Review Article

# Prevalence, Severity and Predictors of Psychiatric Disorders in Patients with Autoimmune Disorder

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**Abstract**

In recent years, there has been growing attention to the idea that immunological pathways may play a role in some types of psychotic disorders. Researchers have become particularly interested in the connection between autoimmune diseases and psychotic disorders. Genetic studies have linked immune-related genetic markers with schizophrenia, and clinical studies have found elevated levels of inflammatory markers in individuals with psychosis. Additionally, several large-scale epidemiologic studies have found a positive association between autoimmune diseases and psychosis. Specifically, autoimmune diseases like multiple sclerosis and lupus are known to have a higher incidence of neuropsychiatric symptoms, including psychosis, compared to healthy individuals. Research has shown a link between autoimmune conditions and greater chances of experiencing mental health problems.

There is a proposed connection between autoimmune diseases and schizophrenia that works both ways. Previous findings underlined an association between autoimmune disorders and schizophrenia, with evidence of a reciprocal relationship. In addition, having a family history of autoimmune diseases may elevate the likelihood of developing psychotic disorders. This review will examine the epidemiological evidence that supports the association between autoimmune diseases and psychosis. Possible explanations for this link will be explored, including shared genetic risk factors, the impact of infections on autoimmunity and psychotic disorders, and the role of the microbiome. The review will also discuss the effects of autoantibodies and T- and B-cell dysregulation on both disease categories and the need for further research. Examining the connection between autoimmune diseases and psychosis is essential in understanding the etiological mechanisms of psychotic disorders and highlighting the significance of somatic comorbidity in patients with these disorders.

**Keywords:** Autoimmune, depression, psychosis, anxiety

## Introduction

Doctors observed the link between immunological processes and mental disorders long before discovering the immune system. Scientists have observed psychosis since Hippocrates in 400 BC and Kraepelin in 1900. This mental disorder often occurs during or after an acute fever. Research has found a link between increased inflammation levels during childhood and adolescence and a greater

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chance of developing psychotic disorders. Research has found a link between increased inflammation levels during childhood and adolescence and a greater chance of developing psychotic disorders. Scientists have observed psychosis since Hippocrates in 400 BC and Kraepelin in 1900.[1] Fever often occurs suddenly or is noticed during the onset. Research has found a link between increased inflammation levels during childhood and adolescence and a greater chance of developing psychotic disorders. It is possible that people with high inflammatory markers may not respond well to treatment, but those who are experiencing inflammation may benefit from anti-inflammatory treatment.[2]

Some experts have suggested that schizophrenia might be an autoimmune disease because of similarities in symptoms and immunological processes. During the studies conducted in the 1990s, it was observed that individuals with schizophrenia had a higher likelihood of having celiac disease than the general population.[2] Studies have indicated that individuals with rheumatoid arthritis are less likely to develop schizophrenia. Research studies have shown that people with rheumatoid arthritis have a lower risk of developing schizophrenia. In the 1950s and 1960s, it was noticed that people who had schizophrenia were more likely to have celiac disease than those in the general population.[2]

Conversely, it was found that individuals with rheumatoid arthritis had a reduced chance of developing schizophrenia.[3,4] Furthermore, in the 1960s, autoantibodies that reacted with brain antigens were identified in patients with schizophrenia.[5,6] During the 1950s and 1960s, researchers observed that individuals with schizophrenia had a higher prevalence of celiac disease than the general population. This finding prompted further investigation. On the other hand, individuals with rheumatoid arthritis were found to have a lower risk of developing schizophrenia.[3,4]

Furthermore, in the 1960s, autoantibodies that reacted with brain antigens were identified in patients with schizophrenia.[5,6] There is a growing interest in studying anti-neuronal antibodies for psychotic disorders. Grown in recent decades, and there have been a rising number of reports on previously unknown antibodies with brain reactivity in individuals experiencing psychosis.[7,8]

Recent studies suggest that there could be a link between immunological processes and psychotic disorders. Studies have revealed that individuals with psychosis exhibit raised levels of bio inflammatory markers in their blood and cerebrospinal fluid, particularly those experiencing their first episode or relapse.[9] Additionally, research suggests that heightened levels of inflammation during childhood and adolescence may raise the risk of developing psychotic disorders. Inflammation treatment can positively impact patients, while those with high inflammatory markers may not respond well to treatment. Some experts have even suggested that schizophrenia may be an autoimmune disease due to similarities in symptoms and immunological processes.

The field of psychoneuroimmunology is currently under development, with various aspects being explored. Researchers are now making progress in psychoneuroimmunology and investigating its different elements. Understanding the link between autoimmune diseases and mental disorders may provide insight into possible causes of psychotic disorders. New treatment options can be developed by understanding the interaction between the immune system and psychotic illness. This could involve identifying subgroups of patients who have ongoing inflammatory processes that would benefit from more targeted treatment. Clinicians should also be aware of somatic comorbidities in patients with psychotic disorders to improve detection and treatment.[10]

Scientists have observed psychosis since Hippocrates in 400 BC and Kraepelin in 1900. It is commonly noticed that a sudden fever occurs, either during or after certain situations. The global incidence of schizophrenia is approximately 1%[11] and most autoimmune diseases have been found in a Danish nationwide study to be 4%.[12] Most epidemiological studies have found a general association between autoimmunity and psychotic disorder.[13,14] In large-scale register-based studies from Denmark, 6% of those diagnosed with schizophrenia also had a hospital contact related to an autoimmune disease during follow-up[15], and a Taiwanese study found that 3.4% of persons with a hospital contact for autoimmune diseases also had a hospital contact

related to schizophrenia.[16] A Danish study based on 7704 patients with schizophrenia found an increased prevalence by about 45% of the occurrence of an autoimmune disease[14] which was later confirmed in a Taiwanese population-based study.[13] Regarding the risk of psychosis after an autoimmune disease diagnosis, a Danish nationwide study found this to be increased by 45%, which diminished to a 29% increased risk when excluding the effect of infections. [14]

Additionally, being diagnosed with schizophrenia increases the lifetime prevalence of autoimmune diseases. Two Danish register-based studies found that individuals with psychotic disorders had a subsequently elevated risk for autoimmune diseases by around 50%.[14,15] Supporting this, the recent meta-analysis found that the risk of having an autoimmune disease was 55% higher among those with a prior diagnosis of a psychotic disorder.[17]

Autoimmune diseases and psychosis are not only associated on an individual level. Research has shown that having a close family member with schizophrenia raises the likelihood of developing autoimmune disorders by 6% (25 cases). Additionally, individuals with a family history of autoimmunity have a 10% higher risk of developing schizophrenia or non-affective psychoses.[12]

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The potential etiological background and the many factors that can influence the association between autoimmune diseases and psychosis are numerous and not mutually exclusive, as outlined in the following sections.

**Antibodies**

The connection between specific autoimmune diseases and mental illness may be partly due to the presence of neuronal surface antibodies (NSAbs). Various neurological issues have been associated with antibodies known as GAD. Individuals with lupus who suffer from neuropsychiatric symptoms often exhibit elevated levels of these antibodies in their bloodstream and cerebrospinal fluid compared to those who do not experience such symptoms. [18] The connection between specific autoimmune diseases and mental illness may be partly due to the presence of neuronal surface antibodies (NSAbs). There is a strong link between GAD antibodies and various neurological problems.[19] Neuropsychiatric lupus patients have higher levels of antibodies in their serum and cerebrospinal fluid than those without neuropsychiatric symptoms.[18] In addition, it has been discovered that patients who have recently developed schizophrenia have elevated levels of gliadin antibodies, which are linked to celiac disease, in their blood.[18]With the discovery of NMDA-receptor encephalitis and its ability to mimic mental disorders, interest spiked further, and with GAD-antibodies being able to induce limbic encephalitis[20] and antibodies reacting with the NR2 subunit of NMDA being present in some cases of lupus, a possible link emerged.[21]

Numerous studies have attempted to assess the existence of varied NSAbs in mental illnesses. However, the lack of uniformity in techniques and examinations has prevented the widespread application of the results.[18] In many studies, there has been a need for a healthy control group for comparison, and most studies have only included serum samples, not CSF samples. The relevance of circulating NSAbs in serum is still unknown, and therefore comprehensive studies, including healthy controls evaluating antibodies in both CSF and serum, are needed to increase knowledge further.

**Dysregulated Immune System**

Maintaining a proper balance between regulatory T cells and Th17 cells is crucial for supporting immune system stability. Various autoimmune disorders have been associated with imbalances. Imbalances in the body have been linked to several autoimmune diseases. One key factor in stabilizing the immune system is ensuring a proper balance between regulatory T cells and Th17 cells. Imbalances have been linked to the development of various autoimmune disorders.[22] Signs of a dysregulated immune system have also been found in mental illnesses and might play a role in the association between the two.

Research has shown that patients with schizophrenia have different levels of specific lymphocytes compared to healthy individuals. A meta-analysis found that regulatory T cells were decreased in individuals with negative symptoms and cognitive deficits, while increased levels of Th17 were linked to psychopathology. The results imply a possible correlation between schizophrenia and the immune system. Research has shown that patients with schizophrenia have different levels of specific lymphocytes compared to healthy individuals. A meta-analysis found that regulatory T cells were decreased in individuals with negative symptoms and cognitive deficits, while increased levels of Th17 were linked to psychopathology. The results indicate a possible correlation between schizophrenia and the immune system.[20]The results show a possible correlation between schizophrenia and the immune system.

In recent years, B cells have received increasing attention in the pathology of autoimmunity and have been implicated to play a significant role in, for example, MS, where it has also been found that anti-B-cell antigen (anti-CD20) has considerable efficacy in the treatment of this disease.[23] Studies have demonstrated that oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF) are present in about 90% of individuals with multiple sclerosis (MS). This indicates continuous activation and development of B-cells that produce antibodies.[24] It is interesting to note that in a recent meta-analysis, it was discovered that OCBs were present in the cerebrospinal fluid of up to 12.5% of individuals with schizophrenia.[9]

It is commonly observed that individuals with schizophrenia often have elevated levels of proinflammatory cytokines and reduced levels of anti-inflammatory cytokines in their bloodstream. [25] When the anti-inflammatory cytokine IL-10 is not functioning correctly, it can lead to abnormal reactions to typical infections and a higher likelihood of developing autoimmune diseases. If the anti-inflammatory cytokine IL-10 is not working correctly, it can cause atypical responses to specific conditions and increase the chances of getting autoimmune diseases. This issue can arise due to the malfunctioning of IL-10. When the anti-inflammatory cytokine IL-10 is not functioning correctly, it can lead to abnormal reactions to typical infections and a higher likelihood of developing autoimmune diseases.[26]

**Infections as a Common Risk Factor**

It is thought that one of the most important triggers for developing autoimmune diseases is infection, and it is known that infectious encephalitis, specifically with herpes-simplex virus, markedly increases the risk of developing NMDA-receptor encephalitis.[13] As was shown in a large Danish nationwide study, prior infection increased the risk of developing schizophrenia in a dose-response fashion, and this finding has been repeated in other extensive studies. [14] The effect of infection on the risk of schizophrenia was present regardless of autoimmune diseases. Still, a significant synergy was found in those with a history of autoimmunity and conditions. For many of the individual autoimmune disorders, it was seen that the effect on the risk of schizophrenia increased when prior hospital contact due to infection was also present.[24]

Exposure to viral or bacterial infection increases the permeability of the blood-brain barrier (BBB), allowing entry into the central nervous system of immune cells and proinflammatory cytokines. This might enable an inflammatory state in the brain, which has been theorized to play a role in the development of psychotic disorders.[27] There is a possibility that the risk of schizophrenia could be higher if an individual has both an autoimmune disease and a history of infections, as the combination may have a synergistic effect. There is a possibility that the risk of schizophrenia could be higher if an individual has both an autoimmune disease and a history of infections, as the combination may have a synergistic effect. This could be because disrupting the blood-brain barrier (BBB) allows circulating antibodies to enter. This theory is supported by evidence of a disrupted BBB in patients with schizophrenia, including an increased albumin CSF: plasma ratio and increased levels of circulating s100-b.[5]

It has also been found that infections during pregnancy increase the risk of schizophrenia in the offspring.[28] On the basis hereof, it has been considered whether infections during the prenatal phase might prime the immune system, making it more vulnerable and perhaps more likely to produce

abnormal responses to later infections, resulting in increased inflammation. However, a new study has shown that even maternal infections before and after pregnancy increases the risk of mental illness, which could also indicate a genetic susceptibility to infections associated with mental illness.[20]

**Genetics**

Both schizophrenia and autoimmune diseases are known to be highly hereditable. The most consistent finding in genetic studies of patients with schizophrenia are differences in genes known to be linked to the immune system, and several genetic loci that increase the risk of autoimmune diseases have been located.[17] As with schizophrenia, some of the discovered genetic loci in autoimmune disorders are located in the MHC region.[24] However, while one study found a significant overlap in genes between MS and schizophrenia (but not MS and bipolar disorder), another study found no genetic association between 25 different autoimmune diseases and schizophrenia.[29] Genetic pleiotropy has also been hypothesized to account for the negative association found between RA and schizophrenia, with genes found to be associated with schizophrenia possibly decreasing the risk of RA.[24]

Another possible role of genetics in the association of autoimmune diseases and psychotic disorders could be a hereditary susceptibility to shared risk factors. It has been hypothesized that some of the genetic findings associated with schizophrenia might increase the risk of having infections, that then subsequently increase the risk of both autoimmune diseases and psychotic disorders.[14] Additionally, it has been theorized whether some individuals with schizophrenia might have a genetic predisposition for an abnormal immune response to common infections and foreign pathogens, for example, via differences in the HLA region and complement system, which in turn could increase the risk of developing autoimmune reactions.[29] The complement system has also been implicated in playing a role in neurodevelopment and -maturation, and evidence of altered complement activity in patients with schizophrenia has been found.[24]

**The Microbiome**

Humans have many bacteria, species, and other microorganisms in their gastrointestinal tract, collectively known as the microbiome. The microbiome contains at least 100 times more genetic material than the human genome. Over the past few years, there has been a substantial focus on researching various illnesses in this area. Research suggests it may contribute to the development of some neuropsychiatric conditions and autoimmune disorders. As early as 1953, interest in gastrointestinal inflammation in psychosis was raised when a group of researchers found in an autopsy study that out of 82 patients with schizophrenia, 50% had gastritis, 88% enteritis and 92% colitis.[30] Scientists have observed microbiome dysbiosis in these people, but further studies have not confirmed these findings. There are notable variations between the groups of cases and controls regarding the existence of bacteria, fungi, and bacteriophages. Due to practical limitations, studies have mainly focused on the oropharyngeal microbiome. One study, however, has looked into the faecal microbiome, finding no significant difference between healthy controls and patients but showing associations between microbiome composition and symptom severity and outcome.[31]

The microbiome's composition has been hypothesized to be very important in developing the central nervous system and the immune system. Dysbiosis of the microbiome has been shown to affect both the Th1/Th2 balance and the ratio of T regulatory and Th17 cells, impacting the immune response to foreign pathogens. Dysbiosis has been found to influence T-cell-mediated inflammation in MS patients.It has also been suspected to play a part in developing celiac disease and non-gastrointestinal autoimmune diseases. In rodents, disruption of the microbiome has been found to impair social functioning , behaviour and cognition and induce neurodevelopmental disorders.[31]

An essential function of the microbiome is its effect on the epithelial cells in the GI wall, with evidence implicating that the microbiome's composition is crucial for the tightness of the gut-blood barrier. Severance et al.found markers in the serum of patients with schizophrenia indicating increased permeability, also known as "leaky gut." A leaky gut

allows the entrance of foreign pathogens and antigens into the blood. There is suspicion that this substance can cause systemic inflammation. Studies conducted on mice have shown that neuroinflammation can increase the risk of mental illness and autoimmune diseases.[32]

There is suspicion that this substance can cause systemic inflammation. Research conducted on mice indicates that there may be a correlation between neuroinflammation and a higher likelihood of developing autoimmune diseases and mental disorders.

Interestingly, both infections and antibiotic treatment can modulate the microbiome, linking the previously mentioned epidemiological findings of the influence of conditions with the microbiome theory. Additionally, it has been theorized that maternal infection might alter the maternal and fetal microbiome, possibly impacting the offspring's immune system and neuropsychiatric development.

A few studies have tried probiotic treatment in patients with schizophrenia, but no evidence of the effect on psychopathology has yet been found. However, further research on the actual composition of the microbiome in patients with mental illness and the possibility of using probiotics as treatment hereof is warranted.[31]

**Psychological Stress**

Psychological stress, such as sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, and bullying, both in childhood and later on, has been associated with an increased risk of psychotic disorders in multiple studies.[33] A register-based Swedish survey found that stress-related conditions increased the risk of subsequent development of autoimmune disorders, and, accordingly, in many other studies, stress is associated with disease onset and disease exacerbations in several autoimmune conditions.

Stress can influence many of those mentioned above possible etiological factors. Acute psychological stress, even in brief episodes, has been found in a meta-analysis to increase circulating proinflammatory cytokines such as IL-6, IL-1β, and TNF-α, possibly via the sympathetic nerve system and the HPA axis. Multiple adverse life events or stressful living conditions might contribute to a more chronic inflammatory state with dysregulation of immune response.[33]

Psychological stress has been thought to influence the microbiome's composition and vice versa, as well as the microbiome's effect on peripheral inflammation. Research has suggested that psychological stress can make people more susceptible to infections. A study found that individuals who scored higher on stress questionnaires were more likely to develop colds and respiratory infections after exposure to respiratory viruses, even if previously healthy. Experiencing acute stress, such as from a psychiatric disorder or hospitalization, can cause autoimmune diseases to worsen and potentially reveal a previously undiagnosed condition.

## Conclusions

Autoimmunity can cause neuropsychiatric disorders that may initially manifest as isolated psychiatric symptoms. In some cases, innate inflammation/autoimmunity may play a role in developing psychiatric symptoms in patients with classical psychiatric disorders. This natural inflammation could be linked to the traditional monoaminergic and glutamatergic abnormalities and increased oxidative injury commonly reported in psychiatric illnesses. Neuropsychiatric disorders can be caused by autoimmunity and often present with isolated psychiatric symptoms at first. In some cases, innate inflammation/autoimmunity may play a role in developing psychiatric symptoms in patients with classical psychiatric disorders. This natural inflammation could be linked to the traditional monoaminergic and glutamatergic abnormalities and increased oxidative injury commonly reported in psychiatric illnesses.

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