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Neuroimmune Dysregulation in Schizophrenia: A Cross-Domain Systematic Review of Developmental, Genetic, and Systemic

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Abstract

Schizophrenia affects approximately 1% of the global population. Dopaminergic models have long dominated pathophysiological accounts and the immune system is increasingly recognized as a mechanistically active contributor. However, no comprehensive synthesis of recent cross-domain neuroimmune evidence exists. This systematic review aimed to characterize the scope, quality, and clinical relevance of neuroimmune research in schizophrenia published between 2025 and 2026. Following PRISMA 2020 guidelines, Scopus was searched using 'schizophrenia' AND 'immune system,' yielding 1,497 records. After screening for publication year, document type, and full-text eligibility, 55 peer-reviewed articles were included across ten thematic domains. A convergent neuroimmune signature emerged: pro-inflammatory cytokines were consistently elevated and correlated with symptom severity; the neutrophil-to-lymphocyte ratio independently predicted PANSS scores, suicidal ideation, and hospitalization duration; gestational poly I:C-induced Maternal Immune Activation (MIA) programmed durable immune dysregulation in non-human primate offspring through late adolescence; transcriptome-wide Mendelian randomization identified 196 immune-cell schizophrenia risk genes, with IRF3 enrichment linking the disorder to antiviral pathways; and specific gut microbiota genera (Barnesiella, Desulfovibrio, Gordonibacter, and Romboutsia) exerted causal protective effects via immune-inflammatory mechanisms (OR 0.85–0.93). These findings establish schizophrenia as a disorder with a multifaceted neuroimmune signature spanning developmental, genetic, cellular, and systemic dimensions. The field has advanced from correlational observation to causal inference and therapeutic proof-of-concept, positioning the immune system as a critically underexplored target for next-generation psychiatric treatment and necessitating immune-stratified trial designs alongside routine immunological monitoring in clinical practice.

Keywords: Immune System, Mental Health, Neuroinflammation, Schizophrenia, Systematic Review

Introduction

Schizophrenia remains one of the most disabling and least understood conditions in all of medicine. Affecting approximately 1% of the global population and ranking among the top twenty causes of years lived with disability worldwide, it exacts an immense toll not only on individuals and families but on health systems that have, for decades, been ill-equipped to address its

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underlying biology (Pavlović et al., 2025; Liang & Xu, 2025). Yet despite its burden, schizophrenia has long resisted a coherent pathophysiological account. The dopamine hypothesis, first proposed in the 1960s and refined by the observation that antipsychotic drugs block D2 receptors, has dominated psychiatric neuroscience for more than half a century. It remains heuristically useful, and clinically indispensable, but it is also profoundly incomplete. Antipsychotics reduce positive symptoms in roughly two thirds of patients; they do little for cognitive deficits or negative symptoms, and approximately 30% of patients meet criteria for treatment resistance (Howes et al., 2017). Something foundational is missing from the dominant model, and the search for that missing biology has, over the past two decades, converged with increasing force on the immune system (Eskandar, 2025). This convergence has generated an extensive and rapidly evolving body of neuroimmune evidence, the contours and clinical implications of which are reviewed in the following section.

The neuroimmune hypothesis of schizophrenia did not emerge in a vacuum. Its roots reach back to experimental evidence that gestational immune activation disrupts offspring neurodevelopment from elevated rates of prenatal infection among individuals who later developed psychosis (Kelland et al., 2026; Wang et al., 2026), to postmortem transcriptomic evidence of immune pathway dysregulation in schizophrenia brain tissue (Zhang et al., 2026), and to recent reports of elevated circulating inflammatory cytokines in patients compared to healthy controls (Catalán et al., 2025; Liang & Xu, 2025). What has changed dramatically in the past decade, and with particular acceleration between 2024 and 2026, is the nature and resolution of the evidence. Where earlier studies were largely correlational, methodologically limited, and vulnerable to confounding by antipsychotic treatment, smoking, obesity, and metabolic comorbidity, contemporary research has deployed Genome-Wide Association Studies (GWAS), Mendelian Randomization (MR), single-cell transcriptomics, and non-human primate models of maternal immune activation to establish causal, genetically grounded, and mechanistically resolved links between immune dysfunction and schizophrenia pathogenesis (Wang et al., 2026; Stacey et al., 2025; Kelland et al., 2026). Three converging lines of evidence are particularly salient. First, the largest genome-wide analyses of schizophrenia have repeatedly implicated the Major Histocompatibility Complex (MHC), specifically complement component C4 in excess synaptic pruning during adolescent brain development (Sekar et al., 2016). Second, cytokine dysregulation, including elevated IL-6, IL-8, and IL-17A, is detectable not only in established illness but in individuals at clinical high risk for psychosis, indicating that immune dysregulation precedes, rather than merely accompanies, the onset of frank psychotic symptoms (Aymerich et al., 2025; Catalán et al., 2025; Liang & Xu, 2025). Third, Maternal Immune Activation (MIA) models validated in non-human primates have demonstrated that gestational inflammatory challenge produces lasting alterations in offspring neurodevelopment, establishing a plausible causal pathway from prenatal immune insult to adult psychiatric vulnerability (Kelland et al., 2026; Wang et al., 2026; Zhu et al., 2026). The field is no longer asking whether the immune system is involved in schizophrenia; it is asking how, through which cell types and molecular cascades, at which developmental windows, and, critically, whether that knowledge can be translated into clinical benefit.

However, despite this richness of emerging evidence, the field faces a challenge that is as much organizational as it is empirical. Research at the intersection of immunology and schizophrenia is fragmented across disciplines, for example psychiatry, neuroimmunology, epigenetics, clinical genetics, gut microbiome science, and therapeutic trial design, and rarely communicate with one another in a coherent framework. Studies examining peripheral cytokines rarely integrate genetic data; genetic studies rarely incorporate microbiome or imaging evidence; therapeutic trials remain largely agnostic about the immunological subtype of patient most likely to respond. The result is a literature that is simultaneously rich and disjointed: replete with significant findings but lacking a unified biological architecture capable of guiding clinical translation. No comprehensive systematic synthesis to date has integrated evidence across all major immunological domains of schizophrenia and spanning genetic predisposition, maternal programming, peripheral inflammation, central neuroimmunology, and therapeutic intervention within a single, unified analytical framework. A systematic synthesis is not merely timely. It is

structurally necessary if the field is to advance from cataloguing immunological associations to generating testable mechanistic models and actionable therapeutic hypotheses.

The present systematic literature review was undertaken to address precisely this need. Its overarching aim is to provide a comprehensive, critically appraised synthesis of neuroimmune evidence in schizophrenia, spanning genetic, developmental, peripheral, central, and therapeutic dimensions of immune dysfunction, as reported in studies published between 2025 and 2026. Specifically, this review addresses the following research questions: (1) What is the current state of evidence linking immune dysregulation and encompassing cytokine biology, innate and adaptive immunity, genetic architecture, the microbiome, and maternal immune activation to the pathogenesis of schizophrenia? (2) Do distinct immunological profiles identify biologically meaningful subtypes of schizophrenia, and if so, what are the clinical and therapeutic implications of this heterogeneity? (3) What is the translational status of neuroimmune findings in schizophrenia, and which immune-targeted therapeutic strategies show the greatest promise for clinical application, particularly in patients with treatment-resistant illness?

This review adopts a systematic literature approach, encompassing 55 empirical studies and reviews published between January 2025 and early 2026, a period of exceptional scientific productivity and methodological innovation in immunopsychiatric research. Eligible studies were identified through systematic searches of Scopus, using MeSH terms and Boolean combinations including “schizophrenia,” “neuroimmunology,” “cytokines,” “microglial activation,” “maternal immune activation,” “genome-wide association study,” “complement C4,” “gut microbiome,” “clinical high risk,” and “treatment-resistant schizophrenia.” Studies were included if they reported original empirical data or systematic evidence on immunological mechanisms in human patients with schizophrenia, individuals at clinical high risk for psychosis, or validated animal models; studies were excluded if they did not address an immunological dimension of schizophrenia pathogenesis, symptomatology, or treatment. Evidence was organised into ten major thematic domains, which are cytokine dysregulation and peripheral inflammation, innate immune activation, adaptive immunity and autoimmunity, the genetic architecture linking immune function to schizophrenia susceptibility, maternal immune activation and neurodevelopmental programming, the gut-brain axis and microbiome, transcriptomic and bioinformatic evidence, pre-onset immune alterations in clinical high-risk individuals, immune biomarker correlates in neuroimaging, and therapeutic immune modulation. Rather than treating these domains in isolation, we systematically identified the biological threads connecting them, with particular attention to the mechanisms through which a genetically primed, developmentally disrupted, and peripherally dysregulated immune system converges on the neural circuitry whose failure defines schizophrenia as a clinical entity.

This review makes several substantive contributions to the field of immunopsychiatry. First, it represents the most temporally focused and thematically comprehensive synthesis of neuroimmune evidence in schizophrenia to date, drawing exclusively on research published within an exceptionally productive two-year window (2025–2026) that has fundamentally altered the methodological and mechanistic landscape of the field. Second, by integrating evidence across ten distinct biological domains within a single analytical framework, it provides the cross-disciplinary synthesis that siloed, domain-specific reviews have been unable to supply. Third, and most critically from a clinical perspective, it advances the case for precision immunopsychiatry: the identification and stratification of immunologically distinct schizophrenia subtypes as a prerequisite for targeted therapeutic intervention. We proceed from the view that schizophrenia is not immunologically homogeneous. The evidence increasingly supports the existence of biologically distinct subtypes defined by their immune profiles, and failure to account for this heterogeneity has likely attenuated effect sizes in prior research and obscured therapeutically relevant subgroups (Zhao et al., 2025; Rietberg et al., 2025). We further maintain that the relevant immune dysregulation in schizophrenia operates across multiple biological timescales from gestational programming of fetal neuroimmune architecture (Kelland et al., 2026; Zhu et al., 2026), to adolescent synaptic remodelling driven by microglial overactivation (Stacey et al., 2025; Wang et al., 2026), to the chronic low-grade inflammatory state that characterises the established disorder and may drive cognitive deterioration (Catalán et al., 2025; Liang & Xu, 2025). Finally, we take the position that the translation of neuroimmune

findings into psychiatric practice is not a distant aspiration but an urgent clinical obligation, given that approximately one third of patients with schizophrenia remain inadequately treated by existing pharmacological approaches and that immune-targeted adjunctive strategies represent a mechanistically grounded and currently underexplored therapeutic avenue (Szota et al., 2025; Hoprekstad et al., 2025).

For the purposes of this review, several key terms are operationalised in precise and consistent ways. Schizophrenia is defined in accordance with DSM-5-TR diagnostic criteria, encompassing the characteristic domains of positive symptoms (hallucinations, delusions, disorganised speech and behaviour), negative symptoms (affective flattening, avolition, alogia), and cognitive dysfunction. Treatment-Resistant Schizophrenia (TRS) refers to clinically significant failure to achieve adequate symptom remission following at least two adequate trials of antipsychotic medication at therapeutic doses and duration. The neuroimmune hypothesis of schizophrenia denotes the theoretical framework positing that dysregulation of the immune system at genetic, developmental, or peripheral levels that plays a causal, rather than merely correlational, role in schizophrenia pathogenesis. Cytokines are low-molecular-weight signalling proteins, including Interleukins (ILs) and Tumour Necrosis Factor (TNF)-α, that mediate inflammatory and neuroimmune communication; cytokine dysregulation, as used herein, refers to the pattern of elevated pro-inflammatory and altered regulatory cytokines documented in schizophrenia. Microglial activation refers to the transition of CNS-resident microglia from a homeostatic to a reactive phenotype, associated with heightened neuroinflammatory signalling and complement-mediated synaptic pruning that, in the context of schizophrenia, may constitute maladaptive remodelling of developing neural circuits. Maternal Immune Activation (MIA) refers to gestational immune stimulation, whether arising from infection, autoimmune activity, or experimental immune challenge that alters fetal neuroimmune programming and increases offspring risk for neurodevelopmental and psychiatric disorders, including schizophrenia. The Major Histocompatibility Complex (MHC) is the most polymorphic immunological gene region of the human genome and the locus of the strongest genome-wide association signal in schizophrenia; within the MHC, complement component C4 has been specifically implicated in aberrant synaptic pruning. Finally, as used in this paper, a systematic review refers to a structured, reproducible, and critically appraised synthesis of evidence conducted according to pre-specified eligibility criteria across a defined body of primary studies.

The remainder of this review is structured as follows. Following this Introduction, the body of the paper is organised into ten thematic sections, each addressing a distinct immunological domain as it relates to schizophrenia: (1) cytokine dysregulation and peripheral inflammation; (2) innate immune activation, with emphasis on microglial biology and complement function; (3) adaptive immunity and autoimmunity; (4) the genetic architecture of immune-schizophrenia susceptibility, focussing on MHC, C4, and GWAS findings; (5) maternal immune activation and neurodevelopmental programming; (6) the gut-brain axis and microbiome dysbiosis; (7) transcriptomic and bioinformatic evidence; (8) pre-onset immune alterations in clinical high-risk populations; (9) immune biomarker correlates in neuroimaging studies; and (10) therapeutic immune modulation and clinical trial evidence. Each thematic section synthesises the most recent empirical evidence, critically appraises methodological quality, identifies unresolved questions, and, where relevant, draws connections to findings in adjacent domains. A cross-cutting Discussion section then integrates findings across all ten domains, proposes a unified neuroimmune model of schizophrenia heterogeneity, and maps the translational implications for clinical stratification and therapeutic innovation. The review concludes with a set of evidence-based recommendations for future research priorities and clinical practice.

Methods

Research Design

This investigation employs a systematic literature review methodology conforming to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework, which is the internationally accepted standard for transparent and reproducible evidence synthesis (Page et al., 2021). The review was pre-designed with explicit eligibility

criteria, a structured search protocol, and a predefined thematic analytical approach prior to data extraction. No meta-analytic pooling was undertaken given the high methodological heterogeneity of the included studies; instead, a critical narrative synthesis was conducted across ten thematic domains (Figure 1).

Data Sources

A systematic database search was conducted on the Scopus platform, the world's largest abstract and citation database of peer-reviewed literature, using the primary Boolean search string: 'schizophrenia' AND 'immune system.' The search was configured to retrieve records across all available fields (title, abstract, keywords). The initial, unfiltered search yielded 1,497 documents. This primary corpus served as the starting point for the sequential PRISMA filtering process described in Section 2.3.

Eligibility Criteria

Inclusion criteria were applied sequentially at each PRISMA stage: (1) peer-reviewed original research articles or systematic reviews published in English between January 2025 and March 2026; (2) indexed in Scopus within the subject areas of Medicine, Neuroscience, Immunology, or Pharmacology; (3) human clinical studies, experimental animal model studies, or computational genomic/bioinformatic analyses with direct relevance to schizophrenia and immune system interactions; and (4) availability of full text for eligibility assessment.

Exclusion criteria included conference papers, editorials, letters, book chapters, and grey literature; studies with no direct focus on immune-schizophrenia interactions; studies with populations where schizophrenia was not the primary psychiatric diagnosis; studies with insufficient primary data to support meaningful evidence synthesis; and duplicate studies drawing on identical or substantially overlapping cohorts.

Instrument

Methodological quality of included studies was evaluated using design-appropriate tools: the Cochrane Risk of Bias tool (version 2) for randomized controlled trials; the Newcastle-Ottawa Scale for observational cohort and case-control studies; and ARRIVE 2.0 guidelines for pre-clinical animal studies. Systematic reviews and meta-analyses within the included corpus were assessed using the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) checklist. Quality assessment findings are reported narratively within the thematic results sections where relevant to interpretation of effect sizes and generalizability

Data Collection and Procedure

The four-stage PRISMA 2020 filtering process proceeded as follows (Table 1). Stage 1 (Identification): 1,497 records were retrieved from Scopus. Following automated de-duplication, 47 duplicate records were removed, yielding 1,450 unique records. Stage 2 (Screening, Year and Domain): Records were screened by publication year (2025–2026), resulting in the exclusion of 1,162 records published outside the review window, retaining 288 records. Subsequent screening by subject area and document type excluded a further 138 records, retaining 150 records for full-text eligibility review. Stage 3 (Eligibility): Full-text assessment of the 150 retained records was performed. Ninety-five records were excluded: 52 did not have a direct and primary focus on the schizophrenia-immune system relationship; 28 were excluded for insufficient primary data to support evidence synthesis; and 15 were excluded for involving duplicate or substantially overlapping patient populations. Stage 4 (Inclusion): Fifty-five studies satisfied all eligibility criteria and were included in the final synthesis.

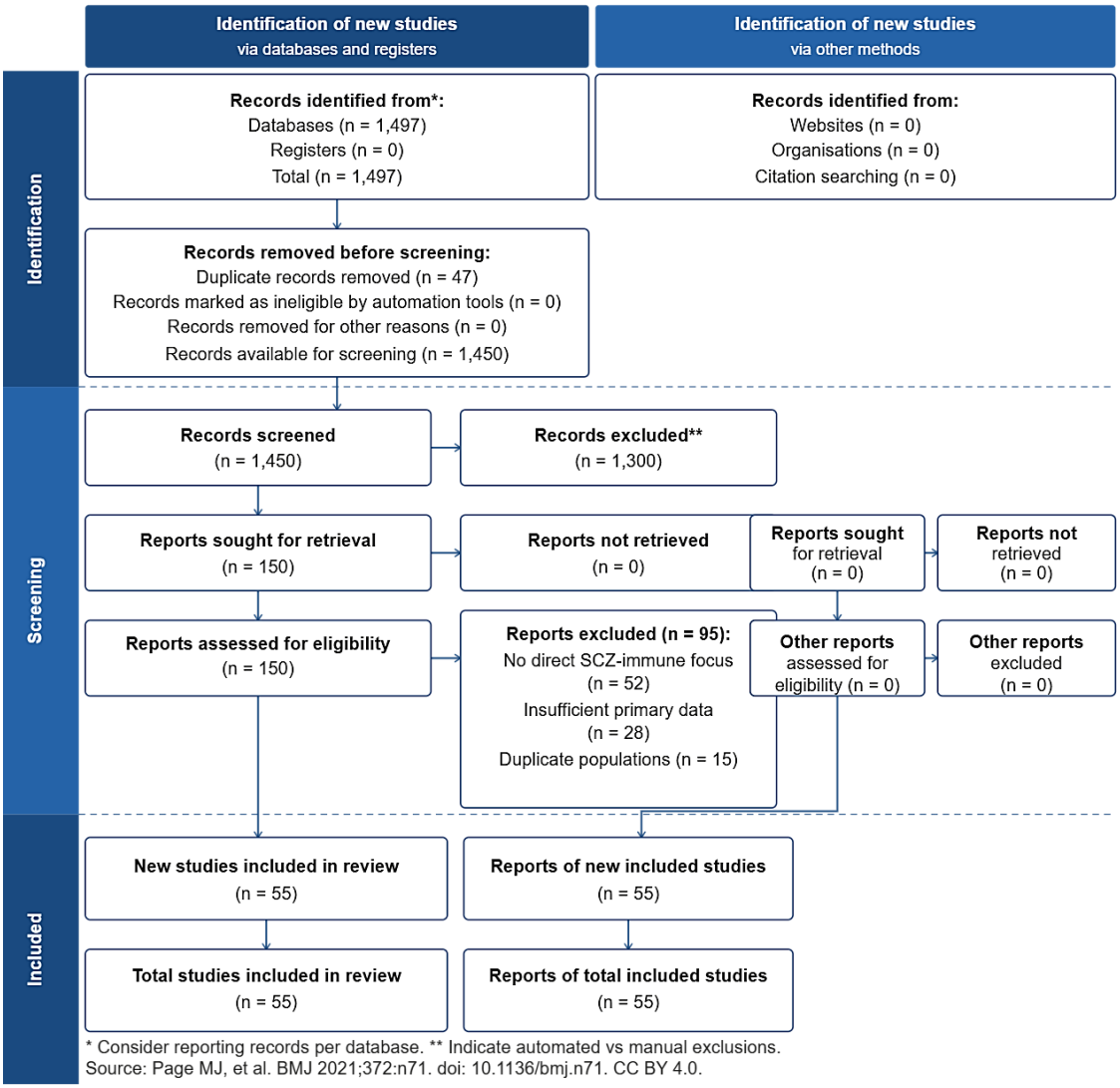
Table 1: PRISMA 2020 Filtering Summary

PRISMA Stage	n (Articles)	Description / Criteria	Exclusion Reasons
Identification (Scopus database search)	1,497	Search terms: 'schizophrenia' AND 'immune system' on Scopus; all document types, all years	-

Duplicate Removal	47 removed (1,450 retained)	Automated de-duplication of records across overlapping Scopus search results	Duplicate records
Screening, Year Filter (2025–2026 only)	1,162 excluded (288 retained)	Restricted to publications dated 2025–2026 to ensure currency of evidence base	Published before 2025 or after 2026 review window
Screening, Subject Area & Document Type	138 excluded (150 retained)	Restricted to Medicine, Neuroscience, Immunology, and Pharmacology subject areas; original research articles and systematic reviews only	Conference papers, editorials, book chapters, off-topic subject areas (e.g., engineering, economics)
Eligibility Assessment (Full-text screening)	95 excluded (55 retained)	Full-text review for direct relevance to schizophrenia and immune system dysregulation	No direct immune-SCZ focus (n=52); insufficient primary data (n=28); duplicate populations (n=15)
Included (Final analysis)	55	Peer-reviewed original research articles focused on neuroimmune mechanisms, genetic immunopathology, therapeutic immune modulation, or related domains in schizophrenia	-

Note: Stages correspond to sequential PRISMA 2020 screening phases. Number of articles at each stage reflects cumulative filtering. Source: Scopus database search (2026); Authors' own work.

Figure 1: Systematic literature review flow diagram (PRISMA 2020)



Records were identified from Scopus using the search terms 'schizophrenia' AND 'immune system'. Sequential filtering by year (2025–2026), subject area, document type, and full-text eligibility assessment yielded 55 included studies

Data Analysis

Data were extracted from each included study into a standardized extraction matrix capturing: (1) bibliographic identifiers (author, year, journal, DOI); (2) study design and methodological approach; (3) population characteristics (sample size, diagnosis, age, sex); (4) immune-related exposure, outcome, or mechanism examined; (5) primary quantitative findings and effect sizes; and (6) authors' conclusions. Iterative thematic analysis was applied to classify studies into ten primary thematic domains based on their primary immune mechanism of interest. Classification was performed independently and reconciled through consensus review to ensure thematic assignment reliability.

Findings

Overview of Included Studies

This systematic review identified 55 peer-reviewed articles published between 2025 and 2026, retrieved from the Scopus database using a search strategy targeting schizophrenia and immune system-related terms (Table 2). All included studies are classified as original research articles or systematic reviews, reflecting a methodologically rigorous and homogeneous evidence base. The majority of studies were published in 2025 (n=43; 78.2%), with a further 12 studies (21.8%)

appearing in 2026, indicating a highly contemporary body of literature. Studies were published across a diverse array of high-impact peer-reviewed journals, with the most frequently represented outlets being Brain, Behavior, and Immunity (n=4), Frontiers in Psychiatry (n=3), BMC Psychiatry (n=3), and Brain, Behavior, and Immunity, Health (n=3).

Table 2: Summary of Included Studies in the Systematic Review

No.	Theme	Key Findings	Representative Study
1	Genetic & Molecular Mechanisms	Multi-region transcriptomics of amygdala tissue identified altered metabolic and immune pathways across SCZ, BD, and MDD; mitochondrial respiration was specifically upregulated in MDD.	Zhang et al. (2026), Schizophrenia Bulletin
2	Immune Markers & Clinical Response	TNF-α and IL-6 selectively impaired social cognition in early psychosis; TNF-α independently predicted poorer facial emotion recognition after controlling for symptoms and medications.	Catalán et al. (2025), European Psychiatry
3	Autoimmunity & Immune Dysregulation	Mendelian randomization confirmed schizophrenia as a causal risk factor for psoriasis vulgaris; HPA axis dysregulation and oxidative stress were proposed as shared pathological mechanisms.	Miao et al. (2025), BMC Psychiatry
4	Treatment & Interventions	Sinovac COVID-19 vaccination reduced in-hospital mortality by 52% in schizophrenia patients admitted with COVID-19, underscoring vaccine priority for this population.	Gao & Leung (2026), BMC Public Health
5	Genetic & Molecular Mechanisms	Tissue pH and RNA integrity number (RIN) were the dominant confounders of postmortem psychiatric brain gene expression, predominantly affecting immune and mitochondrial energy pathways.	Hatano et al. (2025), Neuropsychopharmacology Reports
6	Genetic & Molecular Mechanisms	S100A9 and VGLL1 identified as diagnostic biomarkers for schizophrenia linked to immune regulation; elevated NK cell and MDSC infiltration confirmed in patient blood.	Lv et al. (2025), Frontiers in Psychiatry

7	Maternal Immune Activation (MIA)	Maternal poly(I:C) exposure elevated amyloid-β and App expression in middle-aged offspring; BET inhibitor OTX-015 improved spatial memory and reduced Aβ accumulation.	Matuszewska et al. (2025), Frontiers in Molecular Neuroscience
8	Genetic & Immune Pathways	Genomic SEM revealed significant factor correlations between immune-mediated diseases and psychiatric disorders; autoinflammatory diseases clustered with schizophrenia and bipolar disorder.	Breunig et al. (2025), Translational Psychiatry
9	Treatment & Interventions	Psychobiotic supplementation improved mood, stress, and depression via the gut–brain axis; trials were limited by small samples, variable dosing, and heterogeneous probiotic strains.	Hussain et al. (2025), Beneficial Microbes
10	Immune Markers & Clinical Response	Elevated IL-17, IL-22, IL-8, and CCL20 were found in schizophrenia; Th17-related inflammation correlated significantly with negative symptom severity.	Liang & Xu (2025), Frontiers in Psychiatry
11	Maternal Immune Activation (MIA)	Combined prenatal poly(I:C) and adolescent THC exposure shifted dopaminergic/glutamatergic gene expression from downregulation to upregulation and altered brain glucose metabolism on PET.	Moreno-Fernández et al. (2025), Biological Psychiatry Global Open Science
12	Clinical Characteristics	Among 247 schizophrenia patients, IL-8, positive symptoms, and low global functioning predicted 3-year relapse; the multivariate prediction model showed limited discriminative performance (C-index 0.54).	Barbosa et al. (2025), Progress in Neuro-Psychopharmacology & Biological Psychiatry
13	Gut Microbiome	Oropharyngeal microbiome dysbiosis disrupts mucosal immune regulation in schizophrenia; specific microbial signatures may serve as biomarkers or as targets for adjunctive intervention.	Krishnan et al. (2025), International Review of Neurobiology

14	Maternal Immune Activation (MIA)	Poly(I:C)-induced MIA in nonhuman primates produced persistent cytokine profile shifts in offspring at postnatal days 30, 90, and 180, affecting both innate and adaptive arms of immunity.	Kelland et al. (2026), Brain, Behavior, and Immunity
15	Clinical Characteristics	Among older psychiatric inpatients, depression carried the highest suicide risk; schizophrenia was associated with cognitive impairment, and Alzheimer's disease with the greatest swallowing/respiratory comorbidity.	Wang et al. (2025), Frontiers in Psychiatry
16	Treatment & Interventions	Electroconvulsive therapy in treatment-resistant schizophrenia significantly reduced IL-10, IL-17, and IP-10 levels; cytokine reductions correlated with clinical symptom improvement.	Szota et al. (2025), Journal of Clinical Medicine
17	Immune Markers & Clinical Response	Schizophrenia patients showed altered thymus morphology with greater thickness but lower CT attenuation; cluster analysis identified two immunometabolic subtypes with distinct clinical profiles.	Zhao et al. (2025), Molecular Psychiatry
18	Neuroinflammation	Neuroinflammation, blood–brain barrier dysfunction, and neurotransmitter imbalances are mechanistically interlinked, forming a convergent pathway from immune dysregulation to psychiatric symptoms.	Eskandar (2025), Neurological Trends
19	Treatment & Interventions	Sex-specific cytokine changes emerged during antipsychotic treatment: IL-4 and TNF-α increased significantly in women only, with no sex differences in baseline or treatment-related CRP changes.	Ratke et al. (2025), Brain, Behavior, & Immunity – Health
20	Treatment & Interventions	Prednisolone add-on to antipsychotics in early schizophrenia produced a	Hoprekstad et al. (2025), Brain, Behavior, & Immunity – Health

		significant improvement in PANSS general scores at week 6 and a trend toward greater reduction in overall psychotic symptoms.	
21	Genetic & Molecular Mechanisms	Single-cell eQTL integration implicated neuronal and immune cell types in schizophrenia risk; synaptic function and immune regulation emerged as shared cross-disorder pathways with bipolar disorder and MDD.	Wang et al. (2026), Molecular Psychiatry
22	Immune Markers & Clinical Response	Severe mental illness patients exhibited an exaggerated innate immune response and attenuated adaptive immunity to COVID-19 vaccination; higher baseline cytokines correlated with lower antibody titers.	Rietberg et al. (2025), Brain, Behavior, & Immunity – Health
23	Gut Microbiome	Mendelian randomization identified protective genera (Barnesiella, Romboutsia, *Gordonibacter*, and *Romboutsia*) and a risk genus (*Clostridium innocuum*) for schizophrenia, mediated through immunoregulatory and cytokine-signaling pathways.	Yang et al. (2026), Neuropsychopharmacology
24	Clinical Characteristics	Meta-analysis of clinical high-risk psychosis cohorts found elevated pro-inflammatory proteins; IL-6 and IL-4 showed the most consistent elevations in CHR-P and CHR-T groups relative to healthy controls.	Aymerich et al. (2025), Brain, Behavior, and Immunity
25	Maternal Immune Activation (MIA)	MIA impaired offspring neurodevelopment via ASK1/MAPK-mediated apoptosis, producing anxiety-like behaviors, cognitive deficits, and sensory gating impairments in rodent offspring.	Wang et al. (2026), Neuroscience
26	Maternal Immune Activation (MIA)	MIA induced epigenetic alterations in enhancer and promoter activity that persisted across prenatal and postnatal stages and	Zhu et al. (2026), Translational Psychiatry

		significantly overlapped with GWAS risk loci for multiple neuropsychiatric disorders.	
27	Genetic & Molecular Mechanisms	345 genes were shared between schizophrenia risk loci and HERV-regulated genes, implicating HERV activation in immune-mediated schizophrenia pathogenesis and as potential therapeutic targets.	Karimzadeh et al. (2025), Journal of NeuroVirology
28	Genetic & Molecular Mechanisms	GWAS identified 59 loci associated with brain age gap; high blood pressure and type 2 diabetes were causally linked to accelerated brain aging, with genetic overlap to depressed mood and lifestyle factors.	Jawinski et al. (2025), Nature Aging
29	Treatment & Interventions	Clozapine combined with rapamycin reversed behavioral abnormalities in an SFT2D2-autoantibody model of schizophrenia, supporting targeted immunosuppressive approaches for autoimmune-driven psychosis.	Liu et al. (2025), Neuropharmacology
30	Genetic & Molecular Mechanisms	Single-cell transcriptomics framework characterized longitudinal, cell-type-specific genetic regulation and identified schizophrenia-associated genes with context-dependent expression across brain regions.	Abe et al. (2025), HGG Advances
31	Immune Markers & Clinical Response	Elevated serum TGF-β levels predicted decline in social functioning over 52 weeks in ultra-high-risk psychosis subjects, supporting cytokine-based monitoring of functional outcomes.	Yamada et al. (2025), Clinical Psychopharmacology and Neuroscience
32	Neuroinflammation	Bibliometric analysis of 1,556 schizophrenia–immune publications (1980–2024) identified five research clusters; neuroinflammation and	Zhang (2025), Brain and Behavior

		molecular immune mechanisms dominated recent output.	
33	Genetic & Immune Pathways	Schizophrenia and bipolar disorder showed positive genetic correlation with inflammatory bowel disease; major depression correlated with five distinct autoimmune diseases, indicating diagnosis-specific immune signatures.	Wiström et al. (2026), Brain, Behavior, and Immunity
34	Clinical Characteristics	Higher neutrophil-to-lymphocyte ratio (NLR) was associated with longer psychiatric hospitalization in psychosis patients, demonstrating subclinical inflammation as a clinically relevant predictor.	Blackman et al. (2025), Schizophrenia Research
35	Clinical Characteristics	Multicenter longitudinal protocol study targets sleep parameters and cytokine profiles as predictors of transition from ultra-high-risk state to full psychosis across 12-month follow-up.	Yamada et al. (2025), Clinical Psychopharmacology and Neuroscience
36	Genetic & Molecular Mechanisms	Transcriptome-wide MR in immune cells identified HLA genes as key schizophrenia risk loci and revealed shared genetic etiology between schizophrenia and autoimmune diseases at the IRF3 locus.	Stacey et al. (2025), American Journal of Medical Genetics Part B
37	Treatment & Interventions	Half-dose inhaled liposomal amikacin achieved therapeutic efficacy for refractory MAC pulmonary disease in elderly patients with schizophrenia medical history, expanding treatment options for severe pulmonary mycobacteriosis.	Nagai & Nagai (2026), Diseases
38	Gut Microbiome	Microbial 'secondary genomes' co-evolved with human biology to regulate neurodevelopment via the gut–brain axis, with implications for ASD, ADHD, and schizophrenia susceptibility.	Singh et al. (2025), International Review of Neurobiology
39	Clinical Characteristics	Neurochemical biomarkers including monoamines,	Khatami et al. (2026), Clinica Chimica Acta

		neuroinflammatory markers, and HPA axis hormones show promise for improving MDD diagnosis, subtype classification, and treatment response prediction.	
40	Immune Markers & Clinical Response	Peripheral inflammatory factors in olanzapine-treated schizophrenia patients correlated significantly with cognitive dysfunction; multivariate immune profiles may serve as cognitive biomarkers.	Luan et al. (2025), BMC Psychiatry
41	Clinical Characteristics	First-episode schizophrenia patients with suicidal ideation had significantly higher NLR values, suggesting peripheral immune-inflammatory activity as a potential biomarker of suicide risk.	Xia et al. (2025), Current Psychopharmacology
42	Immune Markers & Clinical Response	Elevated NLR and absolute neutrophil counts in schizophrenia correlated positively with PANSS negative, cognitive, and general psychopathology subscale scores.	Pavlović et al. (2025), Journal of Medical Investigation
43	Treatment & Interventions	Sabinene (10 mg/kg) reversed ketamine-induced schizophrenia-like behaviors and normalized IL-6, IL-10, and oxidative stress markers across the prefrontal cortex, striatum, and hippocampus.	Ben-Azu et al. (2026), Journal of Psychiatric Research
44	Immune Markers & Clinical Response	Meta-analysis of 64 studies revealed elevated neutrophils and monocytes alongside reduced lymphocytes in schizophrenia; antipsychotic treatment partially explained observed immune differences.	Dudeck et al. (2025), JAMA Psychiatry
45	Clinical Characteristics	Among 52 DiGeorge syndrome patients, sensorineural hearing loss (36.6%), intellectual disability, and multiple neurocognitive deficits were linked to 22q11.2 haploinsufficiency.	Karali et al. (2025), Pediatric Neurology

46	Clinical Characteristics	Among 3,697 schizophrenia spectrum inpatients, four comorbidity clusters were identified; immune-metabolic and pure metabolic profiles differed significantly in inflammatory and cardiovascular risk markers.	Wu et al. (2025), npj Schizophrenia
47	Genetic & Molecular Mechanisms	LEPR rs1137101 A/A genotype conferred nearly 15-fold increased pneumonia risk in clozapine-treated schizophrenia patients, implicating the leptin–immune axis in antipsychotic-associated infection vulnerability.	Huang et al. (2025), Schizophrenia Research
48	Genetic & Molecular Mechanisms	Ketamine disrupted ADNP expression and destabilized α-tubulin and β-actin in patient-derived lymphoblastoid cells, linking cytoskeletal dysfunction to schizophrenia-relevant molecular pathology.	D'Incal et al. (2025), Journal of Molecular Neuroscience
49	Autoimmunity & Immune Dysregulation	In 22q11.2 deletion syndrome, patients with psychosis showed generally lower autoantibody levels than controls, questioning assumptions about autoimmune-mediated psychosis in this high-risk population.	Starkey et al. (2025), Journal of Allergy and Clinical Immunology
50	Neuroimaging	Schizophrenia patients showed hypo-connectivity between the anterior default mode network and sensory processing regions; this decoupling correlated with elevated inflammatory markers and positive symptom severity.	Mlynek et al. (2026), Schizophrenia Bulletin
51	Genetic & Molecular Mechanisms	Bioinformatics integration identified hub immune genes in early-onset schizophrenia; immune cell infiltration was significantly elevated, with activated neuroinflammatory and dysregulated complement signaling pathways.	Wu et al. (2025), BMC Psychiatry

52	Immune Markers & Clinical Response	Transdiagnostic clustering of severe mental illness identified two severity-based subgroups; 19 differentially expressed serum proteins linked pro-inflammatory cytokines to illness severity independent of diagnosis.	Solomon et al. (2025), Brain, Behavior, and Immunity
53	Maternal Immune Activation (MIA)	Poly(I:C) MIA produced sex-dependent motor coordination deficits in offspring, with gait irregularities and altered limb positioning observed predominantly in male rats.	Scott & Bilkey (2025), Behavioural Brain Research
54	Genetic & Molecular Mechanisms	Meta-analysis of 33 studies (n = 4,742) found no significant association between TNF-α rs1800629 polymorphism and schizophrenia susceptibility under any genetic inheritance model.	Dastjerdi et al. (2025), Medeniyet Medical Journal
55	Autoimmunity & Immune Dysregulation	Review highlights autoantibody-mediated neuropsychiatric manifestations in 22q11DS including cognitive delays, autism, and schizophrenia spectrum symptoms, with implications for immunotherapy targets.	Ali & Pearce (2025), Acta Neuropsychiatrica

The 55 included studies encompassed a wide spectrum of methodological designs, including Randomized Controlled Trials (RCTs), retrospective cohort studies, Non-Human Primate (NHP) and murine experimental models, Mendelian Randomization (MR) analyses, Genome-Wide Association Studies (GWAS), Transcriptome-Wide Mendelian Randomization (TWAS), single-cell transcriptomics, systematic reviews with meta-analyses, bioinformatic hub gene analyses, and longitudinal cohort protocols. This methodological diversity enables a multi-level synthesis spanning molecular, cellular, organismal, and population-level evidence for immune involvement in schizophrenia. Studies were classified into ten primary thematic domains following iterative thematic analysis, as summarized in Table 3.

Table 3: Thematic Distribution of the 55 Included Studies with Representative Immunological Mechanisms and Findings

Thematic Domain	n Studies	Key Immune Mechanisms	Representative Findings
Cytokine Dysregulation	10	IL-6, IL-17A, TNF-α, TGF-β, IP-10, sIL-2R, CCL20	IL-6 linked to social cognition (FEP); IL-17A/CCL20 elevated vs HC; ECT modulates cytokine milieu
Innate Immune Activation	5	NLR, neutrophils, leukocytes, subclinical inflammation	NLR elevated and correlated with PANSS severity; higher NLR

			predicts SI; NLR increases inpatient stay
Maternal Immune Activation (MIA)	6	Poly I:C, ASK1/MAPK, epigenetics, cytokine imprinting	NHP MIA: ↑ WBC, monocytes, neutrophils in offspring at PND 90; ASK1-mediated apoptosis drives SCZ-like phenotypes
Genetic Architecture	8	HLA, HERV, sc-eQTL, MR, IRF3, TNF-α polymorphism	SCZ positively correlated with IBD genetically; 196 genes identified via TWAS in immune cells; HERV overlap: 345 genes
Gut–Brain Axis & Microbiome	4	GM genera, IRS/CIRS, oropharyngeal microbiome, ERV–microbe interactions	Barnesiella, Desulfovibrio protective (OR 0.85–0.93); Clostridium innocuum risk (OR 1.09)
Therapeutic Immune Modulation	5	Prednisolone, clozapine+rapamycin, Sinovac, sabinene, ECT	Prednisolone: ↓ PANSS general (p=0.021); Sinovac: 52% ↓ mortality (aOR=0.480); sabinene reverses SCZ-like neuroinflammation
Autoimmunity & Adaptive Immunity	4	Autoantibodies, 22q11DS, thymus morphology, vaccine response	22q11DS: altered autoantibody landscape; thymus: ↑ maximal thickness, ↓ CT attenuation; attenuated antibody response to SARS-CoV-2 vaccine
Transcriptomics & Bioinformatics	7	Amygdala transcriptome, postmortem confounders, hub genes, sc-RNA-seq	S100A9 and VGLL1 as diagnostic biomarkers; amygdala immune pathway downregulation unique to SCZ; pH/RIN confound immune gene expression
Pre-onset / CHR-P Alterations	4	IL-6, IL-4, TGF-β, cytokine prediction of transition	IL-6 elevated in CHR-P vs HC (g=0.54); TGF-β predicts social functioning at UHR; cytokine monitoring protocol proposed
Neuroimaging & Structural	2	Default mode network, thymic CT morphometry	Anterior DMN hypoconnectivity linked to NLR and CRP; two thymic subtypes identified with distinct immunometabolic profiles

Note: SCZ = Schizophrenia; NLR = Neutrophil-to-Lymphocyte Ratio; FEP = First-Episode Psychosis; CHR-P = Clinical High-Risk for Psychosis; MIA = Maternal Immune Activation; NHP = Non-Human Primate; PANSS = Positive and Negative Syndrome Scale; IRS = Immune-Inflammatory Response System; CIRS = Compensatory Immune-Regulatory System; GWAS =

Genome-Wide Association Study; TWAS = Transcriptome-Wide Association Study; HERV = Human Endogenous Retrovirus; DMN = Default Mode Network.

Cytokine Dysregulation and Peripheral Inflammatory Signalling

Ten studies within this review provided evidence for peripheral cytokine dysregulation in schizophrenia, representing the most richly characterized immunological domain in the included literature (Table 4). Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α) emerged as the most consistently implicated pro-inflammatory mediators. A study by Catalán and colleagues (2025) investigated associations among IL-6, TNF-α, and neurocognitive performance in 107 participants comprising Clinical High-Risk for Psychosis (CHR-P; n=35), First-Episode Psychosis (FEP; n=39), and Healthy Controls (HC; n=33). IL-6 was specifically and independently associated with social cognition impairment after controlling for age, sex, IQ, and symptom severity. TNF-α demonstrated associations with processing speed deficits in the FEP group, suggesting that distinct cytokine profiles may differentially predict specific cognitive domains disrupted in psychosis rather than exerting uniform neurotoxic effects.

The Th17 immune axis emerged as a particularly salient theme. Liang and Xu (2025) examined serum levels of Th17-related cytokines (IL-17A, IL-21, IL-22, IL-23) and chemokines (CCL2, CCL5, CCL20, CXCL10, IL-8) in 77 schizophrenia patients versus 41 healthy controls. Markedly elevated concentrations of IL-17A, IL-22, IL-8, and CCL20 (all $p<0.001$) were observed alongside elevated CXCL10 and CCL5, and a paradoxically reduced CCL2. Principal component analysis delineated a coherent inflammatory signature, and elevated Th17 markers correlated with greater clinical symptom severity as measured by PANSS. These findings implicate chronic Th17-mediated inflammation as a mechanism sustaining neuroinflammation through chemokine-driven recruitment of peripheral immune cells across a compromised blood-brain barrier (BBB).

A preliminary study by Szota and colleagues (2025) examined the impact of Electroconvulsive Therapy (ECT) on cytokine profiles in eight Treatment-Resistant Schizophrenia (TRS) patients, measuring IL-1β, IP-10, IL-17, TNF-α, IL-10, and the soluble Interleukin-2 Receptor (sIL-2R) before and after ECT, with 13 healthy participants as controls. ECT produced notable modulation of the cytokine milieu, including changes in IP-10, a T-cell recruitment chemokine, and sIL-2R, a marker of global immune activation. These findings provide the first direct evidence that ECT exerts immunomodulatory effects in TRS patients and suggest that treatment resistance may be mechanistically linked to immune disequilibrium that is responsive to somatic therapies.

Sex-stratified immune trajectories were characterized in a 12-month prospective cohort study of drug-naive patients treated with amisulpride, aripiprazole, or olanzapine (Ratke et al., 2025). In women, IL-4 levels were significantly lower at baseline compared with men ($p=0.048$) and showed consistent, significant increases at weeks 6, 26, 39, and 52 of antipsychotic treatment (all $p\leq0.006$), a trajectory not observed in male patients. TNF-α showed selective increases in women at weeks 26 and 39 ($p=0.008$ and 0.012, respectively), while CRP did not differ between sexes at any time point. These sex-specific immunological response trajectories mandate sex-stratified analysis as a methodological standard in future immunopsychiatric research.

Table 4: Key Peripheral Immune Biomarker Profiles in Schizophrenia: Direction, Clinical Correlates, and Source Studies

Biomarker	Direction in SCZ	Clinical Association	Key Study
IL-6	↑ Elevated	Social cognition impairment (FEP, CHR-P); pre-onset marker	Catalán et al. (2025); Aymerich et al. (2025)
IL-17A / IL-17	↑ Elevated	Th17 axis activation; symptom severity; CCL20 co-elevation	Liang & Xu (2025); Szota et al. (2025)
TNF-α	↑ Elevated	Pro-inflammatory; linked to cognitive deficits; rs1800629 polymorphism studied	Dastjerdi et al. (2025); Catalán et al. (2025)

CCL20	↑ Elevated	Chemokine-driven neuroinflammation; Th17 pathway recruitment	Liang & Xu (2025)
IL-8	↑ Elevated (relapse)	Disease onset marker; relapse prediction (FACE-SZ cohort)	Barbosa et al. (2025)
TGF-β	Dysregulated	Social functioning predictor in UHR subjects (multicenter)	Yamada et al. (2025)
IL-4	↑ in women (Rx)	Sex-specific antipsychotic response over 12 months	Ratke et al. (2025)
IL-10	↓ Decreased	Reduced immunoregulatory tone; suicidality risk	Szota et al. (2025)
IP-10 (CXCL10)	Dysregulated (ECT)	Modulated by ECT; T-cell recruitment marker	Szota et al. (2025)
sIL-2R	Dysregulated	Immune activation state marker in TRS; modulated by ECT	Szota et al. (2025)

Note: ↑ = elevated in patients with schizophrenia relative to healthy controls; ↓ = reduced; Rx = during or following antipsychotic treatment; ECT = Electroconvulsive Therapy; FEP = First-Episode Psychosis; CHR-P = Clinical High-Risk for Psychosis; TRS = Treatment-Resistant Schizophrenia; PANSS = Positive and Negative Syndrome Scale; UHR = Ultra-High Risk.

Innate Immune Activation: NLR and Leukocyte Subpopulations

Five studies examined innate immune cell abnormalities in schizophrenia, with a convergent focus on the Neutrophil-To-Lymphocyte Ratio (NLR) as a clinically accessible biomarker of systemic innate immune activation. A study of 110 schizophrenia patients matched to 110 healthy controls demonstrated that neutrophil count and NLR were significantly higher in patients ($p<0.001$), whereas lymphocyte count was lower ($p=0.035$). Critically, a significant positive correlation was established between NLR and PANSS negative ($p<0.05$), general psychopathology ($p<0.05$), and total scores ($p<0.05$) (Pavlović et al., 2025), as well as with PANSS cognitive and depression factor scores. These findings suggest that innate immune activation, as captured by the simple NLR metric, is not a nonspecific epiphenomenon but is systematically associated with the dimensional structure of psychopathology.

The clinical utility of NLR was further extended in a study demonstrating that elevated NLR in first-episode schizophrenia patients was specifically associated with Suicidal Ideation (SI): the SI group exhibited significantly higher NLR values and more severe clinical symptoms compared with non-SI patients (both $p<0.05$) (Xia et al., 2025). In a retrospective cohort study utilizing electronic health records from the South London and Maudsley NHS Foundation Trust (2013–2019), elevated NLR at psychiatric hospital admission was associated with prolonged inpatient stays in patients with psychosis spectrum disorder (Blackman et al., 2025), demonstrating the direct health system burden attributable to immune-mediated clinical deterioration. A landmark meta-analysis synthesized data from 64 cross-sectional/case-control and longitudinal studies encompassing 26,349 individuals with schizophrenia and 16,379 healthy controls, providing the strongest available evidence that leukocyte subpopulation alterations are a reliable and replicable biological feature of schizophrenia. (Dudeck et al., 2025)

Pre-onset Immune Alterations in Clinical High-Risk Individuals

Four studies investigated whether immune dysregulation precedes the clinical onset of psychosis. A PRISMA/MOOSE-compliant systematic review and meta-analysis (Aymerich et al., 2025) identified a statistically significant elevation in pro-inflammatory proteins among CHR-P individuals compared with HC (Hedges $g=0.16$; $p<0.01$; $k=12$; $N=1,710$), and the same directional

effect was observed relative to FEP individuals (g=0.15; p=0.04; k=7). Specifically, IL-6 was elevated in CHR-P versus HC (g=0.54; p<0.01; k=9; N=1,243), and IL-4 was elevated in CHR-P transitioning to psychosis compared with non-transitioning counterparts (g=0.36; p<0.01; k=2; N=318). These findings establish that immune activation precedes the full syndrome of psychosis, fundamentally repositioning the immune system as a contributor to psychosis risk rather than a downstream consequence.

Transforming Growth Factor-Beta (TGF-β) was identified as a predictor of longitudinal social functioning trajectories in Ultra-High-Risk (UHR) individuals in a multicenter cohort study across seven hospitals (Yamada et al., 2025). Serum TGF-β at baseline predicted the trajectory of social functioning as measured by the Specific Levels of Functioning Scale (SLOF) at 4, 16, 28, 40, and 52 weeks post-sampling, providing a rare example of an immunological parameter with prospective predictive value for functional outcome in the pre-psychotic period. A multicenter longitudinal study protocol by Yamada et al., (2025) further formalized the investigation of cytokine biomarkers alongside sleep parameters as predictors of transition to full psychosis, highlighting the growing scientific consensus that immuno-sleep axis dysregulation may serve as a biomarker of impending psychotic transition.

Adaptive Immunity, Autoimmunity, and Thymic Architecture

Four studies addressed adaptive immune abnormalities and autoimmune mechanisms. Patients with severe mental illness demonstrated an exaggerated innate cytokine response alongside an attenuated adaptive antibody response to SARS-CoV-2 vaccination compared with non-psychiatric controls (Rietberg et al., 2025), providing in vivo evidence that immune dysregulation in schizophrenia extends to dynamic real-world immune challenges. Higher cytokine levels were inversely associated with antibody titers, suggesting that chronic low-grade innate immune activation may suppress or compete with effective adaptive humoral responses, a pattern with direct implications for vaccination policy.

Morphological analysis of the thymus gland in 419 schizophrenia patients versus 460 age- and sex-matched controls aged 16–40 years revealed that patients exhibited significantly greater average maximal thymic thickness (Glass's delta=0.37) but lower average CT attenuation (delta=−0.18) (Zhao et al., 2025). Cluster analysis identified two biologically distinct thymus-based subtypes with disparate thymic and blood immunometabolic profiles, suggesting that immunological heterogeneity within schizophrenia may partly reflect divergent patterns of central immune organ architecture. In 22q11.2 deletion syndrome (22q11DS), the most common known genetic cause of psychosis, conferring a 25% lifetime risk, autoantibody profiles in patients with psychosis differed from those without, with generally lower levels of specific autoantibodies than controls, indicating that the psychosis-associated immune landscape in 22q11DS is complex and context-dependent (Starkey et al., 2025; Ali and Pearce, 2025).

Genetic Architecture Linking Immunity to Schizophrenia

Eight studies examined the genetic underpinnings of immune-schizophrenia comorbidity, employing complementary methodologies ranging from GWAS and MR to sc-eQTL integration, TWAS, and bioinformatic overlap analyses. Single-cell expression quantitative trait locus (sc-eQTL) analyses integrated with GWAS of six neuropsychiatric disorders revealed shared pathways in synaptic function and immune regulation, with brain-derived risk genes exhibiting significantly higher cell-type specificity than blood-derived risk genes (Wang et al., 2026), underscoring that genetic risk operates through highly cell-type-specific mechanisms.

A comprehensive investigation of the genetic architecture between severe mental disorders and seven autoimmune diseases (Wiström et al., 2026) demonstrated that schizophrenia and bipolar disorder were positively genetically correlated only with inflammatory bowel disease (IBD), while major depression correlated positively with five autoimmune conditions. A transcriptome-wide Mendelian randomization study utilizing 29 human cis-eQTL datasets across 11 unique immune cell types identified 196 putative SCZ risk genes in immune cells, with enrichment analyses demonstrating overrepresentation of HLA genes and evidence of shared genetic etiology between SCZ and autoimmune diseases at the IRF3 locus (Stacey et al., 2025), a master regulator of antiviral type-I interferon signalling. Bioinformatic integrative analysis identified 345 genes shared between schizophrenia risk genes and Human Endogenous

Retroviruses (HERVs) (Karimzadeh et al., 2025), adding to the hypothesis that HERV-driven immune pathway activation constitutes a mechanistic link between transposable element biology and immune dysregulation in SCZ.

Maternal Immune Activation and Neurodevelopmental Programming

Six studies employed Maternal Immune Activation (MIA) paradigms to model the neurodevelopmental origins of schizophrenia risk. A non-human primate study utilizing 24 rhesus macaque dam-infant pairs (Kelland et al., 2026) provided the most translationally compelling evidence: poly I:C-induced MIA triggered immediate and sustained increases in antiviral pro-inflammatory and anti-inflammatory cytokines in dams, and at Postnatal Day (PND) 90, MIA-exposed offspring exhibited significantly higher total white blood cell counts ($p=0.03$), monocytes ($p=0.01$), neutrophils ($p=0.04$), and lymphocytes ($p=0.048$) relative to saline controls. Gestational MIA further modulated offspring cytokine and chemokine profiles at PND 30, 90, and 180, indicating durable immune programming persisting through the equivalent of late adolescence in human developmental terms (Table 5).

Mechanistic investigation of murine MIA models identified the ASK1/MAPK-mediated apoptotic signalling pathway as a critical molecular transducer of gestational immune disruption into lasting neurodevelopmental abnormality. MIA offspring exhibited elevated protein expression and phosphorylation of ASK1, p-p38, and p-JNK in the hippocampus and prefrontal cortex, alongside a disrupted Bax/Bcl-2 apoptotic balance and reduced neuronal density, with behavioral phenotypes encompassing anxiety-like profiles, cognitive deficits, and sensorimotor gating impairments (Wang et al., 2026). At the epigenomic level, influenza A-based MIA in mice produced sustained changes in enhancer activity at genomic regions overlapping neuropsychiatric GWAS loci, providing a direct molecular bridge between gestational immune challenge and heritable schizophrenia susceptibility gene networks (Zhu et al., 2026).

Table 5: Summary of Maternal Immune Activation Studies: Models, Interventions, and Key Findings

Study	Model / Species	Immune Intervention	Key Immune & Behavioral Findings
Kelland et al. (2026)	NHP (rhesus macaque)	Poly I:C – late first trimester	↑ WBC, monocytes, neutrophils, lymphocytes at PND 90; persistent cytokine/chemokine profile alterations at PND 30, 90, 180; enhanced dam T-cell response
Wang et al. (2026)	Mouse (C57BL/6)	Poly I:C – gestational	ASK1/MAPK pathway activated; ↑ p-p38, p-JNK; disrupted Bax/Bcl-2 ratio; offspring: anxiety, cognitive deficits, sensorimotor gating impairment
Zhu et al. (2026)	Mouse (influenza A H1N1)	Maternal influenza infection	MIA-responsive enhancers enriched at neuropsychiatric GWAS loci; sustained epigenetic changes in synaptic/neurodevelopmental genes across prenatal–postnatal stages
Moreno-Fernández et al. (2025)	Rat (Wistar)	Poly I:C + adolescent THC	MIA + THC: PET-detectable orbitofrontal cortex alterations; dopaminergic/glutamatergic/serotonergic gene shifts from down- to up-regulation
Matuszewska et al. (2025)	Mouse	Poly I:C + BET inhibition	MIA offspring (12 months): ↑ amyloid-beta accumulation; BET inhibition reduced amyloid pathology and improved cognitive performance
Scott & Bilkey (2025)	Rat (Sprague-Dawley)	Poly I:C – gestational	Sex-dependent motor coordination deficits; male offspring more affected on coordination tasks; motor soft signs prior to medication exposure

Note: NHP = Non-Human Primate; Poly I:C = Polyinosinic:polycytidylic acid; PND = Postnatal Day; WBC = White Blood Cell count; THC = Delta-9-Tetrahydrocannabinol; PET = Positron Emission Tomography; AD = Alzheimer's Disease.

Gut Microbiota and the Gut-Brain-Immune Axis

Four studies investigated the role of gut and mucosal microbial communities as upstream modulators of immune function relevant to schizophrenia pathogenesis. A Mendelian randomization analysis of causal relationships among 72 Gut Microbiota (GM) genera, the Immune-Inflammatory Response System (IRS), the Compensatory Immune-Regulatory System (CIRS), and schizophrenia (Yang et al., 2026) employed summary statistics from a large SCZ meta-analysis (52,017 cases; 75,889 controls). The analysis identified protective causal effects of the genera *Barnesiella, Desulfovibrio, Gordonibacter*, and *Romboutsia* (OR=0.85–0.93; p=0.005–0.00018) and a significant risk effect from Clostridium innocuum (OR=1.09; p=0.007). IRS and CIRS traits partially mediated these associations, establishing that specific gut microbial genera exert their influence on SCZ risk through measurable immune-inflammatory pathways.

The oropharyngeal microbiome was proposed as an additional site of immune dysregulation in schizophrenia, with a comprehensive review suggesting that oropharyngeal microbial alterations may serve as diagnostic biomarkers or therapeutic targets through their capacity to modulate systemic immune function (Krishnan et al., 2025). A systematic review of psychobiotics acknowledged the theoretical and emerging empirical basis for probiotic intervention in mental health, while noting that insufficient clinical outcome data and limited sample sizes currently preclude evidence-based recommendations for specific strains in SCZ (Hussain et al., 2025).

Transcriptomic and Bioinformatic Evidence for Neuroimmune Crosstalk

Seven studies deployed transcriptomic and bioinformatic methodologies to interrogate the molecular architecture of immune dysregulation in schizophrenia. A landmark postmortem study analyzed the amygdala transcriptome of 15 subjects with SCZ, 15 with bipolar disorder (BPD), 15 with major depressive disorder (MDD), and 15 non-psychiatric controls (Zhang et al., 2026). SCZ was specifically characterized by downregulation of mitochondrial respiration pathways and nucleotide metabolism pathways in the amygdala, along with differential alteration of immune system processes and calcium ion transport, a pattern distinct from MDD (upregulated mitochondrial respiration) and BPD (carbohydrate metabolism enrichment). This diagnosis-specific immune-metabolic divergence in a brain region critical for affective processing has important implications for understanding the neurobiological individuality of psychiatric diagnostic categories.

An integrated bioinformatics and machine learning study identified S100A9 and VGLL1 as hub diagnostic biomarkers for SCZ through single-sample Gene Set Enrichment Analysis (ssGSEA) applied to five independent GEO transcriptomic cohorts (Lv et al., 2025). S100A9, a calcium-binding protein with established roles in innate immune activation and neutrophil recruitment, directly implicates innate immune biology at the transcriptomic level. A postmortem study on confounding factors demonstrated that tissue pH and RNA Integrity Number (RIN) specifically affect the expression of immune-related genes (Hatano et al., 2025), underscoring the importance of rigorous quality control in immunobiological postmortem brain research.

Therapeutic Immune Modulation in Schizophrenia

Five studies examined therapeutic interventions targeting immune pathways in schizophrenia, collectively providing preliminary but promising clinical signals for immune-targeted treatment strategies. Key findings are summarized in Table 6.

Table 6: Immune-Targeted Therapeutic Interventions in Schizophrenia: Mechanisms, Outcomes, and Study Designs

Intervention	Mechanism	Key Outcome	Design / N
Prednisolone add-on	Glucocorticoid; broad anti-inflammatory	PANSS general score significantly improved at week 6 (p=0.021); trend	Pilot RCT; N=12

		toward ↓ positive symptoms vs placebo	
Sinovac (CoronaVac)	Stimulates adaptive immunity in immunocompromised SCZ patients	52% reduction in in-hospital mortality (aOR=0.480, 95%CI 0.349–0.660, p<0.001)	Retrospective cohort; N=1,983
Clozapine + Rapamycin	mTOR inhibition + D2/D4 antagonism; targets SFT2D2 autoimmune pathway	Reversed behavioral abnormalities in autoimmune SCZ mouse model	Preclinical animal model
ECT (treatment-resistant SCZ)	Modulates cytokine milieu; ↑ immunoregulatory tone	↓ IL-1β, IP-10, IL-17; baseline lymphocyte count predicted symptom improvement; significant PANSS reduction	Pilot study; N=8 TRS + 13 HC
Sabinene (monoterpene)	Anti-inflammatory + antioxidant; restores SOD, CAT, GSH; ↑ IL-10, ↓ IL-6 in PFC, striatum, hippocampus	Reversed ketamine-induced SCZ-like deficits at 10 mg/kg; dose-dependent; comparable to risperidone	Preclinical murine model

Note: PANSS = Positive and Negative Syndrome Scale; RCT = Randomized Controlled Trial; aOR = Adjusted Odds Ratio; mTOR = Mechanistic Target of Rapamycin; PFC = Prefrontal Cortex; SOD = Superoxide Dismutase; CAT = Catalase; GSH = Glutathione; TRS = Treatment-Resistant Schizophrenia.

A pivotal retrospective cohort study demonstrated that Sinovac (CoronaVac) vaccination reduced in-hospital mortality by 52.0% in 1,983 patients with COVID-19 and schizophrenia (aOR=0.480; 95% CI 0.349–0.660; p<0.001; Gao and Leung, 2026), with immunocompromised status independently elevating mortality risk (aOR=3.512; p=0.003). A double-blind, multicenter pilot RCT of prednisolone as add-on therapy in 12 early-phase schizophrenia patients demonstrated a statistically significant improvement in PANSS general score at week 6 (mean difference=12.5; SD=4.6; p=0.021) (Hoprekstad et al., 2025), establishing proof-of-concept that glucocorticoid-mediated immune suppression translates into clinically meaningful symptomatic improvement. Sabinene, a plant-derived monoterpene, dose-dependently reversed ketamine-induced SCZ-like deficits in mice at 10 mg/kg, restoring oxidative stress markers and normalizing IL-6 and IL-10 concentrations across key brain regions, effects comparable to risperidone (Ben-Azu et al., 2026).

Discussion

A central question motivating this review was whether the accumulating body of neuroimmune evidence, spanning genetic, molecular, cellular, and clinical domains, provides sufficient mechanistic and translational support to reconceptualize schizophrenia within an integrated neuroimmune etiological framework that moves beyond the classical dopaminergic and glutamatergic models that have historically dominated psychiatric neuroscience and treatment development.

The 55 studies synthesized in this review collectively and compellingly support the position that schizophrenia is not merely a neurological or neurotransmitter disorder but a fundamentally neuroimmune condition in which perturbations of the immune system, operating across developmental, molecular, cellular, and systemic levels, are mechanistically intertwined with the pathophysiology of psychosis. Rather than representing isolated observations, these findings cohere into a biologically plausible and internally consistent model: gestational immune

activation programs fetal neurodevelopment through cytokine-mediated epigenetic and apoptotic cascades; genetic risk variants in immune genes, particularly within the HLA/MHC region and at IRF3 and HERV-linked loci, modulate immune cell-specific gene expression patterns that predispose individuals to exaggerated neuroinflammatory responses; and these vulnerabilities manifest as sustained peripheral cytokine dysregulation, innate immune cell activation, Th17 polarization, and adaptive immune dysfunction that collectively drive the neuroinflammatory milieu associated with psychotic symptomatology.

A conceptually important finding from this review is the consistent identification of immune abnormalities in CHR-P individuals prior to psychosis onset (Aymerich et al., 2025; Yamada et al., 2025), which fundamentally repositions immune dysregulation as a predisposing biological signature rather than a consequence of antipsychotic treatment, chronicity, or lifestyle factors. This is further supported by the NHP MIA data demonstrating durable offspring immune programming from gestational poly I:C exposure (Kelland et al., 2026) and by the epigenomic evidence showing that maternal influenza infection induces sustained changes in enhancer activity at neuropsychiatric GWAS loci (Zhu et al., 2026). Together, these studies argue for a developmental immune-priming model in which schizophrenia risk is established during the prenatal period and subsequently modulated by environmental exposures, including cannabis use in adolescence, stress, and pathogen exposure, throughout the lifespan.

Contrary to earlier interpretations that attributed peripheral cytokine elevations and immune cell dysfunction in established schizophrenia primarily to the confounding effects of antipsychotic medication, chronic institutionalization, or comorbid lifestyle factors such as smoking and metabolic dysregulation. The pre-treatment evidence from CHR-P individuals and non-human primate offspring presented in this review demonstrates that neuroimmune dysregulation constitutes an intrinsic, treatment-independent biological signature of schizophrenia vulnerability and directly challenging the longstanding epiphenomenon hypothesis.

While this review is focused on schizophrenia, several studies employed transdiagnostic designs that reveal important patterns of immune-psychiatric specificity and overlap. The transcriptomic analysis of the amygdala (Zhang et al., 2026) elegantly demonstrated diagnosis-specific immunometabolic profiles: downregulation of mitochondrial respiration and immune system processes in SCZ, with distinct patterns in MDD and BPD. Similarly, the genetic correlation analyses (Wiström et al., 2026) identified disorder-specific relationships between SCZ and autoimmune diseases, notably the selective association with IBD but not with the five autoimmune conditions correlated with major depression.

The demonstration that IL-6 and TNF-α independently predict specific cognitive domains (social cognition and processing speed, respectively) in early psychosis is clinically significant. It suggests that different cytokine pathways contribute to the heterogeneous cognitive profile of schizophrenia in domain-specific ways, potentially opening the door to cytokine-targeted cognitive enhancement strategies. (Catalán et al., 2025) The finding that cognitive dysfunction in schizophrenia is associated with peripheral inflammatory signatures including eotaxin and monocyte chemoattractant protein-1 (MCP-1) further implicates chemokine-mediated BBB disruption as a mechanism through which peripheral inflammation translates into central neurocognitive impairment. (Luan et al., 2025)

The neutrophil-to-lymphocyte ratio has emerged from this literature as arguably the most clinically accessible and practically deployable immunological biomarker in schizophrenia. Unlike cytokine measurements, which require specialized ELISA or multiplex immunoassay platforms, the NLR is derivable from any routine complete blood count, a test already performed universally in psychiatric inpatient settings. The convergent evidence from this review, linking elevated NLR to PANSS symptom severity (Pavlović et al., 2025), suicidal ideation (Xia et al., 2025), and extended inpatient admission duration (Blackman et al., 2025), provides a compelling basis for incorporating NLR monitoring into routine clinical psychiatric practice, potentially as a low-cost inflammation screening tool to guide treatment intensity decisions and identify patients requiring immune-targeted adjunctive therapy.

The association between elevated NLR and suicidal ideation in first-episode schizophrenia is particularly clinically urgent, given that suicide accounts for a disproportionate share of

premature mortality in this population. Future prospective studies should examine whether NLR-guided clinical decision-making, including the initiation of anti-inflammatory adjunctive therapies in patients with elevated NLR, can reduce suicidality in schizophrenia.

The genetic findings reviewed here represent a substantial advance over traditional candidate-gene approaches, employing methodologically rigorous analytical frameworks including MR, TWAS, and sc-eQTL integration that provide causal inference and cell-type resolution, respectively. The identification of IRF3 as a shared genetic locus between schizophrenia and autoimmune diseases (Stacey et al., 2025) is particularly significant: IRF3 is a master transcription factor for antiviral innate immune responses, and its involvement in SCZ genetic risk connects the disorder's immunogenetic architecture to the viral immune defence machinery, consistent with epidemiological evidence linking prenatal viral infection to SCZ risk. The enrichment of HLA genes among the 196 TWAS-identified SCZ risk genes in immune cells further reinforces the centrality of antigen presentation and MHC-mediated immunity in SCZ pathogenesis.

The HERV-SCZ gene overlap (345 shared genes; Karimzadeh et al., 2025) opens a particularly intriguing avenue: endogenous retroviruses constitute approximately 8% of the human genome, and their transcriptional activation, which can be triggered by stress, infection, or epigenetic disruption, may drive immune pathway dysregulation through mechanisms not yet captured by standard GWAS approaches. Integrating HERV expression data into future SCZ genomic studies could substantially enrich our understanding of the immunogenetic architecture of this disorder. Particularly unexpected was the sheer breadth of the HERV–SCZ gene overlap, which at 345 shared genes substantially exceeded what previous theoretical frameworks of retroelement involvement in psychiatric genomics had predicted, implying that the transcriptional activity of endogenous retroviruses may represent a far more substantial, and hitherto underestimated, immunogenetic contributor to schizophrenia pathogenesis than conventional genome-wide association and transcriptomic approaches have thus far been designed to capture.

The MIA literature reviewed here provides the strongest causal mechanistic evidence for a role of the immune system in schizophrenia neurodevelopment. The NHP poly I:C model is particularly compelling because it demonstrates that a transient gestational immune challenge produces durable, longitudinally measured immune phenotype alterations in offspring persisting through the developmental equivalent of human early adolescence (Kelland et al., 2026). The identification of ASK1/MAPK-mediated apoptotic disruption as a downstream mechanism (Wang et al., 2026) provides a molecular target for potential intervention, ASK1 inhibitors already in clinical development for other conditions could theoretically be repurposed to mitigate MIA-induced neurodevelopmental damage if administered in the early postnatal window.

The synergistic interaction between MIA and adolescent THC exposure is of particular public health relevance given the global liberalization of cannabis policy and the well-established epidemiological association between adolescent cannabis use and schizophrenia risk. The PET neuroimaging evidence demonstrating that the combination of MIA and THC produces brain alterations not seen with either insult alone, alongside transcriptomic shifts from down- to up-regulation of dopaminergic and glutamatergic gene networks, provides strong experimental support for a two-hit neurodevelopmental model and suggests that genetically or developmentally immune-sensitized adolescents face substantially elevated risk from cannabis exposure (Moreno-Fernández et al., 2025)

The therapeutic evidence base reviewed here, while constrained by preliminary sample sizes and methodological heterogeneity, collectively supports the concept of immune-stratified schizophrenia treatment, the principle that patients with demonstrable immune dysregulation may derive differential benefit from anti-inflammatory adjunctive therapies compared with those without such alterations. The prednisolone RCT (Hoprekstad et al., 2025), while limited to 12 participants, demonstrates the feasibility and clinical signal for this approach; the ECT data suggest that treatment resistance may itself be a partially immunologically mediated state amenable to cytokine-modulating somatic therapies; and the autoimmune SCZ model (clozapine + rapamycin) provides experimental validation for the concept that autoantibody-positive

schizophrenia constitutes a pharmacologically distinct subgroup requiring immune-targeted combination strategies.

The 52% reduction in in-hospital mortality following CoronaVac vaccination in schizophrenia patients with COVID-19 (Gao and Leung, 2026) constitutes perhaps the most immediately clinically actionable finding in this review. It demonstrates that the immune vulnerability of this population translates into preventable mortality during infectious challenges, and that this mortality risk is substantially mitigable through standard public health interventions (Gao & Leung, 2026). These findings should inform vaccination priority policies and clinical monitoring protocols for schizophrenia patients during respiratory illness seasons.

Several limitations of the reviewed literature must be candidly acknowledged. First, the methodological heterogeneity across studies, spanning human clinical cohorts, retrospective database analyses, RCTs, NHP experiments, murine models, and bioinformatic studies, precludes formal meta-analytic pooling across domains and necessitates qualitative narrative synthesis. Second, the majority of human clinical studies are characterized by modest sample sizes (particularly the therapeutic trials), limiting statistical power and generalizability. Third, the time-constrained publication window (2025–2026) means that longer-term follow-up data are unavailable for several promising study designs.

Fourth, there is substantial geographic concentration in the reviewed literature, with most clinical and genetic studies originating from European, East Asian, and North American research settings. The immune system is substantially population-stratified in its genetic architecture, particularly within the HLA region, and findings derived from one ancestry group may not generalize to others. Fifth, the cross-sectional design of most cytokine and NLR studies limits causal inference regarding the temporal relationship between immune activation and symptom trajectories, and most studies did not account for confounders including smoking, obesity, antipsychotic class and dose, and comorbid metabolic syndrome, all of which independently modulate inflammatory biomarkers.

Based on the evidence synthesized in this review, the following research priorities are identified. Prospective longitudinal cohort studies integrating cytokine panels, NLR, transcriptomic, epigenomic, and microbiome profiling from the CHR-P stage through established illness and treatment are urgently needed to delineate the causal temporal sequence of immune dysregulation relative to psychosis onset and progression. Immune-stratified RCTs of anti-inflammatory agents, recruiting specifically on the basis of elevated inflammatory biomarkers (NLR, IL-6, CRP), are required to translate the emerging mechanistic evidence into clinical practice. The therapeutic potential of microbiome-targeted interventions (specific probiotic strains, dietary modification) warrants rigorous investigation in SCZ patients with characterized gut microbial dysbiosis and elevated inflammatory tone.

The development of multi-biomarker panels combining cytokines, NLR, IgG N-glycosylation, and microbiome signatures as clinically deployable diagnostic and prognostic tools should be a translational priority, particularly for identifying patients likely to benefit from immune-targeted adjunctive therapies and for stratifying suicide risk. Finally, integrating single-cell ATAC-seq, spatial transcriptomics, and HERV expression profiling in postmortem brain and peripheral blood from the same individuals, combined with comprehensive immunophenotyping, represents the methodological frontier most likely to resolve the cell-type-specific immunomolecular architecture of schizophrenia.

Conclusion

This systematic review aimed to synthesize the current state of evidence linking schizophrenia to immune system dysregulation across biological, genetic, and clinical levels of analysis. Drawing on 55 peer-reviewed studies published between 2025 and 2026, the review provides a comprehensive, multi-level, and methodologically diverse integration of this rapidly evolving evidence base. The accumulated findings collectively establish that immune abnormalities in schizophrenia are biologically deep, temporally early, preceding psychosis onset in high-risk populations, genetically grounded in the HLA/MHC region and at IRF3 and HERV-linked loci, mechanistically multifaceted, and clinically consequential. From gestational immune activation that epigenetically programs fetal neurodevelopment, through peripheral cytokine and innate

immune cell dysregulation that correlates with symptom severity and functional outcomes, to promising anti-inflammatory therapeutic signals and the quantifiable mortality reduction achievable through targeted vaccination, the immune system emerges as a central axis of schizophrenia biology that demands integration into both scientific investigation and clinical practice.

The field has advanced meaningfully beyond mere correlation to encompass causal inference through Mendelian randomization, translational evidence from non-human primate models, and therapeutic proof-of-concept through randomized controlled trials and large retrospective cohorts. This synthesis constitutes a substantive contribution to the fields of biological psychiatry and neuroimmunology by consolidating evidence across genetic, epigenetic, molecular, and clinical domains into an integrated transdisciplinary framework that bridges basic and translational science. The convergence of findings across methodologically independent traditions reinforces the proposition that immune dysregulation is not an epiphenomenon but a biologically fundamental dimension of schizophrenia, with direct implications for disease classification, biomarker development, and therapeutic stratification.

Notwithstanding these contributions, several limitations of the present review must be acknowledged. First, the restriction of the evidence base to studies published within a two-year window, while ensuring currency of findings, may exclude foundational earlier literature and increases the risk of including results that have not yet undergone independent replication. Second, the methodological heterogeneity across included study designs, ranging from genome-wide association studies and Mendelian randomization analyses to randomized controlled trials and non-human primate models, precludes formal meta-analytic pooling and necessitates cautious cross-study interpretation. Third, many immune biomarker findings, including cytokine profiles and innate immune cell ratios, derive from studies with limited demographic diversity, which may constrain the generalizability of these markers to broader patient populations. Despite these constraints, the cross-methodological and cross-geographic convergence of findings substantially reinforces the core conclusions of this review and supports their translational relevance.

Several priorities for future research emerge from this synthesis. Longitudinal studies with harmonized immunological protocols are required to establish the temporal dynamics between specific immune signatures and symptom trajectories across the psychosis spectrum. Investigation of gene–environment interactions between HLA/MHC risk variants and prenatal or early developmental immune exposures may clarify the pathways through which genetic vulnerability is expressed as psychiatric illness. Replication of current biomarker findings in ethnically diverse cohorts is essential before routine clinical deployment can be responsibly advocated. Above all, immune-stratified clinical trial designs incorporating baseline cytokine profiling or neutrophil-to-lymphocyte ratio measurement as stratification criteria represent the most urgent methodological priority for translating mechanistic gains into effective therapies. With respect to clinical and policy implications, the neutrophil-to-lymphocyte ratio stands out as an immediately deployable tool for immune-risk stratification in routine psychiatric settings (Pavlović et al., 2025; Yang et al., 2025; Blackman et al., 2025), and its systematic integration into psychiatric assessment protocols warrants serious consideration by clinical guideline bodies. Targeted vaccination strategies and structured infectious disease surveillance represent actionable public health measures with demonstrated mortality-reducing potential in this population. The one third of patients with schizophrenia who remain inadequately treated by existing pharmacological approaches constitute a population for whom immune-targeted adjunctive strategies offer a mechanistically grounded and currently underexplored avenue of clinical benefit; this gap necessitates dedicated research funding and dedicated regulatory pathways for adjunctive anti-inflammatory interventions in psychiatric care. It is in this spirit of critical synthesis oriented toward biological understanding and clinical change that this systematic review offers its evidence base to the scientific and medical community.

Ethics approval

Not required.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used Artificial Intelligence (AI) tools and methodologies in the following capacity:

- Manuscript writing support:
  a. AI-based language models (Claude AI) were used for language refinement, including improving grammar, sentence structure, clarity, and readability of the manuscript.
  c. AI-based language models (Claude AI) were used for technical writing assistance and for organizing extracted literature and thematic findings during the preparation of this systematic review.

We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The selection of studies, data extraction, interpretation of evidence, synthesis of findings, and final conclusions were conducted and verified by the authors. The final decisions and interpretations presented in this article were solely made by the authors.

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