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Neuroinflammation in psychosis: Immune pathways, biomarkers, and therapeutic implications: A literature review

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Abstract

Background: Psychosis is increasingly understood as a heterogeneous neuropsychiatric syndrome in which immune dysregulation may interact with dopaminergic, glutamatergic, and neurodevelopmental mechanisms.
Purpose: To synthesize evidence on neuroinflammatory pathways implicated in psychosis and evaluate their potential clinical relevance.
Method: A narrative literature review was conducted through PubMed-based searching between January and June 2026. English- or Indonesian-language full-text publications issued from 2016 to 2026 were considered when they addressed psychosis or schizophrenia in relation to cytokines, chemokines, immune-cell profiles, microglial activation, blood–brain barrier dysfunction, oxidative stress, or the gut–brain axis. Ten highly relevant review-level articles were selected and narratively synthesized using a PICOS-informed extraction framework.
Results: Across the included literature, psychosis was associated with increased pro-inflammatory mediators, particularly interleukin-6, interleukin-1β, tumor necrosis factor-α, interferon-γ, C-reactive protein, and selected chemokines. Peripheral immune-cell alterations, microglial activation, oxidative stress, impaired blood–brain barrier integrity, and microbiome-related immune signaling were repeatedly reported. These processes may disrupt synaptic pruning, N-methyl-D-aspartate receptor signaling, inhibitory interneuron function, and dopamine–glutamate balance. However, heterogeneity across disease stage, medication exposure, comorbidity, biospecimen, and assay method limits diagnostic specificity.
Conclusion: Neuroinflammation is a plausible contributor to the pathophysiology and progression of psychosis, but current biomarkers are better viewed as stratification or prognostic candidates than stand-alone diagnostic tests. Longitudinal, multimodal, and phenotype-stratified studies are required before immune-targeted interventions can be incorporated into routine care.

Keywords: Blood–Brain Barrier; Cytokines; Microglia; Neuroinflammation; Psychosis; Schizophrenia.

INTRODUCTION

Psychosis is a clinical syndrome characterized by impaired reality testing, commonly manifested by delusions, hallucinations, disorganized thinking, and disorganized behavior. It occurs across schizophrenia-spectrum disorders, mood disorders, substance-related conditions, and neurological or systemic diseases. Beyond acute symptoms, psychosis may be associated with persistent cognitive and social impairments, reduced occupational functioning, physical comorbidity, and increased risk of suicide. Psychotic disorders frequently emerge during late adolescence or early adulthood, making early identification and intervention important for reducing long-term functional impairment and improving clinical outcomes (McCutcheon et al., 2020; World Health Organization, 2025; Bourgin et al., 2020).

The dopamine hypothesis remains central to the understanding of positive psychotic symptoms, particularly through the role of dysregulated

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dopaminergic signaling in aberrant salience attribution and psychosis (Corlett & Fraser, 2025). However, dopamine-centered models alone do not fully account for negative symptoms, cognitive impairment, treatment resistance, or the substantial clinical and biological heterogeneity observed across individuals (Howes et al., 2024; Rawani et al., 2024). Contemporary models therefore conceptualize psychosis as a multidimensional and interacting disorder involving dopaminergic and glutamatergic signaling, γ-aminobutyric acid (GABA) dysfunction, oxidative stress, neurodevelopmental abnormalities, and immune dysregulation (Howes et al., 2024; Zahid et al., 2023; Rawani et al., 2024). Within this framework, neuroinflammation may interact with neurotransmitter and neurodevelopmental mechanisms rather than functioning as an independent pathway, providing a more comprehensive account of the biological complexity underlying psychosis (Rawani et al., 2024; Howes & Kapur, 2009; McCutcheon et al., 2020; Carril Pardo et al., 2025; Chen et al., 2024).

Neuroinflammatory processes involve interactions among microglia, astrocytes, endothelial cells, and peripheral immune mediators. Under physiological conditions, these immune mechanisms contribute to neural homeostasis, synaptic plasticity, and protection against harmful stimuli. However, persistent or dysregulated immune activation may disrupt neural function by promoting oxidative stress, altering neurotransmitter signaling, affecting synaptic remodeling, and compromising blood–brain barrier integrity. These processes may represent biological links between environmental and metabolic risk factors and the pathophysiology of psychotic disorders, although the direction and causal significance of these associations remain uncertain (Carril Pardo et al., 2025; Chaves et al., 2024; Chen et al., 2024).

Clinical studies have reported alterations in cytokines, chemokines, acute-phase proteins, and circulating immune-cell profiles in subsets of individuals with schizophrenia and first-episode psychosis. Neuroimaging and experimental studies have also investigated potential alterations in microglial activity and blood–brain barrier integrity. However, findings remain heterogeneous and are not consistently observed across patients or disease stages. Variability in illness duration, antipsychotic exposure, smoking, body mass index, metabolic status, sampling conditions, and laboratory methods may contribute to differences in inflammatory measurements across studies (Dunleavy et al., 2022; Koola, 2016; Lv et al., 2024). Accordingly, the key question is not whether psychosis represents a uniformly inflammatory disorder, but whether distinct immune-related phenotypes are associated with disease onset, symptom severity, cognitive impairment, illness progression, or treatment response (Chen et al., 2024; Chaves et al., 2024; Clausen et al., 2024).

This review aimed to synthesize current evidence on neuroinflammation as a potential pathophysiological component of psychosis, with particular emphasis on cytokines and chemokines, peripheral immune-cell alterations, microglial activity, oxidative stress, blood–brain barrier dysfunction, neurotransmitter interactions, the gut–brain axis, and the potential clinical and therapeutic implications of inflammatory biomarkers and immune-modulating approaches.

RESEARCH METHOD

This study employed a structured narrative literature review design involving systematic literature searching, screening, eligibility assessment, data extraction, and narrative synthesis. The review was guided by the following question: How does neuroinflammation contribute to the pathophysiology, clinical expression, and progression of psychosis? A pragmatic PICOS-informed framework was used to structure the review question and guide the identification and extraction of relevant evidence. The population (P) comprised individuals with psychosis, schizophrenia, first-episode psychosis, or clinical high risk for psychosis. The exposure (I) included immune and neuroinflammatory processes, while comparators (C) included healthy controls when available. The outcomes (O) encompassed inflammatory alterations, neurobiological effects, clinical symptoms, cognitive function, prognosis, and therapeutic implications. Eligible publication types (S) included systematic reviews, meta-analyses, focused narrative reviews, and selected expert-oriented opinion or commentary articles that provided substantive conceptual or mechanistic information relevant to neuroinflammation in psychosis.

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Literature searching was conducted from January to June 2026, primarily using PubMed. The search strategy combined terms related to the major concepts of the review, including *"neuroinflammation," "psychosis," "schizophrenia," "first-episode psychosis," "cytokine," "chemokine," "microglia," "blood-brain barrier," "oxidative stress," "immune cell,"* and *"gut-brain axis."* Publications were considered eligible if they were published between 2016 and 2026, available in full text, written in English or Indonesian, and directly relevant to neuroinflammatory mechanisms in psychosis. Opinion or commentary articles were included only when they provided a substantive conceptual, mechanistic, or clinically relevant contribution to the review question. Publications were excluded if the full text was unavailable, the population or outcomes were unrelated to psychosis, or immune-related findings were incidental and could not be meaningfully interpreted in relation to the review question.

A total of 317 records were identified through the PubMed search. Duplicate records were removed (n = 67), leaving 250 records for title and abstract screening. Of these, 219 records were excluded because they did not meet the predefined relevance criteria. The remaining 31 full-text publications were assessed for eligibility. Following full-text assessment, 21 publications were excluded because they did not meet the predefined eligibility criteria, resulting in 10 eligible publications included in the core narrative synthesis. The study selection process is presented in the PRISMA flow diagram.

Data were extracted from the included publications according to publication type, population or clinical group, neuroinflammatory exposure or mechanism, comparator when available, outcomes, and major conceptual or clinical findings. The extracted evidence was organized according to the predefined domains of the review and subsequently compared and critically interpreted across publications. Particular attention was given to the relationships between inflammatory signaling, peripheral immune alterations, microglial activation, blood–brain barrier dysfunction, oxidative stress, gut–brain interactions, clinical manifestations, cognitive impairment, disease progression, and therapeutic implications.

Because this review incorporated substantial heterogeneity in publication types, populations, neuroinflammatory markers, mechanistic domains, and outcome definitions, quantitative pooling and statistical re-analysis were not considered appropriate. Therefore, the findings were synthesized narratively, emphasizing convergence and divergence across the available evidence and the potential mechanistic links between neuroinflammation and psychosis. No primary patient-level data were collected or analyzed; therefore, ethical approval was not required.

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RESEARCH RESULTS

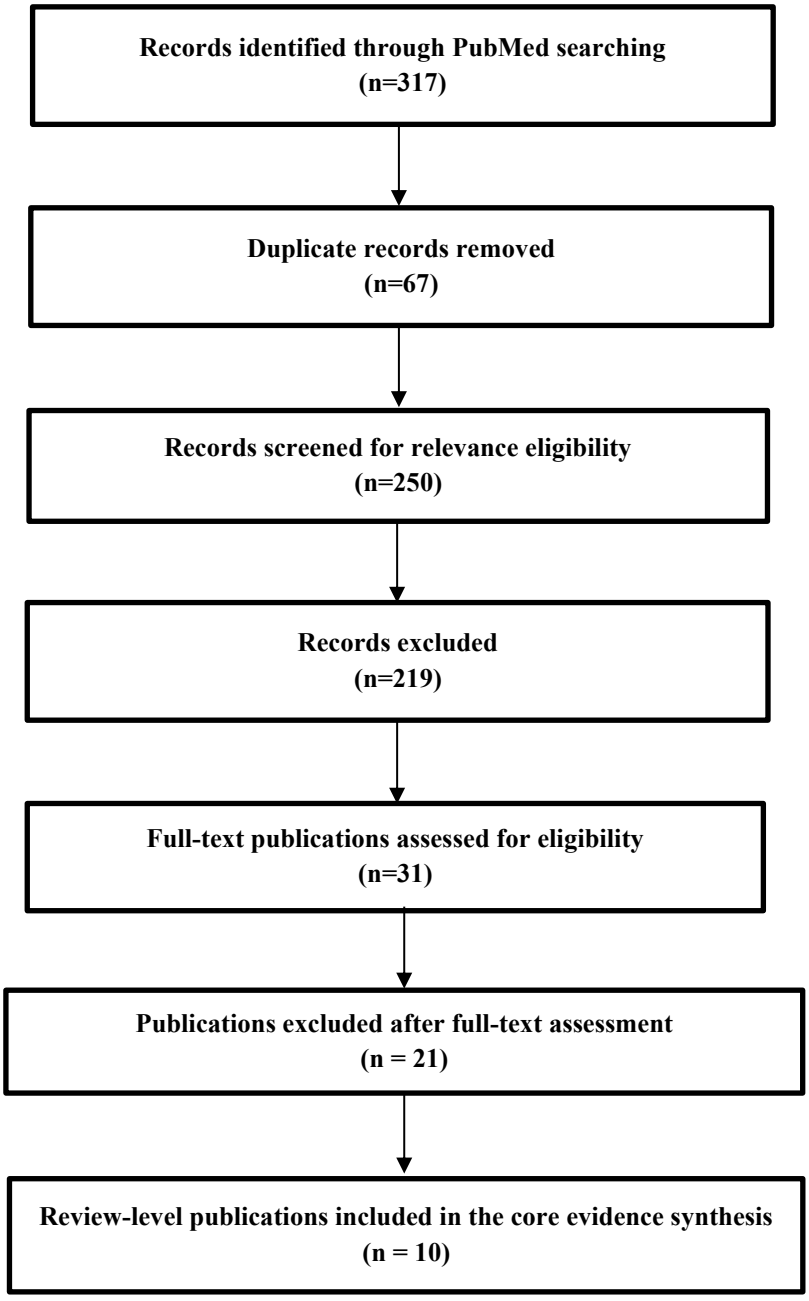


Figure 1. Flow diagram of the literature search and selection of review-level evidence

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Table 1. Characteristics of the Included Evidence

(Author, Year) Country	Population	Factor of Interest	Comparator	Outcome	Study Design
(Barron et al., 2017) Canada	Individuals with psychosis, schizophrenia, and individuals at high risk for psychosis.	Neuroinflammation and oxidative stress, including effects on parvalbumin-containing interneurons (PVIs), NMDA receptor function, and synaptic pruning.	Non-psychotic or healthy individuals, where applicable.	Neuroinflammation and oxidative stress may contribute to psychosis through NMDA receptor dysfunction, PVI impairment, and abnormal synaptic pruning.	Literature Review
(Chaves et al., 2024) Canada/Brazil/Italy	Individuals with schizophrenia, first-episode psychosis, and individuals at risk for schizophrenia.	Immune activation, inflammatory biomarkers, pro-inflammatory cytokines, and maternal immune activation.	Healthy or non-schizophrenia populations, where applicable.	Immune activation and inflammatory biomarkers were associated with psychotic disorders and may contribute to vulnerability to psychosis.	Opinion Article
(Clausen et al., 2024) Denmark/Italy	Individuals with psychotic disorders and healthy controls.	Alterations in circulating immune-cell populations in blood and CSF.	Healthy controls	Increased leukocytes, granulocytes, neutrophils, monocytes, B lymphocytes, NLR, MLR, and PLR, indicating broad immune-system activation.	Systematic Review and Meta-analysis
(Dunleavy et al., 2022) United Kingdom/Australia	Antipsychotic-naïve individuals with first-episode psychosis.	Inflammatory cytokines, including IFN-γ, IL-6, IL-12, IL-17, TNF-α, IL-1β, IL-2, IL-4, IL-8, and IL-10.	Healthy controls	IFN-γ, IL-6, IL-12, and IL-17 were elevated in antipsychotic-naïve FEP; inflammatory biomarkers were also examined in relation to negative symptoms.	Systematic Review and Meta-analysis
(Ermakov et al., 2023) Russia	Individuals with schizophrenia	Dysregulation of chemokines and chemokine receptors, including CXCL8/IL-8, CCL2/MCP-1, CCL4/MIP-1β, CCL11/eotaxin-1, CX3CL1-CX3CR1, and CXCL12-CXCR4.	Healthy/control groups represented in the reviewed studies	Chemokine dysregulation was associated with inflammatory signaling, immune-cell migration, neurogenesis, and neurotransmission.	Systematic Review

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(Author, Year) Country	Population	Factor of Interest	Comparator	Outcome	Study Design
(Lv et al., 2024) China	Individuals with schizophrenia	Alterations in cytokine concentrations in peripheral blood, CSF, and extracellular vesicles.	Healthy/control groups represented in the reviewed studies	Alterations in IL-1β, IL-6, TNF-α, and other cytokines support the involvement of inflammatory processes in schizophrenia and their potential biomarker role.	Systematic Review
(Juckel & Freund, 2023) Germany	Individuals with schizophrenia and individuals in the prodromal phase.	Microglial activation, microbiome alterations, immune dysregulation, and cytokine signaling.	No specific comparator	Abnormal microglial activation and gut dysbiosis may contribute to neuroinflammation and psychotic symptoms through immune and gut–brain-axis mechanisms.	Narrative Review
(Carril Pardo et al., 2025) Chile	Individuals with schizophrenia and first-episode psychosis.	Inflammatory mediators, microglial and astrocytic activation, BBB dysfunction, and gut-microbiota alterations.	No specific comparator	Neuroinflammatory imbalance, microglial activation, BBB dysfunction, and altered neural function were associated with psychotic symptoms and cognitive impairment.	Narrative Review
(Chen et al., 2024) China/Finland	Individuals with psychotic disorders, particularly schizophrenia	Alterations in immune phenotypes, innate and adaptive immune activation, and premature inflamm-aging.	Healthy/non-psychotic populations represented in the reviewed studies	Altered immune phenotypes support the involvement of innate and adaptive immunity; premature inflamm-aging may link chronic inflammation with immune dysfunction in psychosis.	Narrative Review
(Stefanova, 2024) United Kingdom	Individuals with psychotic disorders, particularly schizophrenia and related conditions.	Neuroinflammation, microglial activation, inflammatory biomarkers, BBB dysfunction, and neurotransmitter dysregulation.	No specific comparator	Neuroinflammatory processes were proposed as potential contributors to psychotic symptom progression.	Commentary

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Characteristics of the Evidence Base

The final evidence set comprised review-level studies addressing schizophrenia-spectrum disorders, first-episode psychosis, antipsychotic-naïve populations, clinical-high-risk groups, and mixed psychotic disorders. The evidence base included narrative and descriptive reviews, systematic reviews, and systematic reviews with meta-analysis. Healthy controls were frequently included in the primary studies synthesized by systematic reviews, whereas mechanistic narrative reviews integrated clinical, neuroimaging, experimental, and translational evidence. The principal domains identified across the evidence base were cytokine and chemokine abnormalities, peripheral immune-cell alterations, microglial activation and oxidative stress, blood–brain barrier dysfunction, neurotransmitter interactions, gut–brain signaling, and inflammatory biomarkers.

Cytokines and Chemokines

Pro-inflammatory cytokines were among the most consistently investigated inflammatory markers. Systematic and integrative reviews have reported alterations in interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interferon-γ, and C-reactive protein, although the magnitude and consistency of these findings vary across populations and disease stages. In first-episode or antipsychotic-naïve samples, these findings are particularly informative because they reduce, although do not eliminate, the possibility that inflammatory alterations are attributable to long-term antipsychotic exposure. Elevated IL-6 has been associated with acute illness and symptom burden, whereas persistent inflammatory activity has also been linked to negative symptoms and cognitive impairment.

Chemokines provide a complementary perspective because they regulate immune-cell trafficking and cellular communication. Dysregulation of CXCL8, CCL2, CCL11, and related chemokines has been described in schizophrenia, suggesting alterations in immune-cell recruitment and signaling. However, chemokine findings appear less consistent than broader cytokine patterns, partly because studies differ in analyte panels, biospecimens, patient characteristics, and statistical thresholds.

Overall, the evidence supports inflammatory heterogeneity rather than a single universal cytokine signature. Some inflammatory markers may function predominantly as state-related signals that change with acute illness and clinical stabilization, whereas others may reflect trait vulnerability, comorbid metabolic inflammation, medication exposure, or cumulative illness burden.

Peripheral Immune-Cell Alterations

Meta-analytic evidence indicates alterations in circulating leukocytes and derived inflammatory ratios in psychotic disorders, including changes in neutrophils, monocytes, selected lymphocyte subsets, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio. These findings are broadly compatible with peripheral immune activation and may provide relatively accessible clinical indicators. Nevertheless, these indices are nonspecific and can be substantially influenced by acute infection, smoking, obesity, sleep disturbance, stress-related physiological changes, and antipsychotic-associated metabolic alterations. Accordingly, their potential clinical utility is more appropriately considered within a broader multivariable biological and clinical profile rather than as standalone diagnostic markers.

Microglia, Oxidative Stress, and Synaptic Function

Microglia are resident immune cells that survey the neural environment, remove cellular debris, and participate in synaptic remodeling. Persistent alterations in microglial activity may influence cytokine signaling, reactive oxygen species production, mitochondrial function, and synaptic homeostasis. These processes have therefore been proposed as potential links between neuroinflammation, oxidative stress, and neuronal dysfunction.

Oxidative stress may be particularly relevant to parvalbumin-positive inhibitory interneurons because of their high metabolic demands and role in cortical network synchronization. Oxidative and inflammatory disturbances may impair inhibitory control and alter excitatory–inhibitory balance, potentially contributing to cognitive and network dysfunction. In parallel, inflammatory and oxidative pathways may affect N-methyl-D-aspartate (NMDA) receptor-related signaling, providing a potential biological link between immune dysregulation and glutamatergic models of schizophrenia.

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Although translocator-protein positron-emission tomography (TSPO-PET) has been used as an indirect measure of glial activation, its interpretation remains complex. TSPO binding is not specific to a single microglial phenotype, and findings may vary according to radioligand characteristics, genotype, illness stage, and medication exposure. Thus, available evidence supports potential involvement of microglial processes but does not justify a simple dichotomy between "activated" and "inactive" microglia.

Blood–Brain Barrier and Neurotransmitter Interactions

Inflammatory signaling may affect endothelial tight-junction integrity and alter blood–brain barrier permeability. Changes in barrier function could modify interactions between circulating inflammatory mediators and the central nervous system and may influence local glial responses. Inflammatory pathways have also been implicated in dopamine synthesis and signaling, glutamate metabolism, inhibitory neurotransmission, and the tryptophan–kynurenine pathway. These interactions provide a potential mechanistic framework linking peripheral immune dysregulation with dopaminergic, glutamatergic, GABAergic, and kynurenine-related abnormalities observed in psychotic disorders.

Gut–Brain Axis

The intestinal microbiome has been proposed as a potential contributor to psychosis through interconnected immune, metabolic, neural, and endocrine pathways. Alterations in microbial composition and intestinal permeability may influence peripheral inflammatory signaling and, potentially, neuroimmune processes. However, current evidence remains predominantly associative. Microbiome composition is also influenced by diet, antipsychotic exposure, geography, antibiotic use, and lifestyle, which complicates interpretation and limits causal inference.

DISCUSSION

An Integrated Pathophysiological Model

The reviewed evidence supports an integrated pathophysiological model in which neuroinflammation is neither a singular cause of psychosis nor simply an epiphenomenal consequence of illness. Genetic susceptibility, prenatal or later-life infections, psychosocial stress, substance exposure, metabolic dysfunction, and neurodevelopmental alterations may contribute to immune dysregulation and increase vulnerability to psychosis. In susceptible individuals, inflammatory activation may interact with glial function, redox homeostasis, blood–brain barrier integrity, synaptic remodeling, and neurotransmitter systems. These interconnected mechanisms may converge on neural circuits involved in salience attribution, cognition, affect regulation, and behavioral organization.

An important implication is that a shared clinical diagnosis may encompass biologically heterogeneous subgroups. Some individuals may exhibit more prominent inflammatory and metabolic abnormalities, whereas others may have predominantly neurodevelopmental, synaptic, or neurotransmitter-related vulnerabilities. Mixed biological profiles may also occur. This heterogeneity may help explain why group-level differences in inflammatory biomarkers do not necessarily translate into accurate individual-level diagnosis or prediction. Accordingly, neuroinflammation should be considered a potential biological dimension of psychosis rather than a universal mechanism applicable to all patients.

The temporal relationship between inflammation and psychosis is also likely to be dynamic. Inflammatory abnormalities may be detectable during periods of increased vulnerability, become more pronounced around the first psychotic episode, fluctuate during acute illness or relapse, or coexist with chronic disease and medical comorbidity. However, the predominance of cross-sectional evidence limits the ability to determine whether inflammatory alterations precede psychosis, emerge as a consequence of illness, or reflect bidirectional interactions. Longitudinal studies beginning in clinical-high-risk populations and extending across illness stages and treatment are therefore needed to clarify temporal relationships and determine whether inflammatory phenotypes have prognostic or treatment-response value.

Clinical Utility of Biomarkers

Despite consistent evidence of immune and inflammatory alterations, current inflammatory biomarkers are not sufficiently specific to serve as standalone diagnostic markers for psychosis. Markers

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such as interleukin-6 (IL-6), C-reactive protein (CRP), leukocyte-derived ratios, and related inflammatory measures can also be altered in infectious, metabolic, autoimmune, and other psychiatric conditions. Their clinical value may therefore be greater when incorporated into multimodal assessment rather than interpreted individually. Multimodal approaches combining inflammatory and immune markers with clinical symptoms, cognitive measures, neuroimaging, metabolic characteristics, medication exposure, and other relevant clinical variables may provide greater biological resolution.

Such approaches could potentially help identify clinically meaningful subgroups, including individuals with greater risk of persistent negative symptoms, cognitive impairment, treatment resistance, or cardiometabolic complications. However, these applications remain investigational and require prospective validation before inflammatory profiles can be incorporated into routine clinical decision-making.

Therapeutic Implications

The inflammatory model provides a rationale for investigating adjunctive immune-modulating strategies in psychosis. Nevertheless, the available evidence does not support routine use of broad anti-inflammatory treatment for unselected psychosis populations. Therapeutic effects may depend on biological phenotype, illness stage, baseline inflammatory status, and the specific inflammatory pathway targeted. Future clinical trials should therefore consider enrichment strategies based on validated inflammatory phenotypes, prespecify disease stage, adequately control for metabolic, infectious, medication-related, and lifestyle-related confounders, and evaluate clinically meaningful outcomes beyond short-term changes in positive symptoms.

Potential therapeutic approaches include targeting specific cytokine pathways, oxidative stress, microglial signaling, metabolic inflammation, or gut–brain interactions. Non-pharmacological strategies, including physical activity, sleep optimization, smoking cessation, and cardiometabolic risk management, may also contribute to reducing systemic inflammatory burden while improving overall health. These approaches should be regarded as complementary to, rather than replacements for, evidence-based antipsychotic treatment and psychosocial interventions. Importantly, the clinical effectiveness of inflammation-targeted strategies remains an area for further investigation (Becher et al., 2024; Subramaniam et al., 2021; Fu et al., 2025; Chaves et al., 2024).

Priorities for Translation and Future Research

The current evidence provides a rationale for further translational research but does not yet support routine clinical application of inflammatory biomarkers or immune-modulating therapies in psychosis. Future research should therefore prioritize biological phenotyping, longitudinal characterization, assay harmonization, multimodal validation, and biomarker-guided clinical trials. Particular attention should be given to controlling metabolic, infectious, medication-related, and lifestyle-related confounders, as these factors may substantially influence inflammatory measures. Key priorities for advancing the field from mechanistic evidence toward clinically useful applications are summarized in Table 2.

Table 2. Priorities for Translation and Future Research

Priority	Recommended Approach	Expected Value
Phenotype definition	Combine inflammatory, metabolic, clinical, cognitive, and treatment-related variables to characterize biologically meaningful subgroups.	Identify clinically relevant biological subgroups and improve patient stratification.
Longitudinal design	Collect data before treatment, after clinical stabilization, and during longitudinal follow-up across illness stages.	Distinguish state-related from trait-related inflammatory alterations and clarify temporal relationships.

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Priority	Recommended Approach	Expected Value
Assay harmonization	Standardize biospecimen collection, processing, storage, laboratory methods, and core inflammatory biomarker panels.	Improve reproducibility, comparability, and reliability across studies.
Multimodal validation	Integrate peripheral inflammatory markers with neuroimaging, cognitive measures, clinical characteristics, metabolic variables, and treatment history.	Determine whether multimodal profiles provide greater diagnostic or prognostic value than individual biomarkers.
Targeted clinical trials	Enroll participants according to predefined and validated inflammatory phenotypes and stratify by illness stage.	Determine whether immune-modulating interventions are beneficial for biologically selected subgroups.
Mechanism-specific intervention	Investigate targeted approaches involving cytokine signaling, oxidative stress, microglial pathways, metabolic inflammation, and gut–brain mechanisms.	Evaluate pathway-specific therapeutic effects while minimizing unnecessary treatment of biologically unselected patients.
Confounder control	Systematically account for infection, obesity, smoking, sleep disturbance, medication exposure, physical inactivity, and other cardiometabolic factors.	Improve interpretation of inflammatory biomarkers and reduce confounding.
Public-health integration	Address modifiable inflammatory and cardiometabolic risk factors through physical activity, sleep optimization, smoking cessation, healthy diet, and metabolic risk management.	Reduce systemic inflammatory and cardiometabolic burden and support overall health.
Clinical implementation	Validate biomarker-based models in independent, diverse, real-world populations before routine clinical adoption.	Establish generalizability, clinical utility, and cost-effectiveness before implementation.

Collectively, these priorities may help determine whether inflammatory alterations represent clinically actionable biological phenotypes rather than nonspecific correlates of illness. Progress toward precision medicine will require reproducible biomarker definitions, prospective validation across illness stages, and evidence that biomarker-guided approaches improve clinically meaningful outcomes.

Strengths and Limitations

This review provides an integrated synthesis of immune-cell alterations, inflammatory mediators, glial mechanisms, blood–brain barrier dysfunction, oxidative stress, neurotransmitter systems, and microbiome-related pathways in psychosis. A further strength is the emphasis on biological heterogeneity and the distinction between group-level inflammatory

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abnormalities and their potential individual-level clinical relevance.

Several limitations should nevertheless be considered. First, the evidence base relied predominantly on review-level literature, which may introduce dependence on previously selected studies and limit direct assessment of individual primary-study quality. Second, the literature search was primarily PubMed-based, potentially resulting in incomplete retrieval of relevant studies indexed in other databases. Third, restricting the search to publications from 2016–2026 may have excluded important earlier mechanistic or foundational evidence. Fourth, substantial heterogeneity existed across populations, illness stages, medication exposure, biomarker assays, and definitions of inflammatory abnormalities, limiting direct comparison across studies. Finally, because this review used a narrative rather than quantitative synthesis, it does not provide pooled effect estimates. The protocol was not prospectively registered, and formal risk-of-bias assessment was not performed. Therefore, the findings should be interpreted as a structured synthesis of the current evidence rather than as definitive evidence of causality or treatment efficacy.

CONCLUSION

Neuroinflammation represents a credible and potentially important component of the pathophysiology of psychosis. Convergent evidence implicates cytokine and chemokine dysregulation, peripheral immune-cell alterations, microglial and oxidative mechanisms, blood–brain barrier dysfunction, neurotransmitter interactions, and gut–brain signaling. These interconnected processes may contribute to the emergence and persistence of psychotic symptoms, cognitive dysfunction, and clinical heterogeneity, although their causal and temporal relationships remain incompletely established. Importantly, inflammatory abnormalities are neither universal nor sufficiently specific to serve as standalone diagnostic biomarkers. The most promising path toward clinical translation is therefore the development and prospective validation of longitudinal, multimodal, and phenotype-stratified models capable of identifying biologically distinct patient subgroups in whom immune-related mechanisms may have clinically actionable relevance.

DECLARATIONS

Author contributions: NMJK conceptualized the review, performed literature screening and extraction, and drafted the manuscript. MAJ and IKAB supervised the work, critically reviewed the interpretation, and revised the manuscript for important intellectual content. All authors approved the final manuscript.

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REFERENCES

Barron, H., Hafizi, S., Andreazza, A. C., & Mizrahi, R. (2017). Neuroinflammation and oxidative stress in psychosis and psychosis risk. *International journal of molecular sciences*, *18*(3), 651.

Becher, B., Derfuss, T., & Liblau, R. (2024). Targeting cytokine networks in neuroinflammatory diseases. *Nature Reviews Drug Discovery*, *23*(11), 862-879.

Bourgin, J., Tebeka, S., Mallet, J., Mazer, N., Dubertret, C., & Le Strat, Y. (2020). Prevalence and correlates of psychotic-like experiences in the general population. *Schizophrenia research*, *215*, 371-377.

Carril Pardo, C., Oyarce Merino, K., & Vera-Montecinos, A. (2025). Neuroinflammatory loop in schizophrenia: Is there a relationship with symptoms or cognitive decline? *International Journal of Molecular Sciences, 26*(1), 310.

Chaves, C., Dursun, S. M., Tusconi, M., & Hallak, J. E. (2024). Neuroinflammation and schizophrenia–is there a link?. *Frontiers in Psychiatry*, *15*, 1356975.

Chen, S., Tan, Y., & Tian, L. (2024). Immunophenotypes in psychosis: is it a premature inflamm-aging disorder?. *Molecular Psychiatry*, *29*(9), 2834-2848.

Clausen, M., Christensen, R. H., da Re, M., & Benros, M. E. (2024). Immune cell alterations in psychotic disorders: a comprehensive systematic review

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DOI: https://doi.org/10.33024/minh.v9i6.4030

and meta-analysis. *Biological Psychiatry*, *96*(5), 331-341.

Corlett, P. R., & Fraser, K. M. (2025). 20 years of aberrant salience in psychosis: What have we learned? *American Journal of Psychiatry, 182*(9), 819–829.

Dunleavy, C., Elsworthy, R. J., Upthegrove, R., Wood, S. J., & Aldred, S. (2022). Inflammation in first-episode psychosis: The contribution of inflammatory biomarkers to the emergence of negative symptoms, a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *146*(1), 6-20.

Ermakov, E. A., Mednova, I. A., Boiko, A. S., Buneva, V. N., & Ivanova, S. A. (2023). Chemokine dysregulation and neuroinflammation in schizophrenia: a systematic review. *International journal of molecular sciences*, *24*(3), 2215.

Fu, X., Wu, W., Wu, Y., Liu, X., Liang, W., Wu, R., & Li, Y. (2025). Adult ADHD and comorbid anxiety and depressive disorders: a review of etiology and treatment. *Frontiers in Psychiatry*, *16*, 1597559.

Howes, O. D., Bukala, B. R., & Beck, K. (2024). Schizophrenia: from neurochemistry to circuits, symptoms and treatments. *Nature Reviews Neurology*, *20*(1), 22-35.

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III—The final common pathway. *Schizophrenia Bulletin, 35*(3), 549–562.

Juckel, G., & Freund, N. (2023). Microglia and microbiome in schizophrenia: can immunomodulation improve symptoms?. *Journal of Neural Transmission*, *130*(9), 1187-1193.

Koola, M. M. (2016). Methodological issues in cytokine measurement in schizophrenia. *Indian Journal of Psychological Medicine, 38*(1), 6–9.

Lv, H., Guo, M., Guo, C., & He, K. (2024). The interrelationships between cytokines and schizophrenia: A systematic review. *International Journal of Molecular Sciences, 25*(15), 8477.

McCutcheon, R. A., Reis Marques, T., & Howes, O. D. (2020). Schizophrenia—An overview. *JAMA Psychiatry, 77*(2), 201–210.

Rawani, N. S., Chan, A. W., Dursun, S. M., & Baker, G. B. (2024). The underlying neurobiological mechanisms of psychosis: focus on neurotransmission dysregulation, neuroinflammation, oxidative stress, and mitochondrial dysfunction. *Antioxidants*, *13*(6), 709.

Stefanova, G. (2024). Neuroinflammation as a predictor of psychotic symptom progression. *Journal of Psychiatry, 27*(6), 1000717.

Subramaniam, M., Abdin, E., Vaingankar, J. A., Sambasivam, R., Zhang, Y. J., Shafie, S., & Chong, S. A. (2021). Lifetime prevalence and correlates of schizophrenia and other psychotic disorders in Singapore. *Frontiers in psychiatry*, *12*, 650674.

World Health Organization. (2025). *Schizophrenia*. World Health Organization – Schizophrenia. https://www.who.int/news-room/fact-sheets/detail/schizophrenia.

Zahid, U., Onwordi, E. C., Hedges, E. P., Wall, M. B., Modinos, G., Murray, R. M., & Egerton, A. (2023). Neurofunctional correlates of glutamate and GABA imbalance in psychosis: A systematic review. *Neuroscience & Biobehavioral Reviews, 144*, 105010.

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