# **REVIEW**

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# The role of infections and inflammation in schizophrenia: review of the evidence



Gellan K. Ahmed<sup>1\*</sup>, Haidi Karam-Allah Ramadan<sup>2</sup>, Khaled Elbeh<sup>1</sup> and Nourelhoda A. Haridy<sup>1,3</sup>

# Abstract

**Background** Schizophrenia is a severe mental illness affecting approximately 1% of the population worldwide. While its exact causes remain unknown, emerging evidence suggests that infections and inflammation may contribute to disease development in a subset of individuals. This review comprehensively summarizes the evidence linking infections, immune system dysfunction, and schizophrenia risk.

**Main body** Several population-based studies have linked serious prenatal or childhood infections requiring hospitalization to increased risk of later schizophrenia diagnosis, especially in individuals with genetic predisposition. Both central nervous system infections and systemic infections appear to confer risk. Specific pathogens including *Toxoplasma gondii, herpesviruses, Chlamydophila*, and more have been implicated. Autoimmune diseases are also associated with increased schizophrenia susceptibility, possibly due to blood-brain barrier disruption allowing brain-reactive antibodies access. The recent Coronavirus disease 2019 (COVID-19) pandemic raises questions about SARS-CoV-2 as a risk factor for new-onset psychosis. The mechanisms underlying the infection-schizophrenia link likely involve inflammation, cytokines, microglial activation, and tryptophan/kynurenine pathway modulation. Treatments targeting inflammation showed some efficacy in schizophrenia, further supporting an inflammation hypothesis. While the epidemiological and mechanistic evidence is substantial, further research is needed to conclusively determine the exact mechanisms linking immune dysfunction to schizophrenia requires further study.

**Conclusion** The evidence suggests immune system abnormalities likely play a role, perhaps by interacting with genetic and environmental factors, in instigating schizophrenia pathophysiology in a subset of patients. More research is needed to understand these connections more clearly which may aid future prevention and personalized treatment approaches tailored to specific illness subtypes.

Keywords Infection, Immune system, Inflammation, Schizophrenia

# \*Correspondence:

Gellan K. Ahmed

gillankaram@aun.edu.eg

<sup>1</sup> Department of Neurology and Psychiatry, Assiut University Hospital, Faculty of Medicine, Assiut, Egypt

<sup>2</sup> Department of Tropical Medicine and Gastroenterology, Faculty

of Medicine, Assiut University, Assiut, Egypt

<sup>3</sup> Department of Neuromuscular Disorders, UCL Institute of Neurology,

Queen Square, London, WC1N 3BG, UK

# Background

Although the exact causes of schizophrenia (SCZ) remain elusive, emerging evidence suggests that infections and inflammation may play a role in the development of the disease in a subset of individuals. The correlation between recent hospital infections and the risk of schizophrenia exhibits an upward trend. Throughout history, both bacterial and viral infections, particularly following the 1918 influenza pandemic, have been acknowledged for their potential to trigger psychosis and symptoms resembling schizophrenia [1, 2]. Additionally, Swedish researchers identified a connection between hospital visits and schizophrenia spectrum disorders in 2014 [3].



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This comprehensive review aims to summarize the evidence connecting infections, and immune system dysfunction, with the risk of schizophrenia. The review encompasses hypotheses linking infections to schizophrenia, epidemiological research implicating specific pathogens, maternal immune activation, potential mechanisms such as inflammation and cytokine pathways, immunological markers, and reviewing the clinical studies examining neuroinflammation and anti-inflammatory treatments in schizophrenia. The evidence suggests that immune system abnormalities likely contribute, possibly via interacting with genetic and environmental factors, to initiate schizophrenia in a subset of patients. Further research is essential to gain a clearer understanding of these connections, paving the way for future prevention and personalized treatment approaches tailored to specific illness subtypes.

# Hypotheses about the relationship of infection and inflammation with schizophrenia

Historically, two concepts of studies have examined the potential connection between immunological disorders and severe psychoses. The first concept was based on the direct involvement of infectious agents, whereas the second concept considered the dysregulation of immuno-inflammatory systems [4].

# The infective hypothesis

Schizophrenia has historically been linked to viral infections such as cytomegalovirus and herpes viruses, which have adversely affected the development of the central nervous system (CNS) [5]. Flu infection during pregnancy raises the likelihood of developing schizophrenia later, perhaps because of an imbalance in GABAergic transmission [6].

It was discovered that the levels of toxoplasma antibodies in schizophrenia patients were higher compared to those in the general population [7, 8]. Toxoplasma may contribute to the development of schizophrenia by elevating the levels of kynurenic acid in the central nervous system. This acid acts as an antagonist to the glutamatergic N-methyl-D-aspartate receptor (NMDA), which is involved in the regulation of neurotransmission [9].

# Immuno-inflammatory dysregulation hypothesis

The concept of inflammatory dysregulation in schizophrenia was initially proposed based on the observation of the beneficial effects of anti-inflammatory medication and the decreased incidence of rheumatoid arthritis in schizophrenia patients compared to the general population [10].

Wright and Gilvarry (1996) linked type 1 diabetes to autoimmune thyrotoxicosis and SCZ in various families [11]. Moreover, Danish researchers also identified a 10% increase in SCZ and a 6% increase in autoimmune diseases among parents of individuals with SCZ. Furthermore, parental autoimmune diseases such as autoimmune hepatitis, type 1 diabetes, Sjögren's syndrome, iridocyclitis, multiple sclerosis, psoriasis vulgaris, and dermato-polymyositis were associated with an elevated risk of SCZ [12].

Early 'stressors', such as problems during childbirth, are believed to be linked to the excessive production of certain genetic variations (e.g., inflammatory cytokines) that are responsible for the immunological dysregulation associated with schizophrenia [13].

The biological alterations associated with schizophrenia, such as immunological abnormalities, have usually been described by two perspectives [4]:

- According to a neurodevelopmental hypothesis, the occurrence of symptoms in adulthood can be attributed to a disturbance in brain development that took place during early life.
- According to a progressive hypothesis, symptoms and disruption of neurotransmitters are believed to cause changes in the immune system that can be noticed during an illness [14].

# Evidence of the role of infection in immune dysregulation in schizophrenia

# Specific pathogens implicated in increasing schizophrenia risk

# Genetic predisposition

In populations genetically predisposed to the condition, maternal immune responses to viral illnesses may disrupt fetal brain development, contributing to the onset of SCZ [15]. Women with SCZ have been found to have higher levels of postpartum antibodies [16]. The largest Danish study, encompassing 3722 SCZ patients, indicated that maternal infections increased the risk of infant SCZ by 39%, decreasing to 23% after adjusting for parental mental illness [17].

This risk persisted whether infections occurred during or outside pregnancy, suggesting a genetic component [12]. Factors such as infections, autoimmune diseases, and genes related to inflammation may increase the risk of SCZ [18]. HLA genes, which play a role in regulating immunity, have been linked to both SCZ and autoimmune diseases [18]. In large-scale genome-wide association studies (GWAS), most of the associations between SCZ and HLA genes were found on chromosome 6 [18]. When stratifying studies on autoimmune diseases and infections, a family history of mental illness did not increase the risk of SCZ. Several autoimmune diseases share HLA markers, which may explain their connection to SCZ. The inverse association between SCZ and rheumatoid arthritis may have a genetic basis [19, 20].

Ascertainment bias or the anti-inflammatory and analgesic properties of antipsychotic medications may account for this weak association [21, 22]. The association between the HLA region and SCZ is supported by the complement component 4 (C4) gene, which is involved in synaptic pruning during postnatal development [23]. Interestingly, the polygenic risk score for SCZ did not increase the risk of infections [24]. This is intriguing because parents with SCZ had a higher risk of immune-related diseases outside of pregnancy, suggesting a genetic link. However, shared genes related to susceptibility to infections that are not included in the polygenic risk score for SCZ may influence this relationship. The polygenic risk score for SCZ was found to increase by 2.30-fold in the highest quartile of genetic load and by 3.39-fold in individuals with infections [24]. Another study found that the SCZ polygenic risk score predicted the risk of type 1 diabetes, rheumatoid arthritis, and Crohn's disease [25]. Researchers have examined inflammation-related genes in blood, lymphoblastoid cell lines, and postmortem brains of individuals with SCZ using microarrays. The largest postmortem brain transcriptome analysis found no changes in 600 inflammation-related genes [26, 27]. However, other unbiased transcriptome profiles have identified alterations in immune-related gene expression in the blood and brains of individuals with SCZ. The largest GWAS for SCZ did not identify immune loci beyond the major histocompatibility complex [28]. While C-reactive protein has been associated with SCZ in studies of interleukin-6 (IL-6), this association was not confirmed in Mendelian randomization studies [29, 30].

# Specific pathogens implicated in increasing schizophrenia risk

In a Danish study, encompassing a younger population and involving comprehensive follow-up of all hospital contacts from birth, it was revealed that 45% of psychotic patients had a prior history of hospital infections. This antecedent increased the risk of SCZ by 41% and the risk of bacterial infections by 63% [31]. Köhler et al. (2017) determined that less severe infections treated by general practitioners (GPs) also heightened the risk of schizophrenia, albeit not to the same extent as hospitalizations. Notably, most GP-treated bacterial illnesses, particularly those necessitating broad-spectrum antibiotics, exhibited an associated increased risk [32].

Since the 1918–1919 influenza pandemic, our understanding of influenza and schizophrenia has expanded significantly. Studies suggest a season-of-birth effect in schizophrenia, with maternal influenza infection increasing the likelihood of psychosis in offspring [33]. Stem cell technology could analyze the impact of influenza infection on the induced pluripotent stem-cell microglia-like cells, providing insights into neurodevel-opment [34].

*Toxoplasma gondii* [35], human herpesvirus 2, Borna disease virus, human endogenous retrovirus, *and Chlamydophila psittaci* have all been found to increase the risk of SCZ [36]. In a large population-based study, *Toxoplasma gondii* serum titres were found to be dose-dependently associated with an increased risk of SCZ [37].

Herpes simplex virus infection has been linked to SCZ [38]. Patients with SCZ exhibited higher serum cytomegalovirus (CMV) antibody titres, particularly among those newly diagnosed and untreated [2, 39]. Although the brains of individuals with SCZ did not display neuropathological signs of CMV, elevated CMV levels were identified in their cerebrospinal fluid [40]. Additionally, individuals with SCZ were found to have higher levels of Borna virus in their serum and retroviral products [41, 42].

Furthermore, mental health has been significantly impacted by the recent Coronavirus disease 2019 (COVID-19) pandemic. While some case reports describe psychosis following COVID-19, uncertainties about causality arise due to confounding factors such as pre-existing conditions. Nevertheless, there is biological plausibility for an association between COVID-19 and psychosis [43, 44]. SARS-CoV-2 may adversely affect the brain through direct infection and inflammation [45]. The impact of COVID-19 on regions involved in psychosis, such as dopamine and glutamate pathways, is noteworthy [46, 47]. Inflammation resulting from COVID-19 could disrupt the blood-brain barrier, facilitating immune activation in the brain. Stress induced by COVID-19 might also prime vulnerability in individuals predisposed to psychosi s[48, 49]. Features of COVIDassociated psychosis include a later onset and a positive response to antipsychotics [50]. Overall, while anecdotal data exists, robust evidence confirming a causal link between SARS-CoV-2 and new-onset psychosis is still lacking. More research is needed to unravel the complex interplay between COVID-19, inflammation, and psychotic illness [45, 51–53].

Regarding bacterial infection, patients with SCZ also reported higher rates of *Chlamydophila* infections, which were correlated with genetic markers related to the immune system [54]. Postmortem analysis revealed higher levels of *Chlamydophila* DNA in the brains of individuals with SCZ [55]. Population-based studies linked pneumococcal disease to psychosis [56]. Evidence of Bartonella infection in the blood of patients with schizophrenia and schizoaffective disorder was reported [57]. Notably, state mental hospitals even employed antibiotics in the treatment of neurosyphilis-induced mental illnesses [58].

# Maternal immune activation

Maternal immune activation (MIA) disrupts normal fetal brain development [59–61], potentially causing over 30% of schizophrenia cases [62]. MIA is primarily caused by bacterial, viral, or parasitic illnesses, and antibodies against influenza or toxoplasmosis in maternal serum during pregnancy are linked to an elevated risk of schizophrenia in the offspring [63]. These infections elicit a maternal immunological response that includes the activation of different cytokine pathways such as IL-1, IL-6, TNF $\alpha$ , and IFN $\gamma$  [59]. The effect of MIA on the fetal brain does not require direct infection: even in the absence of the virus, cytokine induction with polyI:C (a synthetic dsRNA) is enough to produce long-lasting effects, implying that the mother's response to the infection is important for altering fetal brain development [64].

Pathological findings in schizophrenia patients include increased GABAA receptor 2 immunoreactivity, dopamine hyperfunction, delayed hippocampal myelination, decreased NMDA receptor expression in the hippocampus, decreased numbers of reelin- and parvalbumin-positive cells, decreased dopamine D1 and D2 receptors in the prefrontal cortex, and increased tyrosine hydroxylase in striatal structures, and similar changes are present in the adult offspring of MIA-exposed mice [65]. Postmortem brain transcriptome studies are crucial for detecting disrupted genes and pathways caused by genetic predispositions and environmental insults [66, 67].

# Factors leading to confusion between schizophrenia and immunological illnesses

Psychological stress before a diagnosis can increase the risk of infections and immunological issues in patients with SCZ [68, 69]. It is important to note that while inflammation and immune-related illnesses may not directly cause SCZ, psychological stress might precede the development of both psychiatric and immunological problems that can be explained by the duration of untreated conditions [70, 71]. Some chronic autoimmune illnesses, when considered alone, do not significantly raise the risk of SCZ. It is worth mentioning that the use of anti-autoimmune steroids and interferon therapy might increase the risk of psychosis, although such iatrogenic consequences are relatively rare. Surprisingly, steroids, in some cases, can actually lower the risk of psychosis [72].

Antibiotics can also influence the gut microbiota, which can have an impact on both the immune system and the risk of SCZ [73]. Additionally, antipsychotic

medications can affect immunological responses, potentially increasing the risk of autoimmune disorders and infections [74]. Unhealthy lifestyle choices, such as smoking, drinking, and drug abuse, can weaken the immune system in individuals without SCZ, making them more susceptible to infections and autoimmune conditions. Furthermore, certain social and behavioral traits may prevent individuals with SCZ from seeking help or adhering to their prescribed medications, which could lead to autoimmune illnesses and hospitalization due to infections. However, having a family history of mental illness or a history of substance addiction did not appear to increase the risk of infection or autoimmune diseases [75]. Also, there is a role of hormones [76, 77] and drugs [78-80] that affect the immune system with mental illness.

The association between NMDAR antibodies and the glutamate/NMDAR hypofunction hypothesis of psychotic disorders is also of interest [81, 82]. Anti-NMDAR encephalitis is a unique and complex autoimmune encephalitis that is the most common type [83]. It is caused by IgG antibodies targeting the NMDAR [84]. Due to early psychiatric symptoms, around 80% of cases first present to psychiatrists, and over 60% are initially admitted to psychiatric units [83, 85]. As a result, psychiatrists play a critical role in diagnosing this disorder and are encouraged to frequently consider it in their practice [86]. Also, Hammer et al. established a correlation between NMDAR antibody seropositivity and influenza virus A or B IgG [87].

During systemic inflammation, substances like autoantibodies, cytokines, and certain T-cell subsets involved in brain surveillance can enter the blood-brain barrier [88]. There is also evidence to suggest that an imbalance in the Th1-Th2 immune system can lead to the development of autoimmune and atopic illnesses in individuals with SCZ. Inflammation can stimulate peripheral neurons or activate pathways like the tryptophan-kynurenine pathway, which can impact neurotransmitters like glutamate, serotonin, and potentially dopamine [89]. Additionally, low-grade brain inflammation resulting from infections and autoimmune diseases may contribute to specific subtypes of SCZ [90]. When activated, microglia, which are immune cells in the brain, can alter brain signaling during inflammation [91]. It's important to note that the immune system might not always recognize infectious agents, and latent infections that emerge after acute infections or inflammation can lead to symptoms [55].

Furthermore, the gut microbiota has been found to influence brain function and behavior through various processes involving neurons, endocrine signaling, and the immune system [73]. It is also possible that immunological factors and brain inflammation might predispose genetically susceptible individuals to SCZ. The observed familial connection between autoimmune diseases and SCZ suggests that certain subgroups of patients with SCZ might exhibit autoimmune symptoms [75, 92]. Hence, both SCZ and autoimmunity share genetic and pathogenic factors [93].

# **Neuroimmunology markers**

Immune dysregulation appears to play some role in the pathophysiology and outcome of major psychoses along with genetic factors and neurodevelopmental disturbances [94, 95]. For this reason, in recent years, researchers have tried to identify neuroimmunology markers, defined as any genetically or environmentally biological parameter, with the aim of identifying individuals at risk and monitoring the progression of illness [96].

# Microglia

Immune cells in the brain, play a critical role in these processes. The link between psychiatric disorders and immune system dysfunction has long been recognized, dating back to observations by Kraepelin and Menninger in the late nineteenth and early twentieth centuries [97, 98]. Advances in immunology and genetics have furthered our understanding of how the immune system impacts brain function and contributes to conditions like depression, SCZ, autism spectrum disorders, and bipolar disorder. Neuroinflammation, characterized by abnormal cytokine and chemokine levels and changes in astrocytes and microglia, is common in these disorders [97, 98].

The concept of inflammation has existed for over 2000 years, defined by Celsus as redness, swelling, heat, and discomfort. Inflammation is critical for tissue recovery after injury [99]. Inflammation in CNS, termed neuroinflammation, involves immune cells and molecules working to fight infections and promote healing, similar to multiple sclerosis, stroke, traumatic brain injury, and CNS infections [97, 98]. However, oversimplifying neuro-inflammation can impede research efforts in mental and neurodegenerative diseases [100].

Microglia, the resident immune cells of the brain, play a key role in neuroinflammation. First described by Nissl and del Rio Hortega in the late nineteenth/early twentieth centuries, they are dynamic cells that monitor and respond to their environment [101]. Recent research has revealed that microglia originate from primitive yolk sac macrophages and have a complex developmental process. They enter the CNS during embryonic development and remain there throughout life. Unlike fetal monocytes, microglia become part of the CNS after the blood-brain barrier has already formed [102, 103].

Microglia have diverse functions in neurodevelopment, regulating neural progenitors, neurogenesis, synaptic pruning, and phagocytosis. They also remodel synapses and support adult neurogenesis [104-107]. Microglia possess receptor networks enabling them to sense neurons and respond via phagocytosis, cytokine release, and more [108, 109]. Beyond immune activities, they impact sleep, learning, memory, plasticity, and neurogenesis through the release of cytokines like IL-1 $\beta$  and TNF $\alpha$ [110]. Dysregulated microglial cytokines may impair cognition in psychiatric patients. In summary, the historical and modern research highlights the critical interactions between microglia and neurons, and the connections between immune dysfunctions and psychiatric illness. Further study of proinflammatory cytokines and their roles is needed.

# Cytokines

Cytokines are signaling molecules released by both innate and adaptive immune cells, playing a role in both the brain and the peripheral immune system. These molecules are responsible for coordinating various immune responses and maintaining the balance between defending the body against pathogens and tolerating self-antigens and beneficial microorganisms. In SCZ, peripheral cytokine changes may impact the brain via several mechanisms [111].

Studying medication-naive patients provides insights into inherent cytokine changes in SCZ [112–115]. Meta-analyses found mixed cytokine alterations in first-episode psychosis, including lower IL-1 $\beta$ , IL-6, and TNF $\alpha$  [116]. Cytokine levels appear to increase during acute episodes and decrease with treatment response [117–120]. Different psychiatric disorders show increased inflammatory cytokines [121–123]. Chronic SCZ patients exhibit elevated TNF $\alpha$ , IL-12, IFN $\gamma$ , and IL-6 [122–124]. Cerebrospinal fluid cytokine changes mirror blood findings [125, 126].

Oxidative stress from glutathione depletion may contribute to SCZ pathophysiology [127–130]. Glutamate dysfunction is implicated in SCZ and depression [131–133]. Inflammation can increase reactive oxygen species, impacting glutathione defense [134–136]. In summary, cytokines are involved in SCZ onset and progression, with intricate links to oxidative stress, glutamate disruption, and inflammation. Table 1 provides an overview of the major cytokines that have been implicated in SCZ research.

# Microbiome and gut inflammation

SCZ has long been associated with gastrointestinal (GI) issues like irritable bowel syndrome, gluten sensitivity,

Cytokine	Level in schizophrenia	Key findings	References
IL-6	Elevated	- Significantly increased in the first episode and chronic schizophrenia - Linked to positive symptoms and cognitive impairment - Higher levels associated with childhood psychosis and early life trauma	[113–121, 137, 138]
CRP	Elevated	<ul> <li>Increased in the first episode and chronic schizophrenia</li> <li>Linked to positive symptoms and cognitive impairment</li> </ul>	[113–115, 121, 137]
IL-1β	Lower in the first episode, elevated in chronic	- Decreased in first episode psychosis - Tended to increase during acute episodes and decrease with treatment	[116, 117]
TNF-α	Elevated	- Increased across schizophrenia, bipolar disorder, and depression - May signal neuroinflammation	[128, 138]
sIL2R	Elevated	- Increased across schizophrenia, bipolar disorder, and depression	[128, 138]
IL-12	Elevated	- Increased in chronic schizophrenia	[128]
IL-1RA	Elevated	- Increased in acute schizophrenia, bipolar disorder, and depression	[138]
TGF-β	Elevated in acute psychosis	- Increased during acute psychotic episodes	[117]
INF-γ	Elevated	- Increased in chronic schizophrenia	[128]
IL-8	Elevated in CSF	- Higher levels in CSF of schizophrenia patients	[128]
BDNF	Decreased	- Reduced schizophrenia, linked to childhood trauma and IL-6	[120]
GSH	Decreased	<ul> <li>Lower in acute psychosis compared to controls</li> <li>Linked to oxidative stress</li> <li>Linked to negative symptoms</li> <li>Decreased gray matter volume</li> </ul>	[127, 130]
Glx	Elevated in early stages	- Higher levels in young adults with acute symptoms	[134]
SOD		- Stable in acute psychosis - Linked to positive symptoms	[127]
CAT		- Stable in acute psychosis	[127]

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BDNF brain-derived neurotrophic factor, CAT catalase, GSH glutathione, Glx glutamate-glutamine, IL interleukin, INF-γ interferon-gamma, SOD superoxide dismutase, TGF-β transforming growth factor-beta, TNF-α tumor necrosis factor-alpha

ulcerative colitis, and Crohn's disease. Patients of SCZ especially those in the early stages and those who are medication-naïve, tend to have elevated antibodies against Saccharomyces cerevisiae (ASCA) that link antigenic foods, gut bacteria, and SCZ [139–144]. Moreover, a previous study found a relationship between cognitive function and gut bacteria [145].

Studies link SCZ to markers like sCD14, LBP, CRP, and food antigen antibodies suggesting microbial translocation causes inflammation and GI problems [146]. A healthy gut is crucial for digestion, absorption, immunity, and maintaining the gut-blood barrier. Factors like stress, drugs, infections, and genetic susceptibility can disrupt this balance [147].

Considering the gut microbiome dysbiosis in SCZ is key, as it can cause neuroinflammation. Translocated GI products can have detrimental effects on brain connections [148]. SCZ may alter endothelial cells and blood-brain barrier permeability. This can cause inflammation and inflammatory cell translocation into the brain [111, 149].

Germ-free rodent models show gut flora impacts brain maturation and function. Fortunately, modifying the bacterial composition, performing vagotomies, and employing probiotic or antibiotic therapies can help mitigate these effects [150]. Changes in the microbiota can affect blood-brain barrier permeability. Metagenomic and 16S rRNA gene sequencing studies reveal differences in the microbiomes of SCZ patients compared to controls. Interestingly, they found that patients of SCZ had more *lactobacilli* and *bifidobacteria* in their oropharyngeal microbiomes, which can contribute to inflammation [151].

Imbalances in commensal bacteria and yeast, often from medications and diet, can lead to dysbiosis and inflammation in SCZ [152]. The gut-brain connection and its role in SCZ involves many intricate factors that require further research.

# Immune cell count

The inconsistency of the findings stems from the fact that most studies analyzed the impact of antipsychotics on drug-naïve patients rather than their lymphocyte distribution. Nevertheless, the findings of most studies are consistent in that drug-naïve patients have a decrease in T cells and an increase in B cells, whereas patients who are medicated exhibit the opposite pattern [153].

## a) Polyunsaturated fatty acids

Several studies have reported that individuals with schizophrenia have reduced levels of polyunsaturated

fatty acids (PUFA) in their brain and peripheral membranes [154]. There is a hypothesis that this decline may be attributed to heightened arachidonic acid degradation caused by compromised immune function and excessive prostaglandin production, specifically prostaglandin E [155].

# Antioxidant defence system

Neuron injury in schizophrenic patients may be attributable to a deficiency in the antioxidant defense system (AODS) [156]. In fact, AODS inhibits the cellular damage caused by the free radicals that proliferate excessively during inflammatory processes. AODS comprises both enzymatic and non-enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase, albumin, bilirubin, uric acid, ascorbic acid, tocopherol, glutathione) [156]. Reduced cellular and plasma antioxidant levels are anticipated in patients with schizophrenia. Schizophrenics exhibited reduced levels of the following non-enzymatic antioxidants in their plasma: albumin [157], bilirubin [158], uric acid [159], ascorbic acid [160], glutathione [161], and tocopherol [162]. Divergent findings were observed with respect to the concentrations of superoxide dismutase in serum and cells.

One hypothesis posits that chronic patients may exhibit elevated levels of this enzyme as a compensatory mechanism against oxidative stress [156]. Nitric oxide, an essential regulator and modulator of numerous inflammatory conditions, is purportedly elevated in schizophrenic patients due to its function as a source of free radicals. However, the lack of consistency in the results [163, 164] precludes the use of NO as a diagnostic indicator to differentiate schizophrenics from healthy controls.

# Clinical evidence of neuroinflammation in schizophrenia Imaging studies

# Imaging studies h

Imaging studies have shown chronic inflammation in the brains of patients with SCZ, with low concentrations of a peripheral benzodiazepine receptor found in the brain by positron emission tomography (PET) scan. This correlated with the chronic inflammation hypothesis as elevated concentrations of a peripheral benzodiazepine receptor are attributed to a microglial response during active neuroinflammation [165, 166].

Although there is a lack of research examining the correlation between peripheral cytokine levels and neuroinflammation in SCZ, studies have found a correlation between elevated IL-6 gene expression in blood leukocytes and reduced left hippocampal volume in SCZ [167]. This suggests that IL-6, brain-derived

neurotrophic factor (BDNF), and cortisol may have a synergistic effect on hippocampal volume [168]. However, the absence of evidence for gliosis in SCZ remains incongruous despite the vast body of literature. Schneider and Dwork [169] have conducted an exhaustive literature review on gliosis and SCZ postmortem. Although some negative findings were also documented, the review incorporated positive studies by Bayer et al. [170], Radewicz et al. [171], and Steiner et al. [172] reported increased immunoreactive microglia in SCZ.

# **Management studies**

Immunotherapies which are targeting distinct symptoms associated with SCZ can be categorized into various classes, each addressing specific aspects of the disease progression:

# Anti-inflammatory drugs

Nonsteroidal anti-inflammatory agents, including aspirin, celecoxib, and minocycline, have demonstrated anti-inflammatory effects in SCZ [173, 174]. The antiinflammatory effects of these medications in SCZ are summarised in Table 2. Further investigation is crucial to comprehend their anti-inflammatory qualities and clinical significance.

# Antioxidants

Antioxidants are substances that protect cells from free radicals. While they may not provide a cure for SCZ, antioxidants can improve overall cell health. Antioxidants, such as N-acetylcysteine (NAC), ascorbic acid,  $\alpha$ -tocopherol, EPA, DHA, melatonin, and L-Theanine, have been explored in SCZ research [174–177]. The role in SCZ is summarised in Table 2.

# Antipsychotics with anti-inflammatory effects

For more than half a century, antipsychotic medications have been an essential component in the management of psychosis. First-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) are the two classifications applicable to these medications. SGAs have been observed to exert an influence on dopamine and serotonin receptors. Additionally, they may indirectly affect glutamatergic receptors, specifically NMDA receptors, through alpha-adrenergic, histaminic, and cholinergic receptors in certain instances. The principal indication for the efficacy of antipsychotics is the treatment of acute positive psychotic symptoms, such as disorganization, hallucinations, and delusions. Additionally, they might offer certain advantages in reducing

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Agent category	Agent	Mechanism of action	Summary of key clinical evidence	References
Nonsteroidal anti-inflammatory agents	Aspirin	Inhibits COX enzymes. reduces inflammatory mediators.	Two RCTs had modest improvements in symptoms.	[173, 174]
	Celecoxib	Inhibits COX-2 enzyme. Inhibits conversion of arachidonic acid to prostaglandins.	Five RCTs had mixed results.	
	Minocycline	Inhibits inflammatory enzymes include NO synthase and 5-lipoxygenase.	Seven RCTs. Modest benefits on negative symptoms.	[174]
Antioxidants, free radical scavengers, and nutrients	N-Acetylcysteine	Reduces hydroxyl radicals; modulates synthesis and degradation of anti- and pro- inflammatory cytokines.	Two RCTs. Modest benefit in negative symp- toms over placebo.	[1 74–1 77]
	Vitamin C (I-ascorbic acid)	Antioxidant effect.	One RCT. Vitamin C improved symptoms vs. placebo.	
	Vitamin E (tocopherols and tocotrienols)	Increases intracellular glutathione and anti- oxidant potential.	<ol> <li>RCTs in tardive dyskinesia patients with no significant benefit.</li> </ol>	
	Melatonin (N-acetyl-5methoxy tryptamine)	Mitochondrial and antioxidant protection. Activates antioxidant enzymes and inhibits NO synthases and lipoxygenases.	Two RCTs: improved sleep and mood. No specific antipsychotic effects.	
	Cotinine	Anti-inflammatory positive allosteric modula- tor of nicotinic cholinergic receptors.	No studies.	
	Omega-3 PUFAs	It modulates microglial activity in the expression of TNF-a, IL-6, NO synthase, and COX-2; inhibits peroxidation (antioxidant).	Eight trials with only two positive effects but had no significant. Largest trial for the prevention of psychosis was negative.	[174] [176]
	L-Theanine	AMPA and Kainic acid receptors antagonist, weak agonist of NMDA receptors.	One RCT for anxiety symptoms.	[175]
	Gluten-free diet	Avoids gliadin and prolamins (wheat gluten, barley, and rye) that cause damaging antibodies.	Equivocal findings. Results vary across stud- ies.	
Biologicals	Tocilizumab	Targets specific cytokine. Anti-IL-6 receptor antibody.	One RCT. No benefit as no crossing for blood-brain barrier.	[178, 179]
Peroxisome proliferator-activated receptors (PPARs)	Rosiglitazone, Pioglitazone	Nuclear receptors activate gene expres- sion and intracellular anti-inflammatory responses.	Rosiglitazone: one clozapine study, no improvement in negative or overall symptoms.	[180]
			Pioglitazone: one RCT showed improvement in negative symptoms and overall scores.	
Neuroprotectors	Davunetide	neuroprotective and lowers TNF-a.	Two-dose davunetide trial. No benefit.	[181]
Hormones	Estrogens	lower antioxidative stress via microglia acti- vation, TNF-a, and NO reduction.	Seven studies, reduced positive symptoms among females.	[174]

Table 2 (continued)				
Agent category	Agent	Mechanism of action	Summary of key clinical evidence	References
Herbals and probiotics	Medicinal herbs, Ginger, turmeric, Ginkgo biloba	Blocking microglia-mediated neuro-inflam- mation. Reducing PGE2, IL-1β, and TNF-a via downregulating COX-2, p38MAPK, and NF-kB expression.	One RCT found Ginkgo increased response in refractory patients.	[175]
	Probiotics		Probiotic trials aim to address SCZ-associated GI and microbial issues, with mixed results.	[182, 183]
<i>IL</i> interleukin, <i>NO</i> nitric oxide, <i>TNF-a</i> tumou Prostaglandin E2, <i>AMP</i> α-amino-3-hydroxy	r necrosis factor alpha, <i>RCT</i> randomized controlled trail, <i>S</i> -5-methyl-4-isoxazolepropionic acid, <i>NMDA</i> N-methyl-D-	:CZ schizophrenia, <i>NF-kB</i> nuclear factor kappa-light-cl aspartate, <i>Gl</i> gastrointestinal. This table was modifier	hain-enhancer of activated B cells, COX-2 Cyclooxyge d from [184]	:nase-2, PGE2

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Agent	Mechanism of action	Summary of key clinical evidence	References
Risperidone and olanzapine	Reduce pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Stimulate anti-inflammatory cytokines such as IL-4, IL-10, and IL-17.	One study: reduced IL-10 and IL1-RA in first episode psychosis.	[119, 176, 188–196]
Clozapine	Attenuates immune activation and oxidative stress.	One study: increased IL-18.	
Haloperidol	Target intra- and intercellular inflammation pathways: p38 MAPK, NF-kB, and COX.	One study. increased levels of CRP after 3 months but no difference from baseline after 12 months.	
Chlorpromazine (phenothiazine)	Inhibits immune cell function. Regulates inflammatory cytokines.	No RCT. Three preclinical experiments, one observational, and 12 opinions exist. Its inhibition of clathrin-mediated endocytosis may affect immune system cells, according to one study. A study found that endotoxin injection in mice raises IL-10 and reduces IL6 and TNF- $\alpha$ levels.	[186, 187].

Table 3 Summary of emerging evidence of different antipsychotic drugs for their anti-inflammatory and anti-infection action

IL interleukin, TNF-a tumor necrosis factor-alpha, RCT randomized controlled trial, NF-kB nuclear factor kappa-light-chain-enhancer of activated B cells, COX cyclooxygenase. This table was modified from [184, 187]

cognitive and negative symptoms; however, their effectiveness may differ [185].

In the context of the relationship between schizophrenia and inflammation and infection, it was found that some psychotropic drugs have antiviral properties [186, 187]. It is of interest that psychotropic compounds commonly used to treat mental disorders exercise a putative preventive effect against the most catastrophic outcomes related to SARS-CoV-2 infection [187]. Regarding antipsychotics, chlorpromazine (phenothiazine) is a well-established antipsychotic medication that has recently been proposed to have antiviral activity against SARS-CoV-2 [186]. Other antipsychotic medications (risperidone and olanzapine, clozapine, and haloperidol) also have been studied. The increasing evidence of antipsychotic anti-inflammatory effects is summarised in Table 3.

# Other agents

Other agents have shown early anti-inflammatory promise for SCZ, but further research is still needed. They include biological therapy, peroxisome proliferator-activated receptors (PPARs), neuroprotectors, and herbs.

# Conclusion

The collective evidence suggests that infections, inflammation, and immune system abnormalities may play an etiological role in schizophrenia. Both prenatal infections and immune insults later in neurodevelopment appear contributory in some cases. There are likely complex interactions between genetic susceptibility and environmental immune triggers influencing schizophrenia risk. However, more research focused on understanding the precise immunological mechanisms and the involved pathways is still needed.

#### Abbreviations

SCZ	Schizophrenia
CNS	Central nervous system
CMV	Cytomegalovirus
GWAS	Genome-wide association studies
DNA	Deoxyribonucleic acid
COVID-19	Coronavirus disease 2019
PET	Positron emission tomography
NAC	N-acetylcysteine
FGAs	First-generation antipsychotics
SGAs	Second-generation antipsychotics
C4	the complement component 4
FEP	First episode psychosis
GI	Gastrointestinal
NAC	N-acetylcysteine
PPARs	Peroxisome proliferator-activated receptors

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## Authors' contributions

GA conceived the original idea of this work and took the lead in writing the manuscript. HR and NE contributed equally to the literature review and writing of the manuscript. KE was responsible for revision. The final version of the manuscript was reviewed and approved by all co-authors.

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# Declarations

**Ethics approval and consent to participate** Not applicable.

## **Consent for publication**

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