identified in clinical populations were biologically plausible. Instead of interpreting inflammatory markers as isolated laboratory findings, they were incorporated into a broader model in which immune activation, metabolic abnormalities, neurotransmitter alterations, and cognitive dysfunction may influence one another.

Phase 6. Evaluation of Confounding and Modifying Factors

Because both inflammation and cognition are influenced by numerous clinical variables, potential confounding factors were systematically considered. These included age, sex, obesity, cardiovascular disease, smoking, physical activity, sleep disturbances, medication exposure, depressive symptom severity, and other chronic medical conditions.

This phase was particularly important for avoiding direct attribution of elevated inflammatory biomarkers to depression when other systemic conditions could explain their presence.

Metabolic factors were also evaluated as possible effect modifiers rather than simple confounders, because evidence suggests that inflammation and metabolic dysregulation may act synergistically in some patients [5], [13].

Phase 7. Synthesis and Interpretation of Findings

After completing the comparative and mechanistic analysis, the evidence was synthesized to establish the principal patterns emerging from the literature.

The synthesis focused on determining whether low-grade inflammation was consistently associated with cognitive dysfunction, which mechanisms were most biologically plausible, and whether the association appeared stronger in patients presenting an immunometabolic phenotype.

The findings were interpreted using an interdisciplinary framework. Neuroscientific evidence was used to explain brain mechanisms, psychiatric evidence to characterize depressive and cognitive manifestations, and internal-medicine evidence to identify systemic and metabolic contributors.

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This approach allowed the study to move beyond a single-biomarker interpretation toward a multidimensional model of depression-related cognitive impairment.

Phase 8. Clinical Integration and Final Interpretation

The final phase translated the analytical findings into clinically relevant considerations. The principal objective was not to establish inflammatory biomarkers as standalone diagnostic tools, but to determine how inflammatory and metabolic information might complement psychiatric and cognitive assessment.

The resulting model proposes that evaluation of cognitive dysfunction in depression may benefit from considering systemic inflammation, cardiometabolic status, and neurobiological mechanisms simultaneously.

This final integration provides the foundation for evaluating whether immunometabolic profiles may eventually contribute to patient stratification, risk assessment, monitoring of persistent cognitive symptoms, and the development of more individualized therapeutic strategies.

RESULTS AND DISCUSSION

Figure 1.
Prevalence of low-grade inflammation in major depressive disorder.

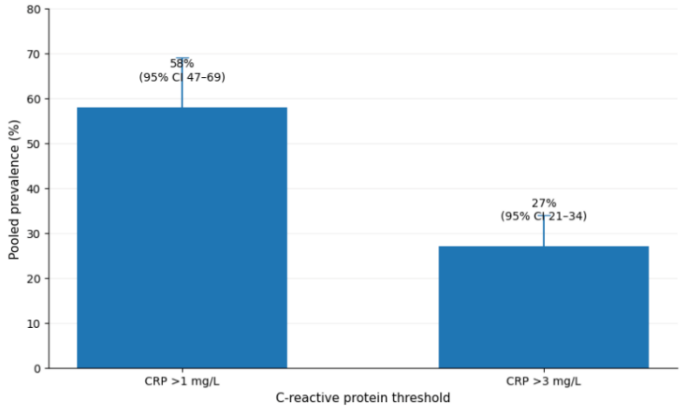


Figure 1 summarizes the pooled prevalence of elevated C-reactive protein (CRP) among individuals with depression according to two commonly reported inflammatory thresholds. The data show that **58% of patients with depression presented CRP concentrations above 1 mg/L**, with a 95% confidence interval (CI) of 47–69%, whereas **27% presented CRP concentrations above 3 mg/L**, with a 95% CI of 21–34% [6]. These estimates were obtained from a systematic review and meta-analysis specifically designed to quantify the prevalence of peripheral low-grade inflammation in depressive disorders.

For the **CRP >1 mg/L threshold**, the pooled analysis included 25 studies and 8,887 individuals with depression. The resulting prevalence of 58% indicates that mildly elevated systemic inflammatory activity was identified in more than half of the analyzed depressed population [6]. The confidence interval extending from 47% to 69% reflects considerable variability among the included studies. Statistical heterogeneity was also high, with an I^2 value of approximately 98.7%, indicating substantial differences across study populations, clinical characteristics, analytical methods, and inflammatory profiles [6].

When the more restrictive threshold of **CRP >3 mg/L** was applied, the pooled prevalence decreased to 27%. This analysis included 30 studies comprising 11,813 patients with depression, with the estimated prevalence ranging from 21% to 34% within the 95% confidence interval [6]. Therefore, approximately one in four individuals with depression met this higher inflammatory threshold. The corresponding heterogeneity remained substantial, with an I^2 value of 97.7%, confirming that the magnitude of inflammatory activation varied markedly between the populations included in the meta-analysis [6].

The difference between the two bars should be interpreted according to the CRP thresholds used rather than as two independent patient groups. Individuals with CRP values above 3 mg/L are also included within the broader category of CRP values above 1 mg/L. Consequently, these percentages are **overlapping prevalence estimates based on different cut-off points**, not mutually exclusive categories. The 58% estimate represents a broader definition of elevated CRP, whereas the 27% estimate corresponds to a more restrictive definition of low-grade inflammation [6].

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Additional analyses from the same meta-analysis showed relatively similar prevalence estimates according to clinical setting. For CRP concentrations above 3 mg/L, pooled prevalence was approximately **30% in inpatient samples, 29% in outpatient samples, and 24% in population-based samples** [6]. For the CRP >1 mg/L threshold, corresponding estimates were approximately **56%, 59%, and 57%**, respectively [6]. These data indicate that elevated CRP was observed across different types of depressive populations rather than being restricted to a single clinical setting.

Sensitivity analyses also provided additional information regarding possible acute inflammatory states. When individuals with CRP concentrations above 10 mg/L, considered suggestive of an acute inflammatory or infectious process in the analyzed methodology, were excluded, the prevalence of CRP >3 mg/L was **16% (95% CI 8–32%)** among 6,948 patients. Under the same exclusion criterion, the prevalence of CRP >1 mg/L was **50% (95% CI 29–72%)** among 4,456 individuals [6]. These estimates were not included as separate bars in Figure 1 because they correspond to sensitivity analyses using different study subsets and are therefore not directly equivalent to the principal pooled estimates.

Comparison with matched non-depressed controls further demonstrated differences in the frequency of elevated inflammatory markers. Across 17 studies including 7,761 depressed patients and 155,728 matched controls, the meta-analytic odds ratio for CRP >3 mg/L was **1.46 (95% CI 1.22–1.75)**. For CRP >1 mg/L, the corresponding odds ratio was **1.47 (95% CI 1.18–1.82)** [6]. These comparative results indicate that elevated CRP occurred more frequently among individuals with depression in the analyzed studies, although the magnitude of this association varied between populations.

Figure 2.
Relationship between inflammatory activity and cognitive domains in depression.

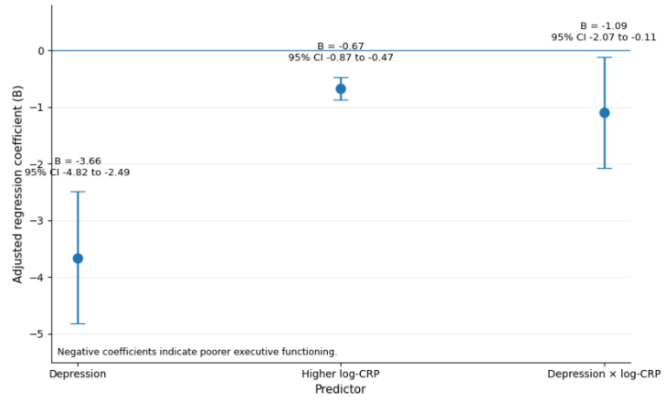


Figure 2 presents the adjusted regression coefficients describing the association of depression, circulating C-reactive protein (CRP), and the interaction between depression and CRP with executive functioning. The data were derived from a population-representative analysis of **43,896 adults** from the Lifelines cohort, with a mean age of 44.13 years (SD = 13.52) [12]. Executive functioning was evaluated behaviorally, while inflammatory status was quantified using high-sensitivity CRP measured after an overnight fast. Multivariable models controlled for age, sex, educational attainment, body mass index, smoking status, exposure to stressful life events and chronic stressors, sedentary behavior, and number of chronic medical conditions [12].

The first estimate shows the independent association between **depression and executive functioning**. Depression was associated with a regression coefficient of **B = −3.66**, with a 95% confidence interval of **−4.82 to −2.49** and a reported *p* value < .001 [12]. The negative direction indicates poorer executive performance among participants with depression after adjustment for the clinical, behavioral, and demographic variables included in the model. Importantly, the confidence interval remained entirely below zero, supporting a statistically detectable association between depression status and reduced executive functioning within this population [12].

The second estimate corresponds to the independent association between **higher log-transformed CRP and executive functioning**. Higher CRP was associated with poorer executive performance, with **B = −0.67** and a 95% confidence interval of **−0.87 to −0.47** (*p* < .001) [12]. Although the magnitude of this coefficient was smaller than that observed for depression status, its direction was consistent with the hypothesis that systemic inflammatory activity is related to cognitive performance. The persistence of the association after adjustment for body mass index, smoking, sedentary behavior, chronic disease burden, and other covariates is particularly relevant because each of these factors can independently influence both CRP concentrations and cognition [12].

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The third estimate represents the **interaction between depression and CRP**. Participants with depression and higher log-transformed CRP demonstrated additional impairment in executive functioning, reflected by an interaction coefficient of **B = −1.09**, with a 95% confidence interval of **−2.07 to −0.11** [12]. This result indicates that the coexistence of depression and greater inflammatory activity was associated with poorer executive performance beyond the independent associations of depression and CRP considered separately. In other words, the inflammatory signal was not merely parallel to the psychiatric condition; the statistical interaction suggests that inflammatory activity modified the relationship between depression and executive functioning within the analyzed sample [12].

Additional analyses from the same study further illustrate this pattern. When the difference in executive functioning between depressed and non-depressed participants was examined at progressively higher CRP levels, the magnitude of the difference increased. At approximately one standard deviation below the mean CRP level, the estimated difference was **−2.11**; at the mean CRP level, it was **−3.45**; at one standard deviation above the mean, it increased to **−4.79**; and at two standard deviations above the mean, it reached **−6.14** [12]. These values describe a progressive pattern in which the executive-function disadvantage associated with depression became larger at higher levels of inflammatory activity.

The age analysis did not provide evidence that this relationship was restricted to older adults. The interaction involving age produced a coefficient of **B = 0.01**, with a 95% confidence interval of **−0.08 to 0.10** and $p = .82$ [12]. Thus, within this dataset, the association between higher CRP and poorer executive functioning among individuals with depression did not significantly vary across the adult age range studied. This observation is relevant because it indicates that the inflammatory-cognitive relationship identified in the analysis was not explained solely by age-related cognitive decline [12].

The figure should also be interpreted according to the scale of the reported coefficients. The values shown are **unstandardized regression coefficients (B)** and therefore represent associations within the specific executive-function measure and statistical model used in the Lifelines study. Consequently, the numerical magnitude of the depression, CRP, and interaction coefficients should not be interpreted as standardized effect sizes or directly compared with coefficients obtained using different cognitive instruments. The authors themselves characterized the magnitude of the associations as modest despite their statistical significance [12].

Nevertheless, the large sample size and extensive covariate adjustment strengthen the relevance of the observed pattern. The persistence of an association between CRP and executive functioning after accounting for body mass index and chronic medical conditions is especially important for an immunometabolic interpretation, because obesity and systemic disease are major determinants of circulating inflammatory activity. The findings therefore indicate that the relationship between inflammatory burden and executive performance cannot be attributed exclusively to these measured covariates within the statistical model [12].

At the same time, the cross-sectional design limits causal interpretation. Figure 2 demonstrates statistical associations but does not establish that elevated CRP directly causes cognitive dysfunction, nor does it determine whether depressive illness promotes inflammatory activity that subsequently influences cognition. Reverse or bidirectional relationships remain possible. This limitation is relevant when integrating the present finding with the broader literature on neuroimmune signaling, metabolic dysfunction, and depression.

The adult data are also complemented by evidence from younger populations. In a separate population-based study of Dutch adolescents, higher CRP was associated with poorer future executive functioning; however, this association was attenuated after controlling for socioeconomic status, body mass index, and sedentary behavior [12]. That result emphasizes the importance of metabolic and behavioral variables when interpreting inflammatory-cognitive relationships and supports the multidimensional analytical framework adopted in the present study.

Figure 3.
Interaction between inflammation and immunometabolic abnormalities.

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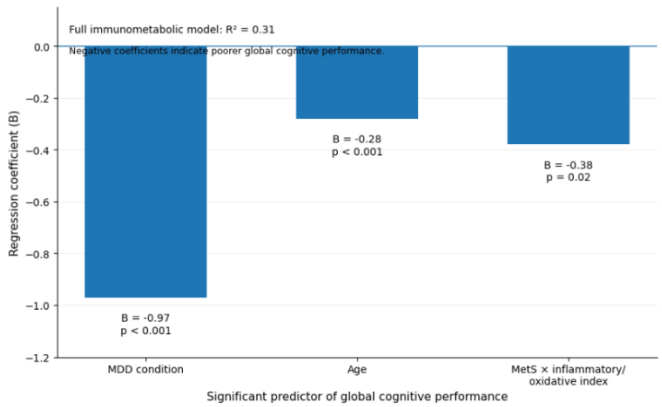


Figure 3 summarizes the significant predictors of global cognitive performance identified in the immunometabolic regression model reported by Sánchez-Carro et al. [13]. The study included **162 participants**, comprising **84 patients with major depressive disorder (MDD) and 78 healthy controls**, and evaluated cognitive performance using the Cambridge Neuropsychological Test Automated Battery (CANTAB). The biological assessment incorporated the presence of metabolic syndrome (MetS) and an inflammatory/oxidative index derived through principal component analysis from tumor necrosis factor, C-reactive protein, and 4-hydroxynonenal concentrations [13].

Before examining the multivariable model, significant differences were identified between patients with MDD and healthy controls in both biological and cognitive measures. The inflammatory/oxidative index differed significantly between groups (**$F(1,157) = 12.93, p < .001$**), while the difference in cognitive performance was even more pronounced (**$F(1,157) = 56.75, p < .001$**) [13]. These findings establish that the MDD group differed from the healthy comparison group not only in cognitive functioning but also in the composite biological measure representing inflammatory and oxidative activity.

The complete immunometabolic regression model incorporated diagnostic condition, sex, age, medication load, metabolic syndrome, the inflammatory/oxidative index, and the interaction between metabolic syndrome and the inflammatory/oxidative index. The model was statistically significant (**$F(7,157) = 11.24, p < .01$**) and accounted for approximately **31% of the variance in global cognitive performance** [13]. Thus, nearly one third of the variability in cognitive performance within the analyzed sample was accounted for collectively by the clinical and immunometabolic variables included in the model.

The strongest negative regression coefficient among the statistically significant predictors corresponded to **MDD diagnostic condition ($B = -0.97, p < .001$)** [13]. The negative coefficient indicates that membership in the MDD group was associated with poorer global cognitive performance after the remaining variables in the model were considered. This finding is consistent with the broader evidence that cognitive abnormalities constitute an important component of major depressive disorder and may involve executive functioning, attention, memory, and processing efficiency.

Age was also independently associated with cognitive performance ($B = -0.28, p < .001$) [13]. The negative direction indicates poorer cognitive performance with increasing age within the statistical model. This variable is particularly important because age can affect multiple cognitive domains independently of depression and may also interact indirectly with metabolic and inflammatory burden. Its inclusion therefore helps distinguish the relationship between immunometabolic alterations and cognition from the expected influence of age on neurocognitive performance.

The most relevant result for the immunometabolic hypothesis was the significant interaction between **metabolic syndrome and the inflammatory/oxidative index**, which showed a regression coefficient of **$B = -0.38$ ($p = .02$)** [13]. This negative interaction indicates that the coexistence of metabolic dysregulation and greater inflammatory/oxidative activity was associated with poorer cognitive performance. Importantly, the interaction term—not merely the presence of either component in isolation—emerged as a significant predictor in the reported model.

This pattern quantitatively supports the concept that metabolic and inflammatory alterations may act jointly in relation to cognitive dysfunction. The inflammatory/oxidative index incorporated **TNF, CRP, and 4-hydroxynonenal**, thereby representing both inflammatory activation and oxidative damage. Metabolic syndrome, meanwhile, represents the clustering of cardiometabolic abnormalities. Their statistically significant interaction indicates that cognitive performance was particularly reduced when these biological dimensions coexisted [13].

An important feature of the results is that the study did not identify the inflammatory/oxidative index or metabolic syndrome alone among the principal statistically significant predictors reported in the final model. Instead, their **interaction** was associated with cognition. This distinction is relevant because it suggests that the relationship between

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systemic biology and cognitive performance may not be adequately represented by assessing a single inflammatory biomarker or a single metabolic diagnosis independently. The combined biological context provided more informative evidence within this analysis [13].

From a descriptive perspective, Figure 3 should not be interpreted by directly ranking the numerical magnitude of the three regression coefficients. Diagnostic condition, age, and the immunometabolic interaction represent variables measured on different scales; therefore, their raw B coefficients cannot be treated as directly comparable standardized effect sizes. The purpose of the figure is to display the **direction and statistical significance** of the predictors identified in the regression model rather than to establish which predictor has the greatest biological effect.

The finding that the full model explained **31% of cognitive variance** also indicates that a substantial proportion of cognitive heterogeneity remained unexplained. Approximately 69% of the variance was outside the explanatory capacity of the variables included in this particular model. This is compatible with the multifactorial nature of cognitive dysfunction in depression, in which educational background, sleep, disease duration, number of depressive episodes, psychiatric comorbidity, vascular factors, pharmacological exposure, genetic susceptibility, neuroplasticity, and other biological mechanisms may contribute to individual differences.

The interaction identified in Figure 3 is especially relevant when considered alongside the concept of **immunometabolic depression** described by Milaneschi et al. [5]. That framework proposes that inflammatory activation and metabolic dysfunction can converge within a subgroup of patients with depression, potentially generating a clinical phenotype characterized by disturbances in energy regulation and systemic metabolism. The data represented here extend this framework to cognitive performance by showing that the simultaneous presence of metabolic syndrome and increased inflammatory/oxidative activity was associated with poorer cognition.

The oxidative component is also relevant. The biological index incorporated 4-hydroxynonenal, a product of lipid peroxidation, together with CRP and TNF. Consequently, the observed interaction does not represent inflammation alone but rather a broader **inflammatory-oxidative state**. This distinction supports the consideration of oxidative stress as an additional component in the biological pathways potentially associated with cognitive dysfunction in depression [13].

The results additionally complement those presented in Figure 2. Figure 2 demonstrated that higher CRP interacted with depression in relation to executive functioning [12], whereas Figure 3 shows that inflammatory/oxidative alterations interacting with **metabolic syndrome** were associated with global cognitive performance [13]. Taken together, these independent datasets show that inflammatory activity can be examined not only in relation to psychiatric diagnosis but also within a wider cardiometabolic context.

However, the findings must be interpreted within the design of the study. Sánchez-Carro et al. explicitly identified the relatively modest sample size and the **cross-sectional design** as limitations [13]. Because the variables were evaluated at a single observational period, the analysis establishes association but cannot determine temporal direction. It therefore cannot demonstrate whether inflammatory and metabolic abnormalities preceded cognitive deterioration, resulted from behavioral or physiological consequences of depression, or developed through reciprocal interactions over time.

Despite these limitations, the results provide quantitative evidence that the combined evaluation of metabolic and inflammatory/oxidative status captures information relevant to cognition in major depressive disorder. The significant **MetS × inflammatory/oxidative interaction (B = −0.38, p = .02)** demonstrates that systemic metabolic abnormalities and inflammatory activity should not necessarily be analyzed as independent biological processes when investigating cognitive impairment.

Figure 4.

Principal biological pathways connecting inflammation with cognitive dysfunction.

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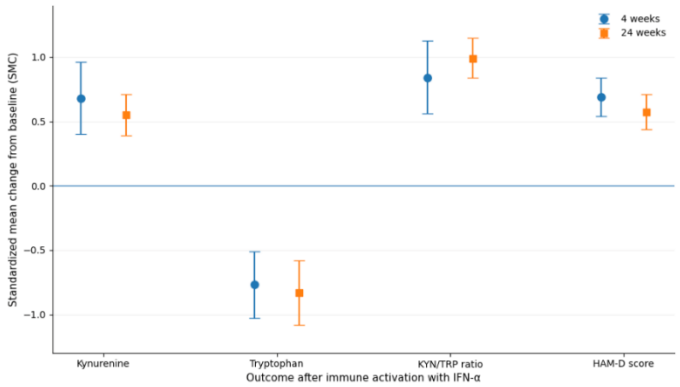


Figure 4 summarizes the pooled changes in kynurenine-pathway metabolites and depressive symptoms following sustained immune activation with interferon-alpha (IFN-α). The data are derived from the systematic review and meta-analysis by Hunt et al. [16], which identified 15 eligible studies and quantitatively analyzed 10 studies comprising **315 medically ill patients treated with IFN-α**. Changes from baseline were expressed as standardized mean change (SMC), with measurements analyzed at approximately 4 and 24 weeks after treatment initiation [16].

The first outcome, **kynurenine (KYN)**, showed a significant increase following immune activation. At 4 weeks, the pooled standardized mean change was **SMC = 0.68 (95% CI 0.40–0.96)**, while at 24 weeks the corresponding value was **SMC = 0.55 (95% CI 0.39–0.71)** [16]. Both confidence intervals remained entirely above zero, indicating a consistent increase in circulating kynurenine relative to baseline. The magnitude of the effect remained within a moderate range at both time points, demonstrating that immune stimulation produced a sustained alteration in tryptophan metabolism rather than a transient biochemical response.

In contrast, **tryptophan (TRP)** concentrations showed a marked decrease. The standardized mean change at 4 weeks was **−0.77 (95% CI −1.03 to −0.51)**, and at 24 weeks it was **−0.83 (95% CI −1.08 to −0.58)** [16]. These negative values indicate that tryptophan availability declined after inflammatory activation, with a similar magnitude at both assessment periods. The absence of overlap with zero in the corresponding confidence intervals supports the consistency of this reduction across the included studies.

The simultaneous increase in kynurenine and reduction in tryptophan is also reflected in the **kynurenine-to-tryptophan ratio (KYN/TRP)**. At 4 weeks, this ratio increased with an **SMC of 0.84 (95% CI 0.56–1.13)**, whereas at 24 weeks the increase reached **SMC = 0.99 (95% CI 0.84–1.15)** [16]. Among the biological variables displayed in Figure 4, the KYN/TRP ratio showed one of the largest standardized changes. The increase was also numerically greater at 24 weeks than at 4 weeks, indicating persistent activation of tryptophan catabolism during prolonged immune stimulation.

The fourth outcome represents changes in **Hamilton Depression Rating Scale (HAM-D) scores**. Depressive symptom scores increased with an **SMC of 0.69 (95% CI 0.54–0.84)** after 4 weeks and **0.57 (95% CI 0.44–0.71)** after 24 weeks [16]. Therefore, the period of experimentally or therapeutically induced immune activation was accompanied not only by metabolic changes within the kynurenine pathway but also by a measurable increase in depressive symptom burden.

The temporal pattern is particularly informative. Changes in KYN, TRP, KYN/TRP ratio, and HAM-D scores were already detectable at the 4-week assessment and remained present at 24 weeks. Kynurenine levels increased moderately at both time points, whereas tryptophan remained reduced. The KYN/TRP ratio increased further by the later assessment, while depressive symptom scores remained elevated relative to baseline. This parallel pattern provides quantitative evidence that sustained activation of the immune system is accompanied by persistent alterations in tryptophan metabolism and depressive symptomatology [16].

From a biochemical perspective, the KYN/TRP ratio is frequently used as an indirect indicator of increased tryptophan catabolism through the kynurenine pathway. Pro-inflammatory cytokines, particularly interferons, can influence enzymes involved in this pathway, including indoleamine 2,3-dioxygenase. Increased conversion of tryptophan to kynurenine can subsequently alter the availability of substrates for downstream metabolites with neuroactive properties [15], [16].

Kynurenine itself occupies a central position in this metabolic pathway because it can be metabolized through different branches. One branch generates **kynurenic acid**, which modulates glutamatergic signaling, while another produces metabolites including **3-hydroxykynurenine and quinolinic acid**. Quinolinic acid can interact with N-methyl-D-aspartate receptors and has been associated with glutamatergic and oxidative mechanisms, whereas kynurenic acid exhibits different, and in some contexts opposing, effects on excitatory neurotransmission [15]. Therefore, an increase

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in overall kynurenine availability does not by itself define the downstream neurobiological consequence; the balance among subsequent metabolites is also important.

The reduction in tryptophan shown in Figure 4 is likewise relevant because tryptophan is the precursor for multiple biologically active compounds, including serotonin. However, the results should not be simplified into a direct assumption that reduced peripheral tryptophan necessarily produces a proportional reduction in central serotonin. Transport across the blood-brain barrier, competition with other amino acids, albumin binding, enzyme activity, and downstream metabolic flux all modify the relationship between peripheral and central availability. The principal result demonstrated here is therefore a shift in systemic tryptophan metabolism under inflammatory stimulation rather than direct measurement of neurotransmitter concentrations [15], [16].

Another important aspect of Figure 4 is the parallel increase in depressive symptoms and kynurenine-pathway activation. Hunt et al. reported that IFN-α treatment was associated with both increased depression scores and alterations in KYN-related measures [16]. Nevertheless, the authors indicated that the available number of studies was insufficient to establish a formal quantitative association between the magnitude of metabolite changes and the magnitude of depressive symptoms. Consequently, the figure demonstrates **concurrent changes**, but it should not be interpreted as proving that a specific degree of KYN increase directly caused a specific increase in HAM-D scores.

This distinction is particularly important for the present article because the population represented in Figure 4 differs from the major depressive disorder cohorts analyzed in Figures 1–3. The participants in this meta-analysis were **medically ill individuals receiving IFN-α**, rather than a sample composed exclusively of patients with primary MDD [16]. Figure 4 therefore provides mechanistic evidence from an immune-activation model rather than a direct estimate of kynurenine-pathway abnormalities in all patients with depression.

Despite this difference in population, the model is informative because IFN-α provides a clinically observable condition in which inflammatory activation precedes subsequent biochemical and affective changes. The sequential exposure to an immune-stimulating intervention followed by increased kynurenine-pathway activity and depressive symptoms offers complementary evidence to the cross-sectional associations described in previous figures. It strengthens the biological plausibility of an immune-to-brain pathway connecting systemic inflammation with neuropsychiatric manifestations.

The meta-analysis also reported that sensitivity analyses did not materially alter the main inferences. Leave-one-out analyses and adjustments for possible publication bias preserved the direction of the primary findings, supporting the robustness of the observed increases in KYN and KYN/TRP ratio and the decrease in TRP [16]. However, the underlying studies were heterogeneous in clinical population, treatment duration, and study design, and most were nonrandomized prospective investigations. These characteristics remain relevant when interpreting the magnitude and generalizability of the pooled effects.

With respect to cognitive dysfunction, Figure 4 does not directly quantify executive function, memory, or attention. Instead, it describes a biological pathway potentially capable of influencing these domains. Changes in kynurenine metabolism can modify glutamatergic signaling, oxidative balance, neuronal excitability, and neuroimmune activity, all of which have relevance to cognitive processing [15], [16]. Thus, this figure serves as the mechanistic link between the systemic inflammatory findings presented earlier and the neurocognitive manifestations evaluated throughout the study.

Figure 5.

Integrated clinical profile of inflammatory cognitive dysfunction in depression.

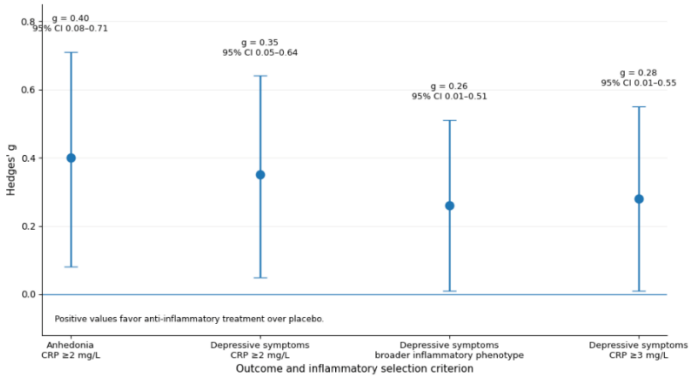


Figure 5 summarizes the pooled effect of pharmacological anti-inflammatory interventions compared with placebo in adults with depressive symptoms and evidence of increased inflammatory activity. The data were obtained from the

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systematic review and meta-analysis by Mac Giollabhui et al. [20], which specifically examined whether selecting patients according to an inflammatory phenotype influenced the observed therapeutic effect. The systematic review included **19 studies**, of which **14 contributed quantitative data to the meta-analysis**, with the primary analyses emphasizing randomized controlled trials that used established thresholds for low-grade inflammation.

Among studies using a predefined threshold of **CRP ≥2 mg/L**, anti-inflammatory treatment was associated with a statistically significant reduction in **anhedonia**, with a pooled **Hedges' g = 0.40 (95% CI 0.08–0.71)** [20]. This analysis comprised four studies and 163 participants. Because the confidence interval remained above zero, the pooled estimate favored anti-inflammatory treatment over placebo. The magnitude corresponds to a small-to-moderate standardized effect and represents the largest effect size among the outcomes displayed in Figure 5.

The effect on **overall depressive symptom severity** was also statistically significant when patients were selected using the same CRP threshold. Across 11 studies comprising 321 participants, the pooled standardized effect was **Hedges' g = 0.35 (95% CI 0.05–0.64; p = .022)** [20]. Although this effect was modest, its direction was consistent with the anhedonia findings and indicates that anti-inflammatory interventions produced a greater reduction in depressive symptom burden than placebo among individuals characterized by increased systemic inflammation.

A relevant pattern emerged when broader definitions of inflammatory status were used. In analyses incorporating a wider range of criteria, such as study-specific or median-split definitions of inflammatory activation, the pooled effect on depressive symptoms decreased to **Hedges' g = 0.26 (95% CI 0.01–0.51; p = .039)** across 14 studies and 376 participants [20]. The confidence interval remained narrowly above zero, but the smaller point estimate demonstrates that the magnitude of the observed treatment effect varied according to how the inflammatory phenotype was defined.

When a more restrictive inflammatory criterion of **CRP ≥3 mg/L** was analyzed, the pooled effect on depressive symptom severity was **Hedges' g = 0.28 (95% CI 0.01–0.55; p = .04)** across 10 studies involving 310 participants [20]. The similarity between this estimate and that obtained using broader inflammatory criteria indicates that changing the CRP threshold did not generate a dramatic alteration in the direction of treatment effects, although the magnitude remained modest. All studies contributing anhedonia outcomes used at least a CRP threshold of 3 mg/L [20].

The pattern displayed in the graph therefore demonstrates that all four pooled estimates favored anti-inflammatory treatment, but the magnitude of the effects remained relatively small. Anhedonia showed the numerically largest standardized effect, followed by overall depressive symptoms among patients selected using CRP ≥2 mg/L. Broader definitions of inflammatory phenotype and the stricter CRP ≥3 mg/L analysis produced somewhat smaller pooled effects.

These results are relevant to the concept of an **inflammatory subtype of depression** because the analyzed trials either recruited individuals with evidence of elevated inflammation or allowed inflammatory subgroups to be examined separately. This differs from studies in which patients with depression are analyzed without considering inflammatory status. Mac Giollabhui et al. proposed that failure to account for inflammatory heterogeneity may partially explain inconsistent results in previous trials of anti-inflammatory interventions [20].

Anhedonia is particularly relevant to the biological framework of the present study. Inflammatory activation has been linked to alterations in corticostriatal and dopaminergic pathways involved in reward processing, motivation, effort allocation, and goal-directed behavior [17]. The observed pooled reduction in anhedonia among individuals with elevated inflammatory markers is therefore consistent with previously described neuroimmune mechanisms, although the treatment data alone do not establish which specific neural pathway generated the clinical improvement.

Importantly, improvement in continuous symptom scores did not translate uniformly into categorical clinical outcomes. Among trials using CRP ≥2 mg/L, the weighted treatment-response rates were approximately **49% in anti-inflammatory conditions and 41% with placebo**, yielding a relative risk of approximately **1.27**, with a confidence interval that included the null value. Similarly, remission occurred in approximately **23% versus 21%**, respectively, without a statistically significant difference [20]. Thus, the results demonstrate modest reductions in symptom severity but do not establish a corresponding increase in response or remission rates.

The safety analysis similarly showed no statistically significant difference in serious adverse events between anti-inflammatory treatment and placebo within the analyzed trials. The pooled relative risk for serious adverse events was **1.08 (95% CI 0.35–3.39; p = .89)** [20]. However, the broad confidence interval and relatively limited number of trials mean that these data should not be interpreted as establishing equivalent safety for every anti-inflammatory intervention or every patient population.

Another important finding was the heterogeneity of individual study effects. The authors noted that several of the largest randomized trials reported very small effects on depressive symptom severity, whereas some smaller studies contributed larger estimates. In addition, a number of included investigations presented methodological limitations or elevated risk of bias, and some inflammatory subgroup analyses were performed post hoc rather than being incorporated into the original recruitment strategy [20]. These characteristics increase uncertainty regarding the precise magnitude of the pooled effect.

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The results shown in Figure 5 should therefore not be interpreted as evidence that anti-inflammatory therapy represents a universal treatment for major depressive disorder. Rather, they demonstrate that **baseline inflammatory status may be an important biological variable when evaluating treatment effects**. The findings are consistent with a precision-medicine framework in which biological heterogeneity is considered when analyzing therapeutic response.

This distinction is particularly relevant when Figure 5 is integrated with the preceding findings. Figure 1 demonstrated that inflammatory activity is present in only a subset of patients with depression. Figure 2 showed that depression and elevated CRP can coexist in association with poorer executive functioning. Figure 3 demonstrated a significant interaction between metabolic syndrome and inflammatory/oxidative abnormalities in relation to global cognition. Figure 4 provided mechanistic evidence that sustained immune activation alters tryptophan–kynurenine metabolism while depressive symptoms increase. Figure 5 extends these findings by showing that **the identification of an inflammatory phenotype may also have measurable clinical relevance when treatment effects are analyzed** [6], [12], [13], [16], [20].

DISCUSSION

The findings of this study support an integrated model in which **low-grade systemic inflammation, metabolic dysregulation, and cognitive dysfunction are interconnected dimensions in a subgroup of individuals with major depressive disorder (MDD)**. Taken together, the results indicate that inflammatory abnormalities are not uniformly distributed across depressive populations and should therefore not be considered a universal biological characteristic of MDD. Instead, the evidence is more consistent with the existence of an inflammatory or immunometabolic phenotype in which systemic immune activation overlaps with metabolic disturbances, alterations in neuroactive biochemical pathways, and poorer cognitive performance [5], [6].

The first relevant observation was the substantial prevalence of elevated inflammatory activity among individuals with depression. Approximately **27% of patients presented CRP concentrations above 3 mg/L**, while approximately **58% had concentrations above 1 mg/L** [6]. These values indicate that low-grade inflammation is clinically relevant in depression while simultaneously demonstrating considerable biological heterogeneity. Most importantly, the results argue against interpreting depression as a uniformly inflammatory disorder. The presence of elevated CRP in only a subset of patients is consistent with contemporary models proposing biologically distinguishable depressive phenotypes rather than a single pathophysiological mechanism [5].

This heterogeneity may have important consequences for the interpretation of previous studies. Investigations that combine patients with markedly different inflammatory profiles into a single diagnostic category may underestimate associations between inflammation and specific symptoms or biological outcomes. The immunometabolic depression model proposed by Milaneschi et al. describes a phenotype in which inflammatory abnormalities coexist with alterations in energy regulation, obesity, insulin signaling, and cardiometabolic dysfunction [5]. The current findings extend this conceptual framework toward cognition by demonstrating that inflammatory burden may be particularly relevant when considered together with metabolic status rather than as an isolated biological variable.

The association observed between CRP and executive functioning provides further evidence supporting this interpretation. In a cohort of **43,896 adults**, depression and higher CRP were independently associated with poorer executive performance, while their statistical interaction was associated with an additional decrement in executive functioning [12]. This relationship remained detectable after adjustment for several demographic, behavioral, and medical variables. Although the magnitude of the association was modest, its persistence in a large population-based sample suggests that systemic inflammation may contribute to the variability in cognitive functioning observed among individuals with depression.

Executive function may be particularly susceptible to inflammatory influences because it depends on highly integrated prefrontal and corticostriatal networks involved in working memory, cognitive flexibility, goal-directed behavior, and allocation of mental effort. Inflammatory signaling has been associated with changes in dopaminergic function within these circuits, providing a plausible connection between systemic immune activity, reduced motivation, psychomotor slowing, anhedonia, and cognitive inefficiency [17]. Nevertheless, CRP itself should be interpreted predominantly as a peripheral marker of systemic inflammatory activity rather than as a direct mediator of executive dysfunction. The observed relationship may reflect multiple upstream and downstream processes acting simultaneously.

The findings regarding immunometabolic status strengthen this multidimensional interpretation. Sánchez-Carro et al. found that the interaction between **metabolic syndrome and an inflammatory/oxidative index** was significantly associated with poorer global cognitive performance in patients with MDD, while the complete model explained approximately **31% of cognitive variance** [13]. This result is particularly relevant because it suggests that

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inflammation may acquire greater cognitive significance when it occurs within a metabolically altered physiological environment.

Several mechanisms could account for this interaction. Visceral adiposity can promote cytokine production, while insulin resistance, endothelial dysfunction, and dyslipidemia may contribute to oxidative stress and impaired neuronal energy metabolism. At the same time, chronic inflammatory activity can further disrupt insulin signaling and metabolic homeostasis. The resulting bidirectional relationship could generate a biological environment in which cerebral networks involved in cognition become progressively more vulnerable. Therefore, cognitive impairment in depression may be better conceptualized as the result of interacting systemic disturbances rather than the consequence of a single inflammatory molecule.

The finding that the immunometabolic model explained 31% of cognitive variability is also important because it simultaneously demonstrates the relevance and the limitations of this biological framework [13]. A substantial proportion of cognitive variability remained unexplained, indicating that factors such as educational level, premorbid cognitive reserve, sleep quality, duration and recurrence of depression, pharmacological exposure, vascular health, lifestyle, genetic susceptibility, and psychiatric comorbidity must also be considered. Thus, inflammation represents one component of a multifactorial cognitive phenotype rather than a complete explanation for cognitive deterioration.

The kynurenine findings provide a mechanistic bridge between systemic immune activation and neuropsychiatric manifestations. Following interferon-alpha-induced immune activation, pooled evidence demonstrated decreased tryptophan, increased kynurenine, an elevated kynurenine-to-tryptophan ratio, and increased depressive symptoms at both 4 and 24 weeks [16]. Unlike cross-sectional associations between naturally occurring inflammation and depression, this model is particularly informative because exposure to a potent immune stimulus precedes the subsequent biochemical and affective changes.

Activation of the kynurenine pathway may influence brain function through metabolites capable of modifying glutamatergic neurotransmission, oxidative balance, and neuronal excitability [15], [16]. These mechanisms could theoretically contribute to disturbances in attention, executive control, memory, and motivational processing. However, the present findings require careful interpretation. The interferon-alpha studies predominantly involved patients with chronic medical diseases rather than populations with primary MDD, and cognitive function was not the principal outcome. Consequently, these results provide **mechanistic plausibility** rather than direct evidence that kynurenine pathway activation causes cognitive impairment in all patients with depression.

The treatment findings further reinforce the importance of biological stratification. The most recent meta-analysis included randomized controlled trials of anti-inflammatory therapies in depressed individuals with elevated inflammatory activity and found significant, although modest, improvements in depressive symptoms and anhedonia. Among studies using **CRP ≥2 mg/L**, effect sizes were approximately **g = 0.35 for overall depressive symptoms and g = 0.40 for anhedonia** [20].

These treatment results are consistent with the hypothesis that inflammatory status may help identify a subgroup of patients in whom immune-targeted interventions have greater relevance. However, several considerations prevent direct translation into universal clinical practice. First, the observed effects were relatively small. Second, improvements in continuous symptom scores were not accompanied by clearly significant differences in categorical response or remission rates [20]. Third, individual trials used different anti-inflammatory agents and inflammatory selection criteria. Therefore, the evidence supports continued investigation of biomarker-guided treatment rather than indiscriminate use of anti-inflammatory therapies in depression.

Furthermore, the therapeutic evidence does not establish that reduction of inflammation improves cognitive impairment. The principal outcomes analyzed were depressive symptom severity and anhedonia, not executive function, memory, attention, or processing speed [20]. This distinction is especially important because affective remission and cognitive recovery are not necessarily equivalent. Future randomized studies should incorporate standardized neuropsychological testing as a primary or secondary outcome to determine whether modifying inflammatory pathways produces parallel improvements in cognition.

An important clinical implication of the current findings is that inflammatory biomarkers should not be interpreted in isolation. CRP, IL-6, and TNF-α are nonspecific and may be elevated because of obesity, infection, autoimmune disorders, smoking, cardiovascular disease, sleep disturbance, medication exposure, or other systemic conditions. Therefore, an elevated CRP concentration in a patient with depression cannot be assumed to represent a depression-specific inflammatory mechanism. A more informative approach would integrate inflammatory biomarkers with metabolic status, medical comorbidities, depressive phenotype, cognitive assessment, and relevant lifestyle variables.

This consideration is particularly relevant from an internal-medicine perspective. Depression frequently coexists with obesity, diabetes mellitus, metabolic syndrome, cardiovascular disease, and other conditions associated with systemic inflammation. The direction of the relationship may also be bidirectional. Depressive symptoms can promote physical inactivity, disrupted sleep, dietary changes, and weight gain, which can increase inflammatory activity, while

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inflammatory and metabolic abnormalities may simultaneously influence neural pathways associated with depressive and cognitive symptoms. Current evidence therefore does not support a simple linear sequence in which inflammation independently initiates depression and cognitive decline. Questions of causality remain unresolved, and longitudinal and experimental designs are necessary to separate shared risk factors from direct mechanistic effects.

Several methodological limitations of the evidence synthesized in this study should be acknowledged. First, many of the studies examining inflammation and cognition are **cross-sectional**, preventing determination of temporal direction. Second, considerable heterogeneity exists in diagnostic procedures, inflammatory thresholds, cognitive instruments, medication status, and adjustment for potential confounders. Third, CRP is the most frequently investigated inflammatory marker because it is readily available, but it provides limited information regarding specific immune pathways. Fourth, peripheral inflammatory markers may not accurately reflect inflammatory activity within the central nervous system. Finally, the cognitive domains assessed vary substantially among studies, limiting direct comparison of effect magnitudes.

Another limitation is the possibility of residual confounding. Even studies controlling for body mass index, chronic disease, smoking, physical activity, and socioeconomic variables cannot completely eliminate unmeasured biological or behavioral influences. As emphasized in methodological analyses of inflammation and depression, shared risk factors may simultaneously increase inflammatory markers, depressive symptoms, and cognitive dysfunction, generating associations without establishing a direct causal pathway [12].

Future research should therefore prioritize **prospective longitudinal designs** in which inflammatory biomarkers, metabolic variables, depressive symptoms, and cognition are measured repeatedly over time. Multimarker panels may be more informative than isolated CRP measurement and could include cytokines, metabolic markers, oxidative stress indicators, kynurenine metabolites, and potentially neuroimaging measures. Studies should also define cognitive outcomes prospectively and include validated measures of executive functioning, attention, working memory, learning, memory, and processing speed.

A further priority is the identification of clinically reproducible inflammatory thresholds and biological profiles. The current literature uses CRP cutoffs ranging from mild elevation to more restrictive inflammatory criteria, while other studies rely on composite inflammatory scores. A standardized framework would improve comparability and help determine whether an immunometabolic phenotype predicts persistent cognitive impairment, treatment resistance, or differential response to targeted interventions.

Overall, the findings support a model in which **inflammation is neither incidental nor universally explanatory in depression**. Instead, chronic low-grade inflammatory activity appears to interact with metabolic abnormalities and neurobiological pathways in a subset of patients, and this biological context is associated with differences in cognitive performance and some therapeutic outcomes. The strongest interpretation of the available evidence is therefore one of **heterogeneity and interaction**: cognitive dysfunction in depression is likely generated by multiple convergent mechanisms, with inflammation and immunometabolic dysregulation representing important contributors in selected individuals.

Integrating neuroscience, psychiatry, and internal medicine may consequently provide a more complete framework for understanding persistent cognitive dysfunction in MDD. Rather than replacing conventional psychiatric assessment, inflammatory and metabolic characterization could eventually complement clinical evaluation by helping define biologically informative subgroups. Establishing whether these subgroups have distinct cognitive trajectories or respond differently to targeted interventions remains a central objective for future precision-oriented research [5], [12], [13], [20].

CONCLUSION

The evidence analyzed in this study indicates that chronic low-grade inflammation constitutes an important biological component in a subset of individuals with major depressive disorder and may contribute to persistent cognitive dysfunction through interconnected immune, metabolic, and neurochemical mechanisms. Elevated inflammatory activity is not uniformly present in depression; rather, it appears to characterize a heterogeneous subgroup in which systemic inflammation frequently overlaps with obesity, insulin resistance, metabolic syndrome, oxidative stress, and alterations in neuroactive pathways.

The findings show that higher inflammatory burden is associated particularly with poorer executive functioning and that this relationship may become more pronounced when depression coexists with elevated C-reactive protein or broader immunometabolic abnormalities. The interaction between metabolic syndrome and inflammatory/oxidative activity further supports the idea that cognitive impairment in depression cannot be explained by a single biomarker. Instead, the available evidence favors a multidimensional model in which immune activation, metabolic dysregulation,

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oxidative stress, altered dopaminergic signaling, and kynurenine-pathway activation interact with neural systems responsible for attention, memory, motivation, processing speed, and executive control.

The results also demonstrate that inflammatory heterogeneity may have clinical relevance. Anti-inflammatory interventions have shown modest improvements in depressive symptoms and anhedonia among individuals with elevated inflammatory activity, suggesting that biological stratification may help identify subgroups with different therapeutic responses. However, current evidence does not establish anti-inflammatory treatment as a universal strategy for depression, nor does it demonstrate that reducing inflammation necessarily produces cognitive recovery.

From a clinical perspective, inflammatory biomarkers such as CRP, IL-6, and TNF-α should therefore be interpreted within a broader medical and psychiatric context. Their value is likely to be greater when combined with assessment of metabolic status, cardiovascular risk, medical comorbidity, depressive phenotype, and standardized cognitive performance. Such integration is particularly relevant because many systemic conditions capable of increasing inflammation also independently affect cognition.

The principal limitations of the current evidence include the predominance of cross-sectional designs, variability in inflammatory thresholds and cognitive instruments, heterogeneity among patient populations, and the nonspecific nature of commonly measured inflammatory biomarkers. These limitations prevent definitive conclusions regarding causality and emphasize the need for longitudinal studies with repeated biological and cognitive assessments.

Future research should focus on reproducible multimarker profiles, prospective cognitive outcomes, standardized inflammatory criteria, and clinical trials specifically designed to determine whether modification of immunometabolic pathways can improve both depressive symptoms and cognition. Integrating inflammatory, metabolic, psychiatric, and neurocognitive variables may ultimately contribute to a more precise characterization of major depressive disorder.

In conclusion, low-grade inflammation should not be viewed as the sole cause of cognitive deterioration in depression, but as one component of a broader immunometabolic network that may substantially influence cognitive vulnerability in selected patients. A multidisciplinary approach combining neuroscience, psychiatry, and internal medicine offers a more comprehensive framework for understanding these interactions and may provide the foundation for future precision-oriented strategies aimed at improving both symptomatic and functional recovery.

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