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# The epidemiological evidence linking autoimmune diseases and psychosis

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## Abstract

This review summarizes the epidemiological evidence linking autoimmune diseases and psychosis. The associations between autoimmune diseases and psychosis have been studied for more than a half century, but research has intensified within the last decades, since psychosis has been associated with genetic markers of the immune system and with excess auto-reactivity and other immune alterations. A range of psychiatric disorders, including psychosis, have been observed to occur more frequently in some autoimmune diseases, such as systemic lupus erythematosis and multiple sclerosis. Many autoimmune diseases involve multiple organs and general dysfunction of the immune system which could affect the brain and induce psychiatric symptoms. Most studies have been cross-sectional observing an increased prevalence of a broad number of autoimmune diseases in people with psychotic disorders. Furthermore, there is some evidence of associations of psychosis with a family history of autoimmune disorders and vice versa. Additionally, several autoimmune diseases, individually and in aggregate, have been identified as raising the risk for psychotic disorders in longitudinal studies. The associations have been suspected to be caused by inflammation or brain-reactive antibodies associated with the autoimmune diseases. However, the associations could also be caused by shared genetic factors or common etiological components such as infections. Infections can induce the development of autoimmune diseases and autoantibodies, possibly affecting the brain. Autoimmune diseases and brain-reactive antibodies should be considered by clinicians in the treatment of individuals with psychotic symptoms, and even if the association is not causal, treatment would probably still improve quality of life and survival.

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Conflict of Interest

All authors report no biomedical financial interests or potential conflicts of interest.

## Introduction

The associations between autoimmune diseases and psychosis have been investigated for more than a half-century(1). Autoimmune diseases are diseases in which tissue damage is mediated by autoantibodies and T-cells inducing diverse symptoms, depending on the affected part of the body(2). Recent studies have indicated that the excess co-occurrence might be due to common features in the etiology of the two disorders. Both schizophrenia and many autoimmune diseases are heritable(3;4) and genetic studies have linked both diseases with the immune-related major histocompatibility complex (MHC), suggesting that schizophrenia might have some involvement of the immune system, and one of the most consistent genetic signal in schizophrenia has been found on chromosome 6p where the MHC genes are located(5–7). Furthermore, diverse immune alterations have been observed in patients with psychosis, with elevated levels of inflammatory markers in both the blood and cerebrospinal fluid (CSF)(8–12), and activated microglia in the brain(13;14). Additionally, infections can induce autoimmunity and have also been suggested as a risk factor for psychosis(15;16).

The associations between autoimmune diseases and psychosis have been investigated since the 1950's where researchers were puzzled by the apparent protective effect of schizophrenia for rheumatoid arthritis(17;18). In the 1950's and 1960's clinicians noticed what seemed to be an unusually high occurrence of celiac disease in persons with schizophrenia(19;20). Also, as early as the 1960's, a variety of autoantibodies with cross-reactivity against brain antigens were described in the sera and CSF of patients with schizophrenia(21–23). More recently a wider range of autoimmune diseases has been implicated in population-based prospective studies as raising risk of psychosis, such as systemic lupus erythematosis, autoimmune thyrotoxicosis, multiple sclerosis, autoimmune hepatitis and psoriasis(15;24). There are several lines of evidence linking adult onset psychiatric disorders as well as other neurological symptoms to brain-reactive antibodies(25), and an increasing number of previously unknown antibodies with reactivity against the central nervous system (CNS) are being reported in recent years(25;26), also in patients with psychosis(27;28).

## Prevalence of autoimmune diseases in people with psychosis

The prevalence of hospital contacts with autoimmune diseases in the general population is about 4%, based on a Nationwide Danish study, whereas the prevalence of schizophrenia is estimated to be around 1% worldwide(29;30). A Danish population-based study on 7,704 patients with schizophrenia showed that the relative risk of schizophrenia for an individual with a history of autoimmune disease, in themselves or in their family, was elevated by about 45%, and schizophrenia was associated with a nearly 50% elevated life-time prevalence of autoimmune diseases(24). Subsequent larger Danish population-based studies on 20,317 patients with schizophrenia and a total of 39,076 patients with non-affective psychosis confirmed the nearly 50% elevated life-time prevalence of autoimmune diseases compared to the general population(15;31;32). Based on the Danish register data, hospital contacts because of autoimmune diseases had occurred in 2.4% of the patients before a schizophrenia diagnosis and autoimmune diseases occurred in 3.6% of patients with schizophrenia after the diagnosis, resulting in 6% of people with schizophrenia

that had a hospital contact with autoimmune diseases during follow-up(15;31). A recent cross-sectional analysis of a national sample from Taiwan on 10,811 individuals with schizophrenia replicated the association of a range of autoimmune diseases with schizophrenia, including specific positive associations with celiac disease, Graves' disease, psoriasis, pernicious anaemia, hypersensitivity vasculitis, and the negative association with rheumatoid arthritis(33). Based on data from the study in Taiwan(33), 3.4% of persons with a hospital contact for autoimmune diseases also had a hospital contact with schizophrenia during the follow-up period, which was shorter than the Danish studies. The incidence of bipolar disorder was increased by 70% during the first five years after an autoimmune disease diagnosis and increased by 20% in the time span after in a Danish population-based study on 9,920 individuals with bipolar disorder(32). These prevalence estimates are based on hospital contacts only, and the actual prevalence of autoimmune diseases in people with schizophrenia is likely much higher if one were to screen the individuals.

## Associations between celiac disease and psychosis

Gluten intake induces the production of anti-gliadin and transglutaminase antibodies by the immune system(34). A wide range of neurological complications are associated with antibodies to gliadin even in the absence of autoimmune disease(35–37). In the 1950's and 1960's clinicians noticed what seemed to be an unusually high occurrence of celiac disease in persons with schizophrenia(19;20). In the 1960's Dohan observed in epidemiological studies that schizophrenia admissions during World War II decreased in countries where consumption of wheat decreased, and increased in countries in which the war produced higher consumption of wheat, and hypothesized that these associations could be associated with incidence or exacerbations of celiac disease(38;39). He later observed that schizophrenia was rare in remote populations in the western Pacific region where grain consumption was rare and that the prevalence of schizophrenia increased when remote populations adapted to western lifestyle with increased grain consumption(40). In line with these findings, small exploratory studies have shown a beneficial effect of gluten-free diet on schizophrenia symptoms in subgroups with gluten sensitivity and celiac disease(41–43). Furthermore, studies have shown increased prevalence of anti-gliadin and transglutaminase antibodies in subgroups of patients with schizophrenia(44). Recently it has been found that antibodies to the self-antigen Tissue Transglutaminase, indicative of celiac disease, are found in about five times as many persons with schizophrenia as in the general population (5.4% vs 0.8% in the CATIE study, n=1401) (44–47). Furthermore, antibodies to Gliadin, indicating sensitivity to wheat not necessarily associated with autoimmune disease, are found in much higher proportion in persons with schizophrenia than in the general population (23.1% vs 3.1% in the CATIE study) (44;47–49). Clinical studies have estimated the prevalence of celiac disease to be 2.1–2.6% in patients with schizophrenia compared to 0.3–1% in the general population(34;44). However, patients with schizophrenia might have a different diet, than the control group which could affect the gliadin and transglutaminase antibody level, and not all studies have shown associations (50). Furthermore, the genetic markers HLA-DQ2 and HLA-DQ8 associated with celiac disease have not been found in excess in patients with schizophrenia(49); however, other genetic markers have also been suggested to be involved (51). Additionally, population-based studies have only found a

small increase of celiac disease in people with schizophrenia but one could argue that the condition is probably under-diagnosed particularly in the population with psychotic symptoms(15;52).

## Rheumatoid arthritis and psychosis

As early as the 1950's investigators were puzzled by the apparent protective effect of schizophrenia for rheumatoid arthritis(17;18), and more than a dozen studies have later confirmed the same negative association(33;53–55). The timing of disease onset is much later for rheumatoid arthritis than for schizophrenia and bipolar disorder, making it unlikely that the occurrence of rheumatoid arthritis raises or lowers risk for schizophrenia and bipolar disorder. The negative association between schizophrenia and rheumatoid arthritis could be due to the interplay of genetic influences, since several of the autoimmune diseases have been associated with different markers in the MHC region, and these markers might be differently associated with psychiatric disorders(1;53;54). Potvin et al.(11) suggest that the negative relationship might be mediated by the interleukin 1 receptor antagonist (IL-1RA), which is elevated in schizophrenia but protective against Rheumatoid Arthritis. It has also been suggested that anti-inflammatory and analgesic effects of antipsychotics might also be involved in this negative association(56). However, a Danish nationwide study confirmed this negative association with rheumatoid arthritis among patients with schizophrenia when comparing to the general population but when comparing with the incidence of other degenerative disorders in the musculoskeletal system the incidence was similarly decreased, indicating that the association could also be due to ascertainment bias and selection as a result of under reporting/treatment of somatic comorbidity among patients with schizophrenia(55). Additionally, nationwide Danish studies did not find a decreased incidence of rheumatoid arthritis before the diagnosis with schizophrenia(15;24). Regarding bipolar disorder, there have not been shown any overall associations with rheumatoid arthritis(55), except for an increased incidence within the first five years after the diagnosis with rheumatoid arthritis(32).

## Autoimmune diseases of the thyroid gland and psychosis

Some patients with autoimmune thyroid diseases also have psychiatric symptoms that have been associated with anti-thyroid antibodies(57). Both autoimmune thyrotoxicosis (Grave's disease) and autoimmune thyroiditis have been associated with a raised risk of schizophrenia in Danish population-based studies(15;32). The prevalence of autoimmune thyrotoxicosis among patients with schizophrenia was also increased in the population-based study from Taiwan(33). Furthermore, studies have indicated a positive family history between both autoimmune thyrotoxicosis and thyroditis with schizophrenia(24;58).

## Type 1 Diabetes and psychosis

Type 1 Diabetes is associated with autoantibodies against glutamic acid decarboxylases (subtype GAD65 with affinity to the pancreas), which may also show affinity towards GAD expressed in the brain (subtypes GAD65 and GAD67). GAD is involved in the formation of the central neurotransmitter gamma aminobutyric acid (GABA) and GAD antibodies are

also associated with neurological diseases, such as the Stiff Person Syndrome(59). In Danish population-based studies the incidence of Type 1 Diabetes is increased in people with schizophrenia both before and after the diagnosis(15;31;32). In the population-based study from Taiwan, Type 1 Diabetes was significantly elevated for females and non-significantly elevated for males with schizophrenia. Three other studies have suggested a positive family history between Type 1 Diabetes and schizophrenia(24;58;60). However, a negative association have been found in other studies(61;62), including a population-based Finnish study that found a decreased incidence of schizophrenia among people with Type 1 Diabetes in a more restricted cohort than the other population-based studies(62), and also a previous Danish study on a smaller cohort showed a small non-significantly decreased incidence(24).

## Systemic Lupus erythematosus and psychosis

Studies indicate that between 14% to 75% of patients with systemic lupus erythematosus (SLE) experience neuropsychiatric symptoms, including psychosis(5). The neuropsychiatric symptoms are suspected to be induced by brain-reactive antibodies(63), including antibodies with affinity toward the anti-N-methyl-D-aspartate (NMDA) glutamate receptor in the brain(25;64;65), which is central to current pathophysiological theories of psychosis(27;66). Approximately 40% of the neuropsychiatric SLE manifestations have been shown to develop before the onset of SLE, or at the time of diagnosis, and about 60% within the first year after diagnosis(67). In a recent Danish register study, patients with systemic lupus erythematosus were also associated with an increased incidence of non-affective psychosis(15); however, the incidence was non-significantly elevated in previous Danish studies(24;32) and also in a recent population-based study from Taiwan(33).

## Multiple sclerosis and psychosis

Multiple sclerosis has been associated with a broad range of psychiatric symptoms(68;69). In multiple sclerosis, there is a large-scale infiltration of cells from the immune system into the brain parenchyma as well as activation of the resident inflammatory cells, astrocytes, and microglial cells, which results in nerve damage(70). Multiple sclerosis has been associated with an increased risk of both schizophrenia, non-affective psychosis and bipolar disorder in Danish population-based studies(15;32), and with psychosis in a population-based study from Canada(71). A family history with multiple sclerosis is associated with schizophrenia and non-affective psychosis, but not bipolar disorder(32). Some medical treatments of multiple sclerosis, such as interferon, have been associated with psychotic symptoms; however, the incidence of psychotic symptoms are also increased before the diagnosis(31).

## Autoimmune hepatitis and psychosis

Autoimmune hepatitis has been associated with an 5–6 fold increased risk of schizophrenia and non-affective psychosis and also an elevated incidence of bipolar disorder(32). Furthermore a family history of autoimmune hepatitis have been associated with schizophrenia and non-affective psychosis(32). Of other notice is that if a person has had both an autoimmune hepatitis diagnosis and a hospital contact with infection, the risk of schizophrenia was increased by almost nine times in a Danish study(15). Autoimmune

hepatitis has also been associated with brain-reactive antibodies(72), and in patients with severe affection of the liver, as seen in coma hepaticum, psychiatric symptoms are dominating in the initial phases(73). However, the associations with inflammation in the liver could also be explained by the effect of, for instance, a metabolic syndrome or substance abuse.

## Guillain-Barré syndrome and psychosis

The incidence of Guillain-Barré is increased both before and after a diagnosis with non-affective psychosis, and also in the delayed period more than 5 years after the diagnosis(31;32). The increased risk of psychosis is confined to persons with a diagnosis of Guillain-Barré syndrome as well as a hospital contact with infection(15). Interestingly, the ganglioside-specific antibodies that are present in patients with Guillain-Barré syndrome are suspected to be induced by molecular mimicry after exposures to infections such as the *Campylobacter jejuni* bacteria(74).

## Psoriasis and psychosis

Psoriasis has been associated with an increased risk of schizophrenia in population-based studies both from Denmark and Taiwan(15;32;33). The risk of non-affective psychosis and bipolar disorder has also been increased in Danish studies(31;32). Additionally, a family history with psoriasis have been associated with schizophrenia and non-affective psychosis but not bipolar disorder(32). To the best of our knowledge psoriasis has not been associated with brain-reactive antibodies but within recent years psoriasis has been considered to be of a more systemic nature than previously thought.

## Associations between infections, autoimmune diseases and psychosis

Infections are among the prime candidates for initiating autoimmune diseases(75) and have also been associated with the development of schizophrenia(15;16) and bipolar disorder(76). A nationwide Danish study on persons with autoimmune diseases showed that the increased risk of schizophrenia diminished from 45% to 29% when restricted to persons without a history of infection(15). Additionally, the study found that when autoimmune diseases and severe infections occurred together they interacted in synergy and increased the risk of schizophrenia by 2.25 times, which did not seem to be confined to one particular pathogen. The same pattern has been observed for bipolar disorder, where individuals with an autoimmune disease but no hospital contact with infection had an increased risk of bipolar disorder by 25%, and individuals with both an autoimmune disease and hospital contact with infection had an increased risk of bipolar disorder by 2.04 times(76). Additionally, we have shown that after the diagnosis with schizophrenia, there was a multiplicative interaction with hospital contact for infections, which together increased the risk of developing an autoimmune disease by a factor of 2.70 (31). Hence, there might be a biological interaction with infection that could be a common risk factor for both autoimmune diseases and schizophrenia.

## Associations with a family history of either autoimmune diseases or schizophrenia

A family history with autoimmune diseases has been shown to increase the risk of schizophrenia by 10% and a family history with schizophrenia increases the risk of autoimmune diseases by 6%(31;32). However, a family history with bipolar disorder was not significantly associated with autoimmune diseases and there was no association in the reverse direction either(31;32). A family history with the following specific autoimmune diseases have been associated with an increased incidence of schizophrenia in the 2010 study by Eaton et al.(32): autoimmune hepatitis, type 1 diabetes, Sjogrens syndrome, iridocyclitis, multiple sclerosis, psoriasis vulgaris and dermatopolymyositis, whereas only a family history with pernicious anemia were associated with bipolar disorder out of the 30 autoimmune diseases studied. The association with a family history of diabetes type 1 and autoimmune thyrotoxicosis with schizophrenia have been confirmed in other populations as well(58;60).

## Brain-reactive antibodies and psychosis

As early as the 1960's, autoantibodies with cross-reactivity against brain antigens have been described in the sera and CSF of patients with schizophrenia(21–23). Through the years, several groups have identified diverse brain-reactive antibodies in patients with schizophrenia, including antibodies against neurotransmitters, but consistency in the findings has not been high(5;77), and the correlation with disease activity ambiguous(77). This could be due to differences in methods and that the findings with brain-reactive antibodies may be too unspecific. Some of the strongest evidence for the potential for autoimmunity to cause psychosis comes from the NMDA antibody-induced limbic encephalitis, which can be induced by both cancer and infections, where psychiatric symptoms are often dominant in the initial and the remission phase of the disorder in up to 70% of the cases(78), which has been demonstrated to be treatable with immunosuppressants or plasmapheresis(25;78). It seems that the same antibodies can cause more than one neuropsychiatric symptom depending on the region of the brain that is exposed to the antibodies(74). Animal studies have additionally shown convincing evidence, where brain-reactive antibodies appear to induce a broad range of neuropsychiatric symptoms, particularly after an induced breach of the BBB with subsequent influx of antibodies into the brain tissue(74;79;80). In line with this, Danish population-based studies have found a synergistic effect of having both autoimmune diseases and hospital contacts with infections on the risk of psychosis(15;76). Furthermore, the group of autoimmune diseases with suspected presence of brain-reactive antibodies was associated with higher risks of subsequent non-affective psychosis and bipolar disorder than the group without(15;31;76). However, since the studies were based on diagnoses and not direct measurements of specific brain-reactive antibodies, it remains speculative whether these diseases are actually caused by brain-reactive antibodies or other related risk factors.

## Limitations

Most of the epidemiologic estimates are from register-based studies and the prevalence might be underestimated, since, in general, only diseases requiring hospital contacts are included. Diagnostic delay and under-treatment of somatic comorbidity is a general problem for patients with schizophrenia(81–83), and possibly explains the increased mortality(83;84). Therefore, the prevalence of autoimmune diseases might be much higher in screening studies of people with psychosis. Furthermore, if the treating physician expects a causal association between the psychiatric symptoms in a patient with autoimmune disease, the patient might not be referred to a psychiatric hospital contact or might have been classified with an organic psychiatric disorder instead, which would contribute to the prevalence of psychosis being underestimated in register studies. There might be further limitations with these large register-based studies considering the autoimmune diseases in aggregate, which could result in insufficient adjustments for specific risk factors regarding the individual autoimmune diseases(62). Randomized studies would be preferable to the epidemiological studies but difficult to conduct due to ethical reasons; however, randomized studies of anti-inflammatory treatment for instance are ongoing and may provide more evidence after the initial promising results(85).

## Views on the nature of the associations

Subgroups of people with schizophrenia may demonstrate features of an autoimmune process, and the hypothesis is strengthened by the findings of an increased familial association between autoimmune diseases and schizophrenia(24;31;60). Additionally, complex etiological mechanisms similar to those of some psychiatric disorders are hypothesized to be involved in the initiation of autoimmunity where genetic susceptibility is required along with triggering events such as infections(77). Different combinations of risk factors may lead to different types of autoimmune diseases and there is high comorbidity of autoimmune diseases(86), which might also be the case for psychiatric disorders.

The association of schizophrenia with a range of autoimmune diseases may reflect inflammation as a common pathway to psychosis. Inflammation can affect the brain through increased permeability of the blood-brain barrier or even without passing the blood-brain barrier through stimulation of peripheral nerves(87) or proinflammatory cytokines activating the tryptophan-kynurenine pathway involved in regulation of the glutamate and serotonin system(87), and probably also indirectly dopamine(10). Inflammation might act as a priming event on microglia, inducing a long-term development of abnormal signal patterns possibly involved in schizophrenia(88). Many diverse immune alterations have been observed in patients with psychosis, with elevated levels of inflammatory markers in both the blood and CSF(8–12), together with observations of activated microglia in post-mortem brains(13;89), and in vivo brain imaging(14). An imbalance between the Th1 and Th2 systems has also been proposed as an etiological component to schizophrenia(10), which would fit with the increased prevalence of autoimmune diseases and atopic disorders in people with schizophrenia(24;90). Furthermore, maternal immune responses during pregnancy have been associated with schizophrenia and might also induce sensitizing or preconditioning effects that can cause the organism to amplify reactions to subsequent immunological challenges

in later life(91;92). However, adjusting for metabolic and lifestyle-related variables in cross-sectional studies of patients with schizophrenia together with medication clearly weakens the association with inflammatory markers(12).

The excess co-occurrence of autoimmune diseases and psychosis, together with an association with a family history of the disorders, might be due to a genetic vulnerability toward dysfunction of the immune system in patients with schizophrenia, which could make them more susceptible to acquiring infections and thereby increasing the risk of autoimmune diseases. However, several of the autoimmune diseases have been associated with different markers in the MHC region, and these markers might be differently associated with psychiatric disorders. This could, for instance, explain the negative association between schizophrenia and rheumatoid arthritis, which has been shown in more than a dozen studies; a fact that could be due to the interplay of genetic influences(1;53;54). Furthermore, MHC may be an important factor in determining the individual response to infectious agents for instance and genetic variation may exaggerate responses to infections and predispose to the development of autoimmunity(4;93).

Factors other than shared etiological components could also be responsible for the observed associations between psychosis and autoimmune diseases. An iatrogenic effect of medical treatment may influence the associations; but only some of the included autoimmune diseases would be treated with medications like steroids or interferon, which might increase the risk of psychosis. Antipsychotic medications and consequent side effects might have an impact on the immune system; however, there is no evidence from prior research that antipsychotic medications induce autoimmune diseases; and the incidence of autoimmune diseases are also elevated before the diagnosis with schizophrenia and initiation of antipsychotic medication(15). The risk of developing autoimmune diseases might be increased by smoking, alcohol and drug abuse. Furthermore, psychological stress associated with psychosis might also be a trigger for autoimmune disease activity leading to hospital contacts or making the individual more vulnerable to the effects of infections leading to autoimmunity. However, if the increased risk was due to life style, psychological stress or medication, the risk could be expected to increase with time after the diagnosis of schizophrenia due to longer exposure periods, which does not seem to be the case(31). Ascertainment bias might also influence the results from the register-based studies but the incidence of psychosis is also increased in the delayed period more than five years after the hospital contact with autoimmune diseases and vice versa(31;32).

Studies of patients with schizophrenia not previously diagnosed with an autoimmune disease have demonstrated excess prevalence of diverse autoantibodies in sera(94–97). Interestingly, recent CSF screening studies of patients with schizophrenia, and no known autoimmune diseases or infection, have detected autoantibodies or antibodies against infectious agents in the CSF of 3.2% to 6% of patients with schizophrenia(98;99). Furthermore, newly discovered brain-reactive antibodies have been identified in the sera and CSF of patients with psychosis(27;28) and more are detected in these years(25). Autoimmune diseases often have an early phase of target organ inflammation followed by a late phase of irreversible tissue damage, and if brain-reactive antibodies are actually causally related to psychotic symptoms, early preventive treatment of prodromal patients would be of utmost

importance to prevent the immunological destruction or alteration of neuronal connections. Potentially, autoimmune processes could be involved in the prodrome and perhaps etiology of a non-negligible proportion of individuals with schizophrenia and other psychosis. Symptom manifestations of autoimmune conditions might particularly resemble the subtype of psychosis with chronic relapsing remitting illness for instance (93). Hence, autoimmune and inflammatory processes should be considered in the evaluation of patients presenting with psychotic symptoms.

## Conclusions

There is a positive association between a broad number of autoimmune diseases and autoantibodies with schizophrenia. Population-based studies from both Denmark and Taiwan have shown an association of a range of autoimmune diseases considered in aggregate and psychosis, including a specific positive association with celiac disease, autoimmune thyrotoxicosis, psoriasis, pernicious anaemia, and a negative association with rheumatoid arthritis. Additionally, small associations between a family history of the disorders have been observed possibly indicating shared familial/genetic risk factors. Whether or not the co-occurrence of autoimmune diseases in people with schizophrenia is causally related to the psychiatric symptoms, the individuals would nonetheless benefit from treatment for their somatic comorbidity to reduce mortality and improve quality of life. The increased mortality in psychiatric patients is mainly due to somatic diseases(84;100); hence, a thorough clinical examination and frequent somatic check-ups is important in patients presenting with symptoms of psychosis and other severe mental illnesses.

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