

# Chapter 6

## The Role of Infections and Autoimmune Diseases for Schizophrenia and Depression: Findings from Large-Scale Epidemiological Studies

Michael Eriksen Benrós and Preben B. Mortensen

**Abstract** An immunologic component to schizophrenia and depression has been increasingly recognized, which has led to extensive research into the associations with infections and autoimmune diseases. Large-scale nationwide epidemiological studies have displayed an increased prevalence of both autoimmune diseases and infections among persons with schizophrenia and depression. Autoimmune diseases, and especially the number of infections requiring hospitalization, increase the risk of schizophrenia and depression in a dose–response relationship. Infections are a common exposure and a broad spectrum of infections are associated with schizophrenia and depression. Particularly the autoimmune diseases with a potential presence of brain-reactive antibodies were associated with psychiatric disorders. However, the associations seem to be bidirectional, since the risk of autoimmune diseases and infections is also increased after diagnosis with schizophrenia and depression. The risk of autoimmune diseases was particularly increased in individuals with prior hospital contacts for infections.

It has been suggested that inflammation and autoimmunity could be involved in the etiology and pathogenesis of some patients with symptoms of schizophrenia and depression. The psychiatric symptoms can be directly triggered by immune components, such as brain-reactive antibodies and cytokines, or infections reaching the central nervous system (CNS), or be secondary to systemic inflammation indirectly affecting the brain. However, the associations could also be caused by shared genetic factors, other environmental factors, or common etiological components. Nonetheless, autoimmune diseases and infections should be considered by clinicians in the treatment of individuals with psychiatric symptoms, since treatment would probably improve the psychiatric symptoms, quality of life, and the survival of the individuals.

---

M.E. Benrós (✉)

Faculty of Health Sciences, Mental Health Centre Copenhagen, Copenhagen University Hospital, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark

National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark  
e-mail: [benros@dadnet.dk](mailto:benros@dadnet.dk)

P.B. Mortensen

National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark

**Keywords** Schizophrenia • Depression • Bipolar disorder • Psychiatry • Autoimmune diseases • Infection • Inflammation • Immunology • Epidemiology • Register-based

## Introduction

Immunological hypotheses have become increasingly prominent within psychiatric research (Muller and Schwarz 2010), suggesting that inflammation and autoimmunity could be involved in the etiology and pathogenesis of some patients with symptoms of schizophrenia and depression (Miller et al. 2009; Drexhage et al. 2011). Previously, the brain was regarded as an immune privileged site, protected by the blood–brain barrier, but particularly within the last decades, studies have demonstrated that the immune system may affect the brain and induce psychiatric symptoms. Many diverse immune alterations have been observed in persons with schizophrenia, such as elevated levels of cytokines and inflammation markers (Muller and Schwarz 2010; Nikkila et al. 2001; Potvin et al. 2008; Dowlati et al. 2010; Howren et al. 2009). Abnormalities of the blood–brain barrier have been indicated in studies of patients with schizophrenia and severe depression (Uranova et al. 2010), together with signs of central nervous system (CNS) inflammation (Bechter et al. 2010). Additionally, increased prevalence of autoimmune diseases has been observed in patients with both schizophrenia and mood disorders, and studies have indicated increased autoantibody reactivity and elevated autoantibody levels even in the patients with no known autoimmune diseases (Laske et al. 2008; Tanaka et al. 2003). Also, both schizophrenia and depression have been associated with genetic markers related to the immune system (Marballi et al. 2010; Stefansson et al. 2009; Shelton et al. 2011).

Inflammatory mechanisms can affect the brain through many different pathways that are not necessarily mutually exclusive (Jones et al. 2005; Dalman et al. 2008; Yolken and Torrey 2008; Niebuhr et al. 2008a; Eaton et al. 2006). During inflammation and infections the permeability of the blood–brain barrier might be increased, making the brain particularly vulnerable to inflammation and immune components, such as antibodies and cytokines. Infections and immune components can particularly affect the brain during periods with increased permeability of the blood–brain barrier, which occurs during trauma and inflammation (Margutti et al. 2006; Irani and Lang 2008). Peripheral inflammation or infections can additionally interact with the neuroendocrine system regarded to be involved in psychiatric disorders through multiple pathways (Dantzer et al. 2008; Rivest 2010). Furthermore, experimental animal studies have found that symptoms of depression and psychosis can be induced by inflammation or brain-reactive antibodies (Katzav et al. 2007; Diamond et al. 2009; Chen et al. 2009). In summary, genetically vulnerable individuals might be at risk of developing neuropsychiatric symptoms like schizophrenia and depression as a consequence of inflammation and immune components

affecting the brain. If the immunological alterations are confirmed to play a role in the pathogenesis of schizophrenia and depression, it could provide an interesting and promising target of future prevention and treatment.

## **A Historical Overview of the Associations**

The possibility that bacterial infections have a causal relationship to psychoses was reported as early as 1896 (Noll 2007), and virus infections have been suspected since the 1918 influenza pandemic was followed by multiple reports of post-influenza psychoses and schizophrenia-like symptoms (Torrey et al. 2006). Later, when antibiotics were introduced, anecdotal data suggests that significant proportions of patients with psychiatric symptoms caused by neurosyphilis were cured also for their psychiatric symptoms (Sullivan et al. 2012). However, interest in the possible connection between infections and the occurrence of psychiatric disorders waned due to lack of further relevant treatment methods, but during the last decades, research on the relationship between infections and psychiatric disorders has re-emerged (Yolken and Torrey 2008).

Research on the associations with autoimmune diseases began in the 1950s, where investigators were puzzled by the apparent protective effect of schizophrenia on rheumatoid arthritis (Trevathan and Tatum 1953; Pilkington 1955). Furthermore, in the 1950s and 1960s, clinicians noticed what seemed to be an unusually high occurrence of celiac disease in persons with schizophrenia (Bender 1953; Graff and Handford 1961). Also, as early as the 1960s, a variety of autoantibodies with cross-reactivity against brain antigens were described in the sera and CSF of patients with schizophrenia (Fessel 1962; Heath and Krupp 1967a, b). In the last decade, a wider range of autoimmune diseases, infections, and autoantibodies have been implicated in population-based prospective studies as increasing the risk for schizophrenia and depression.

## **How Infections Can Induce Psychiatric Symptoms?**

Various infectious agents have the potential to penetrate the blood–brain barrier and invade the CNS directly, possibly after reaching a threshold level of bacteremia (Kim 2008). Furthermore, inflammation in response to infections can affect the brain through many different pathways, hereunder increased permeability of the blood–brain barrier. Peripheral infections and inflammation can also affect the brain without passing the blood–brain barrier through proinflammatory cytokines activating the tryptophan–kynurenine pathway that regulates NMDA glutamate receptor activity together with serotonin production (Dantzer et al. 2008), and this may indirectly also affect dopamine regulation (Muller and Schwarz 2010).

Studies have additionally indicated that peripheral inflammation can affect the brain through stimulation of peripheral nerves such as the vagal nerve (Dantzer et al. 2008) or through alterations of the microbioma (Cryan and Dinan 2012). Several infectious agents can persist in the CNS and may not present with neurological symptoms, such as *toxoplasma* and certain viruses like Borna disease virus, HIV and hepatitis C virus, and even if not directly involved in destruction of CNS tissue, it might trigger CNS immune responses and thereby indirectly cause damage (Wilkinson et al. 2010; Shankar et al. 1992; Fishman et al. 2008). Furthermore, inflammation might act as a priming event on microglia, inducing a long-term development of abnormal signal patterns possibly involved in schizophrenia and depression (Hickie et al. 2009). Infections can additionally induce the development of autoimmune diseases and autoantibodies, possibly affecting the brain through a mechanism called molecular mimicry (Diamond et al. 2009; Rose 1998).

## How Autoimmunity Can Induce Psychiatric Symptoms?

Autoimmune diseases are characterized by “self-reactivity” induced by autoantibodies and T-cells that can react against the body’s own tissues and induce diverse symptoms, depending on the affected part of the body (Davidson and Diamond 2001). Many autoimmune diseases involve multiple organs and general dysfunction of the immune system which could affect the brain and induce psychiatric symptoms. CNS symptoms associated with autoantibodies have mostly been recognized in cancer patients with paraneoplastic symptoms that may in part be caused by an immunologic reaction where antibodies against tumor antigens cross-react with elements of the nervous system (Kayser et al. 2010; Darnell and Posner 2003). Brain-reactive antibodies have also been associated with some autoimmune diseases and are suspected to induce the high prevalence of neuropsychiatric symptoms observed in some autoimmune diseases, such as systemic lupus erythematosus (Margutti et al. 2006; Ballok 2007; Rice et al. 2005; Sundquist et al. 2008). Additionally, experimental studies have demonstrated that neuropsychiatric syndromes can be induced after an influx of brain-reactive antibodies into the brain (Kowal et al. 2004).

## Associations Between Autoimmune Diseases and Schizophrenia

Large-scale Danish population-based studies with up to 20,317 patients with schizophrenia and 39,076 patients with non-affective psychosis have shown that individuals with schizophrenia are associated with a nearly 50 % higher lifetime prevalence of autoimmune disorders (Eaton et al. 2006; Benros et al. 2011). A 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 anemia, hypersensitivity vasculitis, and the negative association with rheumatoid arthritis (Chen et al. 2012). Screening studies of persons with schizophrenia have found antibodies to the self-antigen tissue transglutaminase, indicative of celiac disease, in about five times as many persons as expected (5.4 vs 0.8 % in the CATIE study,  $n=1,401$ ) (Reichelt and Landmark 1995; Cascella et al. 2011; Jin et al. 2012; Samaroo et al. 2010). Furthermore, antibodies to gliadin, indicating sensitivity to wheat not necessarily associated with autoimmune disease, are also found in much higher proportion in patients with schizophrenia (23.1 vs 3.1 % in the CATIE study) (Cascella et al. 2011; Samaroo et al. 2010; Dickerson et al. 2010), which is interesting since a wide range of neurological complications are associated with antibodies to gliadin, even in the absence of autoimmune disease (Irani and Lang 2008; Hadjivassiliou et al. 2010; Jackson et al. 2012). 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 (Cascella et al. 2011; Kalaydjian et al. 2006).

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 who had a hospital contact with autoimmune diseases during follow-up (Benros et al. 2011, 2014). Based on data from the study in Taiwan (Chen et al. 2012), 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. 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, as exemplified by the clinical studies investigating the prevalence of celiac disease, which was much more common than in the register-based studies.

## The Risk of Schizophrenia After an Autoimmune Disease Diagnosis

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 % (Eaton et al. 2006). Subsequent larger Danish population-based studies on 20,317 patients with schizophrenia and a total of 39,076 patients with non-affective psychosis confirmed that the risk of autoimmune diseases was increased by 45 % after an autoimmune disease diagnosis (Benros et al. 2011, 2014; Eaton et al. 2010). However, when restricting to persons without a history of infection, the increased risk of schizophrenia diminished from 45 to 29 % (Table 6.1) (Benros et al. 2011). 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 (Benros et al. 2011).

**Table 6.1** Relative risk of schizophrenia spectrum diagnosis in persons with a hospital contact for autoimmune diseases and infections, Denmark, 1977–2006

| Autoimmune disease   | Schizophrenia spectrum disorders in persons without infections |             |                  | Schizophrenia spectrum disorder in persons with hospital contact with infections |             |                  |
|--|--|-------------|------------------|--|-------------|------------------|
|  | RR <sup>a</sup>  | 95 % CI     | Cases            | RR <sup>a</sup>  | 95 % CI     | Cases            |
| Reference without autoimmune disease or infection                                    | 1.00   | (Reference) | 29,372           | 1.00   | (Reference) | 29,372           |
| <b>Any autoimmune disease</b>  | <b>1.29</b>  | 1.18–1.41   | 483 <sup>b</sup> | <b>2.25</b>  | 2.04–2.46   | 444 <sup>b</sup> |
| <b>Autoimmune diseases with suspected presence of brain-reactive antibodies:</b>     | <b>1.48</b>  | 1.31–1.68   | 244              | <b>2.56</b>  | 2.25–2.89   | 243              |
| Autoimmune hepatitis   | <b>2.75</b>  | 1.38–4.83   | 10               | <b>8.91</b>  | 6.50–11.84  | 43               |
| Autoimmune thyroiditis   | –  | –           | 3                | <b>4.57</b>  | 2.09–8.51   | 8                |
| Celiac disease   | <b>2.11</b>  | 1.09–3.61   | 11               | <b>2.47</b>  | 1.13–4.61   | 8                |
| Guillain Barre syndrome  | 1.22   | 0.58–2.19   | 9                | <b>2.84</b>  | 1.52–4.76   | 12               |
| Multiple sclerosis   | <b>1.44</b>  | 1.03–1.94   | 39               | <b>2.10</b>  | 1.37–3.06   | 24               |
| Sjögren's syndrome   | 2.07   | 0.82–4.20   | 6                | –  | –           | 4                |
| Systemic lupus erythematosus   | 1.84   | 0.92–3.23   | 10               | <b>2.11</b>  | 1.06–3.70   | 10               |
| Thyrotoxicosis (Graves disease)  | <b>1.94</b>  | 1.47–2.49   | 56               | <b>2.47</b>  | 1.68–3.49   | 29               |
| Type 1 diabetes  | <b>1.27</b>  | 1.04–1.53   | 104              | <b>2.04</b>  | 1.68–2.44   | 109              |
| <b>Other autoimmune diseases listed below:</b>                                       | <b>1.19</b>  | 1.05–1.34   | 256              | <b>1.95</b>  | 1.70–2.23   | 212              |
| Ankylosing spondylitis   | 1.38   | 0.79–2.20   | 15               | 1.68   | 0.72–3.25   | 7                |
| Crohn's disease  | 1.22   | 0.88–1.65   | 39               | <b>1.67</b>  | 1.18–2.27   | 36               |
| Iridocyclitis  | 1.32   | 0.87–1.91   | 25               | <b>1.99</b>  | 1.21–3.06   | 18               |
| Juvenile arthritis   | 1.00   | 0.52–1.71   | 11               | 1.77   | 0.95–2.97   | 12               |
| Psoriasis vulgaris   | <b>1.37</b>  | 1.01–1.80   | 47               | <b>2.77</b>  | 2.07–3.63   | 49               |
| Seropositive rheumatoid arthritis  | 0.75   | 0.51–1.06   | 28               | <b>2.15</b>  | 1.52–2.95   | 35               |
| Ulcerative colitis   | 1.22   | 0.97–1.51   | 80               | <b>1.65</b>  | 1.24–2.14   | 52               |
| Autoimmune diseases with too few cases to calculate the individual risk <sup>c</sup> | <b>1.59<sup>d</sup></b>  | 1.13–2.17   | 36               | <b>2.21<sup>d</sup></b>  | 1.53–3.07   | 32               |

Source: Benros et al. Am J Psychiatry. 2011

<sup>a</sup>Boldface indicates that the 95 % confidence interval did not include 1.0. Relative risks were not estimated when there were less than five exposed cases

<sup>b</sup>Cases do not add up as one can have multiple autoimmune diseases

<sup>c</sup>Alopecia areata, autoimmune hemolytic anemia, dermatopolymyositis, idiopathic thrombocytopenic purpura, myasthenia gravis, pernicious anemia, primary adrenocortical insufficiency, primary biliary cirrhosis, pemphigus, pemphigoid, polymyalgia rheumatica, scleroderma, vitiligo, Wegener's granulomatosis

<sup>d</sup>Estimates should be interpreted with caution, but these autoimmune diseases were estimated together for completeness

## The Risk of Autoimmune Diseases After a Diagnosis with Schizophrenia

Individuals diagnosed with schizophrenia had a 53 % increased risk of subsequent diagnoses with autoimmune diseases, particularly the group with suspected presence of brain-reactive antibodies had a 91 % increase of risk (Table 6.2). There was a significant multiplicative interaction between having both a schizophrenia

**Table 6.2** Relative risk of autoimmune diseases after the diagnosis with schizophrenia spectrum disorder in Denmark (1987–2010)<sup>a</sup>

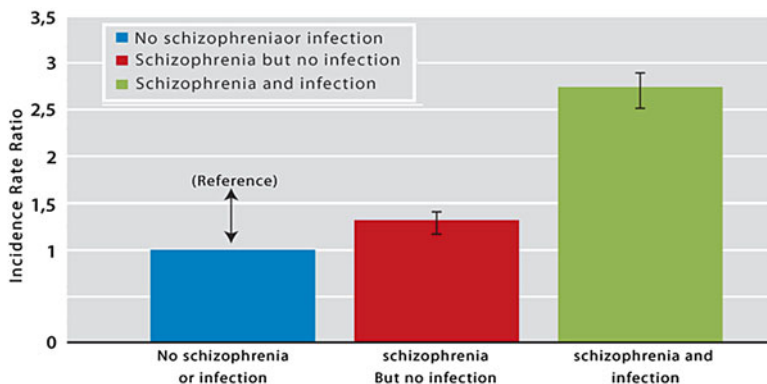
| Autoimmune diseases  | Cases   | RR    | 95 % CI               |
|--|---------|-------|-----------------------|
| Persons without schizophrenia (reference)  |         | 1.00  | (Reference)           |
| <b>Any autoimmune disease</b>  | 142,328 | 1,401 | <b>1.53</b> 1.46–1.62 |
| <b>Autoimmune disease with suspected presence of brain-reactive antibodies</b>         | 75,087  | 849   | <b>1.91</b> 1.78–2.04 |
| Autoimmune hepatitis   | 1,878   | 40    | <b>3.51</b> 2.51–4.73 |
| Autoimmune thyroiditis   | 3,386   | 23    | 0.90 0.58–1.33        |
| Celiac disease   | 2,350   | 20    | 1.33 0.82–2.03        |
| Guillain Barre syndrome  | 1,648   | 24    | <b>2.73</b> 1.77–3.99 |
| Multiple sclerosis   | 9,759   | 83    | <b>1.57</b> 1.29–1.90 |
| Sjögren's syndrome   | 1,994   | 19    | 1.31 0.80–2.00        |
| Systemic lupus erythematosus   | 2,101   | 19    | 1.57 0.96–2.39        |
| Thyrotoxicosis   | 17,308  | 136   | 1.10 0.93–1.30        |
| Type 1 diabetes  | 28,272  | 478   | <b>2.83</b> 2.58–3.10 |
| <b>Other autoimmune diseases</b>   | 80,979  | 642   | <b>1.21</b> 1.11–1.30 |
| Alopecia areata  | 1,377   | 9     | 1.05 0.50–1.90        |
| Ankylosing spondylitis   | 3,661   | 21    | 0.78 0.49–1.16        |
| Crohn's disease  | 12,117  | 98    | <b>1.33</b> 1.08–1.61 |
| Idiopathic thrombocytopenic purpura  | 1,660   | 14    | 1.36 0.76–2.21        |
| Iridocyclitis  | 9,220   | 80    | 1.18 0.94–1.46        |
| Pernicious anemia  | 1,082   | 19    | <b>2.59</b> 1.58–3.95 |
| Polymyalgia rheumatica   | 2,396   | 11    | 0.61 0.31–1.04        |
| Primary adrenocortical insufficiency   | 785     | 20    | <b>3.81</b> 2.36–5.79 |
| Primary biliary cirrhosis  | 478     | 9     | <b>2.65</b> 1.26–4.81 |
| Psoriasis vulgaris   | 13,269  | 190   | <b>2.13</b> 1.84–2.45 |
| Seropositive rheumatoid arthritis  | 15,768  | 82    | <b>0.75</b> 0.60–0.93 |
| Ulcerative colitis   | 22,289  | 146   | 0.99 0.84–1.16        |
| Autoimmune diseases with too few cases to calculate the individual risk <sup>b,c</sup> | 6,701   | 25    | 0.72 0.47–1.04        |

Source: Benros et al. Am J Psychiatry 2014

<sup>a</sup>Incidence rate ratios were adjusted for age and its interaction with sex, and calendar year. Persons without a history of schizophrenia spectrum diagnoses were chosen as reference category. Boldface indicates a significant result

<sup>b</sup>Only estimates building on five or more exposed cases are shown

<sup>c</sup>Estimates should be interpreted with caution, but the following autoimmune diseases were estimated together for completeness: autoimmune hemolytic anemia, pemphigus, pemphigoid, vitiligo, juvenile arthritis, Wegener's granulomatosis, dermatopolymyositis, myasthenia gravis, scleroderma



**Fig. 6.1** Relative risk of subsequent autoimmune diseases in people with schizophrenia (significant multiplicative interaction between schizophrenia and infection on the risk autoimmune diseases ( $p=0.004$ ). Source: Benros et al. Am J Psychiatry 2014

diagnosis and hospital contacts due to infections which increased the risk of subsequent autoimmune diseases by 2.7 times (Fig. 6.1) (Benros et al. 2014). In persons with schizophrenia, but no hospital contacts due to infections, the risk of autoimmune diseases was elevated with 32 % and diminished with time to a non-significant level in the time period 15 or more years after the schizophrenia diagnosis, whereas for persons with schizophrenia and infections the risk remained elevated. The increased incidence of autoimmune diseases following a diagnosis of schizophrenia might in some cases reflect symptoms of schizophrenia resulting from neuropsychiatric manifestations from the not-yet diagnosed autoimmune disease, particularly in the group with suspected presence of brain-reactive antibodies.

## 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 % (Benros et al. 2014; Eaton et al. 2010). However, a family history with bipolar disorder was not significantly associated with autoimmune diseases, and there was no association in the reverse direction either (Benros et al. 2014; Eaton et al. 2010). A family history with the following specific autoimmune diseases has been associated with an increased incidence of schizophrenia in a nationwide Danish study (Eaton et al. 2010): autoimmune hepatitis, type 1 diabetes, Sjögrens syndrome, iridocyclitis, multiple sclerosis, psoriasis vulgaris, and dermatopolymyositis, whereas only a family history with pernicious anemia was 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 has been confirmed in other populations as well (Wright et al. 1996; Gilvarry et al. 1996). A family history of schizophrenia was associated with pernicious anemia, diabetes type 1, iridocyclitis, autoimmune hepatitis, systemic lupus erythematosus, Sjögren's syndrome, and primary biliary cirrhosis.

## Associations Between Autoimmune Diseases and Depression

Several autoimmune diseases, such as diabetes type 1, multiple sclerosis, systemic lupus erythematosus, and autoimmune thyroid disease, have been associated with depression in smaller studies (Korczak et al. 2011; Strous and Shoenfeld 2007; Gold and Irwin 2009; Padmos et al. 2004; Pop et al. 1998; Vonk et al. 2007). Rheumatoid arthritis has been associated with depression in several studies and in a meta-analysis (Dickens et al. 2002). A Danish nationwide study on 91,637 cases with a first-time hospital contact due to mood disorders showed that a prior hospital contact because of autoimmune diseases increased the risk of a subsequent mood disorder diagnosis by 57 %, but when separating the effect of infections, autoimmune diseases were associated with an increased risk by 45 % compared to the general population (Table 6.3) (Benros et al. 2013). The risk of developing mood disorders was elevated to the greatest degree in the group of autoimmune diseases with suspected presence of brain-reactive antibodies (58 %), particularly when combined with an infection (2.49 times increase of risk). In another population-based study (Eaton et al. 2010), a 70 % increased risk was found of developing bipolar disorder within 4 years of an autoimmune disease diagnosis and a 20 % increased risk in the time span from 5 years and onwards after the diagnosis, compared to the background population.

**Table 6.3** Relative risk of mood disorders with a hospital contact in persons with hospital contact for autoimmune diseases and infections in Denmark (1977–2010)<sup>a</sup>

| Autoimmune disease   | Mood disorders in persons without infections |             |                    | Mood disorder in persons with infections |                  |                    |
|--|--|-------------|--------------------|--|------------------|--------------------|
|  | Relative risk <sup>b</sup>                   | 95 % CI     | Case patients      | Relative risk <sup>b</sup>               | 95 % CI          | Case patients      |
| Persons without autoimmune disease (reference)                                   | 1.00   | (Reference) | 60,361             | <b>1.62</b>                              | <b>1.60–1.64</b> | 27,081             |
| <b>Any autoimmune disease</b>  | <b>1.45</b>                                  | 1.39–1.52   | 2,082 <sup>c</sup> | <b>2.35</b>                              | 2.25–2.46        | 2,113 <sup>c</sup> |
| <b>Autoimmune diseases with suspected presence of brain-reactive antibodies:</b> | <b>1.58</b>                                  | 1.49–1.68   | 1,057              | <b>2.49</b>                              | 2.35–2.65        | 1,123              |
| Autoimmune hepatitis   | <b>2.28</b>                                  | 1.53–3.41   | 24                 | <b>3.13</b>                              | 2.39–4.11        | 52                 |
| Autoimmune thyroiditis   | 1.05   | 0.72–1.52   | 28                 | <b>1.63</b>                              | 1.09–2.43        | 24                 |
| Celiac disease   | <b>1.91</b>                                  | 1.41–2.60   | 41                 | <b>1.90</b>                              | 1.32–2.73        | 29                 |
| Guillain Barre syndrome  | <b>1.61</b>                                  | 1.14–2.26   | 33                 | <b>2.24</b>                              | 1.58–3.17        | 32                 |
| Multiple sclerosis   | <b>1.52</b>                                  | 1.30–1.77   | 162                | <b>2.42</b>                              | 2.06–2.86        | 142                |

(continued)

**Table 6.3** (continued)

|  | Mood disorders in persons without infections |           |               | Mood disorder in persons with infections |           |               |
|--|--|-----------|---------------|--|-----------|---------------|
|  | Relative risk <sup>b</sup>                   | 95 % CI   | Case patients | Relative risk <sup>b</sup>               | 95 % CI   | Case patients |
| Autoimmune disease                             |  |           |               |  |           |               |
| Sjögren's syndrome                             | <b>1.79</b>                                  | 1.23–2.61 | 27            | <b>2.58</b>                              | 1.79–3.71 | 29            |
| Systemic lupus erythematosus                   | <b>2.16</b>                                  | 1.61–2.89 | 45            | <b>2.19</b>                              | 1.65–2.92 | 47            |
| Thyrotoxicosis (Graves disease)                | <b>1.28</b>                                  | 1.12–1.45 | 228           | <b>1.90</b>                              | 1.63–2.21 | 165           |
| Type 1 diabetes                                | <b>1.77</b>                                  | 1.61–1.94 | 469           | <b>2.84</b>                              | 2.62–3.07 | 603           |
| <b>Other autoimmune diseases listed below:</b> | <b>1.35</b>                                  | 1.27–1.43 | 1,206         | <b>2.22</b>                              | 2.08–2.36 | 1,282         |
| Ankylosing spondylitis                         | 1.23   | 0.91–1.65 | 44            | <b>2.02</b>                              | 1.46–2.81 | 36            |
| Crohn's disease                                | <b>1.75</b>                                  | 1.52–2.01 | 191           | <b>2.32</b>                              | 2.04–2.65 | 224           |
| Iridocyclitis                                  | 1.22   | 1.00–1.48 | 101           | <b>2.08</b>                              | 1.70–2.54 | 94            |
| Juvenile arthritis                             | 1.20   | 0.88–1.64 | 39            | <b>2.48</b>                              | 1.93–3.19 | 61            |
| Psoriasis vulgaris                             | <b>1.58</b>                                  | 1.38–1.81 | 203           | <b>2.60</b>                              | 2.27–2.97 | 212           |
| Seropositive rheumatoid arthritis              | 1.08   | 0.93–1.25 | 167           | <b>2.18</b>                              | 1.89–2.52 | 183           |
| Ulcerative colitis                             | <b>1.41</b>                                  | 1.27–1.57 | 331           | <b>2.27</b>                              | 2.04–2.54 | 315           |
| Alopecia areata                                | 1.08   | 0.66–1.77 | 16            | <b>2.43</b>                              | 1.60–3.69 | 22            |
| Autoimmune hemolytic anemia                    | <b>2.53</b>                                  | 1.27–5.06 | 8             | <b>2.28</b>                              | 1.02–5.07 | 6             |
| Dermatopolymyositis                            | 1.25   | 0.60–2.62 | 7             | <b>3.40</b>                              | 2.01–5.74 | 14            |
| Idiopathic thrombocytopenic purpura            | 1.18   | 0.71–1.96 | 15            | <b>2.13</b>                              | 1.37–3.30 | 20            |
| Myasthenia gravis                              | 1.19   | 0.62–2.30 | 9             | –  | –         | 4             |
| Pernicious anemia                              | 1.37   | 0.81–2.30 | 14            | <b>2.14</b>                              | 1.24–3.68 | 13            |
| Primary adrenocortical insufficiency           | <b>2.58</b>                                  | 1.53–4.35 | 14            | 1.64                                     | 0.95–2.82 | 13            |
| Primary biliary cirrhosis                      | 1.74   | 0.78–3.88 | 6             | –  | –         | 3             |
| Pemphigus                                      | –  | –         | 2             | <b>4.31</b>                              | 1.94–9.60 | 6             |
| Pemphigoid                                     | –  | –         | 1             | –  | –         | 1             |
| Polymyalgia rheumatica                         | 1.30   | 0.77–2.19 | 14            | <b>3.81</b>                              | 2.53–5.73 | 23            |
| Scleroderma                                    | 1.03   | 0.56–1.92 | 10            | <b>3.18</b>                              | 2.05–4.93 | 20            |
| Vitiligo                                       | 1.24   | 0.70–2.17 | 12            | <b>2.01</b>                              | 1.14–3.54 | 12            |
| Wegener's granulomatosis                       | –  | –         | 2             | <b>2.37</b>                              | 1.18–4.75 | 8             |

Source: Benros et al. JAMA Psychiatry. 2013

<sup>a</sup>Analyses were adjusted for sex, age, and calendar period

<sup>b</sup>Boldface indicates that the 95 % confidence interval did not include 1.0. Relative risks were not estimated when there were less than five exposed cases. Each separate autoimmune disease gives rise to one analysis adjusted for all other autoimmune diagnoses

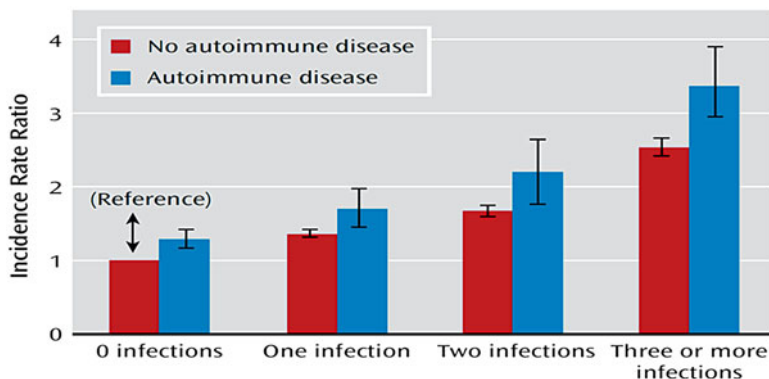
<sup>c</sup>The data reflect that an individual can have multiple autoimmune diseases

## Associations Between Infections and Schizophrenia

Epidemiological studies have indicated a dose–response relationship between urbanicity during upbringing and the risk of schizophrenia (Pedersen and Mortensen 2001), which could be related to, for instance, an increased probability of acquiring infections in urban environments (Yolken and Torrey 2008). An increased risk of schizophrenia has been associated with many different infectious agents, and a recent meta-analysis displayed significant associations between schizophrenia with *Toxoplasma gondii*, human herpesvirus 2, Borna disease virus, human endogenous retrovirus W, *Chlamydomphila psittaci*, and *Chlamydomphila pneumonia* (Arias et al. 2012). *T. gondii* infection has in many studies been associated with schizophrenia (Yolken and Torrey 2008; Niebuhr et al. 2008a; Torrey et al. 2007), and a recent population-based study indicated a dose–response relationship correlating with the serum titer of *toxoplasma* and the subsequent risk of schizophrenia (Pedersen et al. 2011). An increased risk of schizophrenia has also been associated with herpes simplex virus infection, detected by both serum antibodies (Dickerson et al. 2003; Niebuhr et al. 2008b) and CSF antibodies (Bartova et al. 1987). Cytomegalovirus (CMV) antibody titers have been found to be higher in the serum of patients with schizophrenia (Torrey et al. 2006; Leweke et al. 2004) and in the CSF (Torrey et al. 1982). However, studies have shown contradictory associations between CMV and schizophrenia, with stronger associations in newly diagnosed and untreated patients (Leweke et al. 2004), and to date, no neuropathologic evidence of CMV in the brains of patients with schizophrenia has been found (Torrey et al. 2006). Retroviral antigens and products have been identified in patients with schizophrenia (Karlsson et al. 2001; Hart et al. 1999), and other viruses associated with schizophrenia include Borna virus, where an increased serum prevalence having been observed (Chen et al. 1999). An increased prevalence of *Chlamydomphila* infection has also been observed in patients with schizophrenia, especially when linked to genetic markers of the immune system (Fellerhoff et al. 2007). Additionally, post-mortem studies have found increased prevalence of *Chlamydomphila* DNA in brains from patients with schizophrenia (Fellerhoff and Wank 2011). Psychotic disorders have also in population-based studies been associated with higher rates of several infections, such as pneumonia and pneumococcal disease (Crump et al. 2013a, b; Smith et al. 2013; Seminog and Goldacre 2013).

## The Risk of Schizophrenia After Infections

A large-scale Danish nationwide study on 39,076 persons with a diagnosis of schizophrenia spectrum disorders showed that any history of hospitalization with infection increased the risk of schizophrenia by 60 % (Benros et al. 2011).



**Fig. 6.2** Relative risk of schizophrenia spectrum disorders in persons with autoimmune disease and infections. *Source:* Benros et al. *Am J Psychiatry*. 2011

The risk of schizophrenia increased in a significant dose–response relationship with the number of infections (Fig. 6.2) and were increased the most with the temporal proximity of the last infection. The results remained significant after excluding persons diagnosed with substance use disorders, and there were no important differences in the relative risk added in persons with or without a psychiatric family history. Hospital contact due to infection had previously occurred in 23.6 % of persons diagnosed with schizophrenia spectrum disorders, yielded a population-attributable risk of 9 % associated with hospital contacts due to infections. A subsequent nationwide studies from Sweden confirmed the associations with previous hospital contacts with infections and schizophrenia spectrum disorders (Blomstrom et al. 2014). A subsequent Danish nationwide study on a narrower cohort during a period with complete follow-up of all hospital contacts showed that 45 % of persons with schizophrenia had a previous hospital contact with infection, which increased the risk of schizophrenia by 41 %, with bacterial infections increasing the risk by 63 % (Nielsen et al. 2014).

A recent meta-analysis has reported significant associations between childhood CNS infections and schizophrenia (Khandaker et al. 2012). Most studies on individuals with hospitalizations for CNS infections have found an increased risk of schizophrenia, including population-based studies from Denmark, Sweden, Finland, and Australia (Dalman et al. 2008; Benros et al. 2011; Liang and Chikritzhs 2012; Abrahao et al. 2005; Koponen et al. 2004). However, some studies did not find a significant association with CNS infections (Weiser et al. 2010; Suvisaari et al. 2003). In nationwide studies a broad spectrum of infections have been associated with schizophrenia, where sepsis and hepatitis infections were associated with the most elevated risk (2 and 4.9 times, respectively Table 6.4).

**Table 6.4** Relative risk of schizophrenia spectrum diagnosis in persons with autoimmune diseases depending on the site of infection, Denmark, 1977–2006

| Site of infection   | Only infection<br>(no autoimmune disease) |           |        | Autoimmune disease |            |       |
|---|---|-----------|--------|--------------------|------------|-------|
|   | IRR                                       | 95 % CI   | Cases  | IRR                | 95 % CI    | Cases |
| Sepsis infections   | <b>1.95</b>                               | 1.47–2.51 | 55     | <b>4.98</b>        | 2.49–8.73  | 10    |
| Hepatitis infections  | <b>4.89</b>                               | 4.26–5.58 | 212    | <b>8.89</b>        | 6.03–12.53 | 29    |
| Gastrointestinal infections                                   | <b>1.32</b>                               | 1.26–1.39 | 1,847  | <b>1.82</b>        | 1.46–2.24  | 83    |
| Skin infection  | <b>1.71</b>                               | 1.62–1.80 | 1,427  | <b>2.14</b>        | 1.69–2.66  | 74    |
| Pregnancy related infection                                   | 1.14                                      | 0.98–1.31 | 185    | 1.22               | 0.48–2.47  | 6     |
| Respiratory infections  | <b>1.53</b>                               | 1.46–1.61 | 1,885  | <b>2.25</b>        | 1.79–2.79  | 77    |
| Urogenital infections   | <b>1.90</b>                               | 1.79–2.01 | 1,200  | <b>2.70</b>        | 2.10–3.41  | 66    |
| CNS infections  | <b>1.28</b>                               | 1.09–1.50 | 148    | <b>2.62</b>        | 1.31–4.60  | 10    |
| Other types of infections                                     | <b>1.70</b>                               | 1.62–1.78 | 1,818  | <b>1.99</b>        | 1.60–2.43  | 89    |
| Persons without a hospital contact with infection (reference) | 1.00<br>(reference)                       |           | 29,372 | <b>1.30</b>        | 1.18–1.42  | 483   |

Source: Benros et al. *Am J Psychiatry*. 2011

## Associations Between Infections and Depression

Depression has also been associated with infections in several studies (Okusaga et al. 2011; Goodwin 2011; Steiner et al. 2012). In a study in which patients with depression were asked to describe in their own words their current state, the next most common descriptor was of physical changes that were described in terms of “feeling that the subject was coming down with a viral illness, either influenza or glandular fever, along with descriptions of aches and pains and, in particular, headaches or numbness of the head” (Maj 2011). These symptoms appear to be remarkably similar to symptoms of inflammation and infections. A study has demonstrated the associations of seropositivity for influenza and coronaviruses with both bipolar disorder and unipolar depression (Okusaga et al. 2011). Increased prevalence of anti-Borna disease virus antibodies has been detected in studies of patients with mood disorders (Terayama et al. 2003; Bode et al. 2001); however, a larger, blinded case–control study did not find any associations (Hornig et al. 2012). Chronic hepatitis C virus infections have consistently been associated with an increased incidence of depression, but other factors may be involved, for instance, the association may be due to alcohol and substance abuse or to treatment of hepatitis C with interferon, which is known to induce symptoms of depression. However, a recent study took all these factors into account and still found an increased risk of recurrent brief depression in patients with chronic hepatitis C (Carta et al. 2012). HIV infection and AIDS have also been associated with increased incidence of depressive symptoms,

and neuro-HIV infection can replicate in the CNS, which might induce neuropsychiatric symptoms. However, the possible social stigmatization or psychological effect of a HIV/AIDS diagnosis may also increase the risk of mood disorders, which have led to exclusion of HIV/AIDS in larger prospective studies.

## The Risk of Depression After an Infection

A Danish nationwide study on 91,637 cases with a first-time hospital contact due to mood disorders showed that any history of hospitalization with infection increased the IRR of later mood disorders by 62 %. The IRR of mood disorders was increased irrespective of the site of infection, with hepatitis resulting in the most elevated risk for mood disorders (2.8 times), followed by sepsis (2.1 times), and urogenital infections (2.1 times) (Table 6.5). The number of infections increased the risk of mood disorders in a dose–response relationship and the risk were increased the most with the temporal proximity of the last infection. Eight or more hospital contacts due to infections were associated with an increased risk for mood disorders by 3.4 times

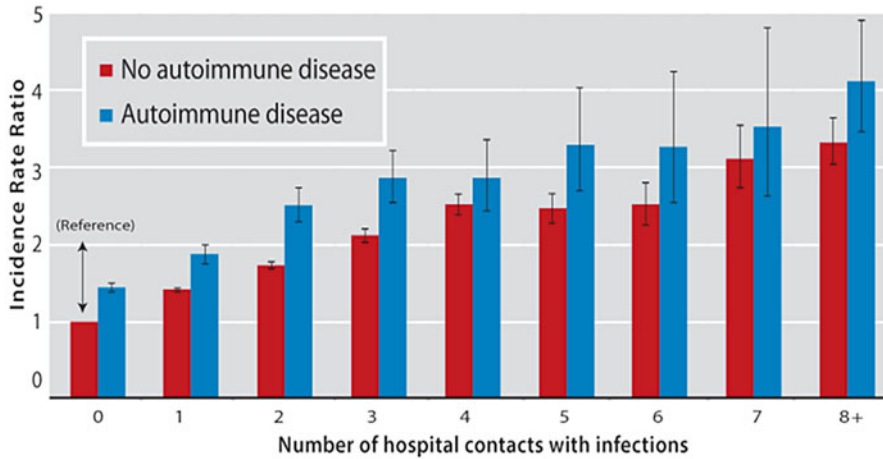
**Table 6.5** Relative risk of mood disorders with a hospital contact among persons with infections according to the infection site<sup>a</sup>

| Site of infection   | Infection but no autoimmune disease |             |                            | Infection and autoimmune disease |           |                            |
|---|-------------------------------------|-------------|----------------------------|----------------------------------|-----------|----------------------------|
|   | Relative risk <sup>b</sup>          | 95 % CI     | Case patients <sup>c</sup> | Relative risk <sup>b</sup>       | 95 % CI   | Case patients <sup>c</sup> |
| Sepsis infections   | <b>2.06</b>                         | 1.85–2.29   | 332                        | <b>3.24</b>                      | 2.61–4.03 | 82                         |
| Hepatitis infections  | <b>2.82</b>                         | 2.58–3.08   | 494                        | <b>3.01</b>                      | 2.33–3.89 | 58                         |
| Gastrointestinal infections                                   | <b>1.62</b>                         | 1.58–1.66   | 7,598                      | <b>2.52</b>                      | 2.34–2.72 | 676                        |
| Skin infection  | <b>1.70</b>                         | 1.65–1.74   | 5,865                      | <b>2.63</b>                      | 2.43–2.84 | 621                        |
| Pregnancy related infection                                   | <b>1.68</b>                         | 1.60–1.76   | 1,708                      | <b>2.26</b>                      | 1.90–2.69 | 128                        |
| Respiratory infections  | <b>1.69</b>                         | 1.65–1.74   | 7,035                      | <b>2.72</b>                      | 2.50–2.97 | 527                        |
| Urogenital infections   | <b>2.05</b>                         | 2.00–2.10   | 7,037                      | <b>2.83</b>                      | 2.62–3.05 | 660                        |
| CNS infections  | <b>1.65</b>                         | 1.54–1.78   | 716                        | <b>2.72</b>                      | 2.17–3.42 | 74                         |
| Other types of infections                                     | <b>1.81</b>                         | 1.76–1.86   | 5,729                      | <b>2.53</b>                      | 2.32–2.75 | 531                        |
| Persons without a hospital contact with infection (reference) | 1.00                                | (reference) | 60,361                     | <b>1.45</b>                      | 1.39–1.52 | 2,082                      |

<sup>a</sup>Analyses were adjusted for sex, age, and calendar period

<sup>b</sup>Calculated in nine separate analyses adjusted for sex, age, calendar period, and other infections. Boldface indicates that the 95 % confidence interval did not include 1.0

<sup>c</sup>Notice that one individual may have more than one diagnosis



**Fig. 6.3** Relative risk of mood disorders in persons with autoimmune disease and infections. *Source: Benros et al. JAMA Psychiatry. 2013*

(Fig. 6.3), and five or more different types of infections raised the risk of mood disorders by 4.8 times. Another recent study found an association between infections in early life and the occurrence of a broad range of mental disorders, including major depression, during youth (Goodwin 2011).

## Associations Between a Family History of Infections and Schizophrenia

A number of epidemiological studies suggest that maternal infection during pregnancy is a risk factor for schizophrenia (Yolken and Torrey 2008; Brown et al. 2005; Brown and Derkits 2010; Mednick et al. 1988; Mortensen et al. 2007). It has been suggested that it is not a specific infectious agent causing the disorder, but instead a maternal immune response common to various infectious agents influencing fetal brain development and, in consequence, leading to schizophrenia in later life, most likely in genetically susceptible individuals (Ozawa et al. 2006). As part of the immune response, elevated levels of antibodies are found in mothers of schizophrenic offspring at the end of pregnancy (Buka et al. 2001).

A Danish nationwide study on 3,722 individuals with schizophrenia showed that maternal infections were associated with a 39 % increased risk of schizophrenia in the offspring, and the risk was increased with 23 % after adjustments for parental mental illness (Nielsen et al. 2013). However, there was no significant difference in the increased risk of schizophrenia if the infections occurred during or outside the pregnancy period, and the risk of schizophrenia was similarly increased

when comparing infections in the mother or father (39 and 46 %, respectively). The data on a family history with infections could reflect a genetic susceptibility towards acquiring infections in individuals with schizophrenia, which is in line with genetic studies of individuals with schizophrenia (Stefansson et al. 2009).

## **The Combined Effect of Infections and Autoimmune Diseases as Risk Factors for Schizophrenia and Depression**

Animal studies have shown that if brain-reactive antibodies are present in the blood and agents that increase the permeability of the blood–brain barrier are given, they cause a temporary opening of the blood–brain barrier, with influx of brain-reactive antibodies into the brain and a subsequent development of a neuropsychiatric syndrome (Kowal et al. 2004). This indicates that brain-reactive antibodies in the circulation might not have pathological consequences until there is a breach of blood–brain barrier integrity (Diamond et al. 2009).

Therefore, studies have investigated the combined effect of hospital contacts due to autoimmune diseases and infections on the risk of developing schizophrenia and mood disorders. The combined effect was larger than predicted by a combination of the single effects of the two disease groups, indicating the presence of a synergistic effect of the two exposures, which increased the risk of schizophrenia by 2.3 times and the risk of mood disorders by 2.4 times (Tables 6.1 and 6.3) (Benros et al. 2011, 2013). The risk of developing schizophrenia or mood disorders was elevated to the greatest degree in the group of autoimmune diseases with a suspected presence of brain-reactive antibodies and infections. The findings could support that CNS autoimmune disorders may require a “double-insult” of circulating pathogenic serum antibodies present at the time when the blood–brain barrier is compromised by, for instance, infection, fever, or stress (Irani and Lang 2008). In persons with an autoimmune disease, three or more hospital contacts due to infections increased the risk of schizophrenia by 3.4 times and eight or more hospital contacts due to infections increased the risk of mood disorders by 4.1 times (Figs. 6.2 and 6.3). Sepsis is the type of infection that would probably increase the blood–brain barrier permeability the most, and it is interesting that persons with a sepsis infection and an autoimmune disease had a fivefold increased risk of schizophrenia and a 3.3 times increased risk of mood disorders. Of other notice is that having both a hepatitis infection and an autoimmune disease, the risk of schizophrenia is increased by 8.9 times, whereas the risk of mood disorders is increased by 3.0 times. If a person had an autoimmune hepatitis diagnosis and an infection, the risk of schizophrenia was increased by 8.9 times and the risk of mood disorders by 3.1 times. The association between inflammatory diseases in the liver and particularly schizophrenia (Benros et al. 2011), but also mood disorders, is interesting, since autoimmune hepatitis is also associated with brain-reactive antibodies (Kimura et al. 2010), and in patients with severe affection of the liver, as seen in coma hepaticum in the initial phases, psychiatric symptoms are dominating (Butterworth 2011).



## Somatic Co-morbidity in Patients with Schizophrenia and Depression

Both schizophrenia and depression are associated with excess somatic co-morbidity and mortality (Goldman 1999; Laursen et al. 2007, 2011; Moussavi et al. 2007). However, recent research indicates that the somatic co-morbidity, as exemplified in this chapter by autoimmune diseases and infections, is not only increased after the diagnoses of psychiatric disorders but also before the diagnosis and therefore probably not only due to the effects of psychiatric medication or lifestyle (Benros et al. 2009, 2011, 2013; Pedersen et al. 2012). Both schizophrenia and mood disorders have an excess co-occurrence of medical diseases involving inflammatory pathophysiological mechanisms, such as atopic disorders, autoimmune diseases, type 2 diabetes, and cardiovascular diseases (Chen et al. 2012; Moussavi et al. 2007; Pedersen et al. 2012). Depression is also a frequent co-morbidity to many chronic physical illnesses with inflammation, such as cancer (Moussavi et al. 2007). Additionally, Danish large-scale prospective population studies have shown that elevated C-reactive protein levels in the general population are associated with an increased risk of depression but also late-onset schizophrenia (Wium-Andersen et al. 2013, 2014).

## Genetics

Inflammation-related genes have been associated with susceptibility to both schizophrenia and mood disorders (Shelton et al. 2011), in which environmental influences, such as infections and autoimmune diseases, may interact with genetic factors. Genetic markers within the human leukocyte antigen (HLA) region, which contains genes related to immune function, have been associated with occurrence of both autoimmune diseases and schizophrenia (Stefansson et al. 2009; Jones et al. 2005; Ripke et al. 2011). GWAS studies on schizophrenia patients have consistently implicated chromosome 6 in the HLA region as a common susceptibility factor, and this has been shown in three large-scale GWAS studies (Stefansson et al. 2009; Ripke et al. 2011). Nonetheless, studies of autoimmune diseases and infections as risk factors for either schizophrenia or mood disorders stratified by a psychiatric family history showed that no additional increase in risk was added in persons with a psychiatric family history (Benros et al. 2011, 2013). However, several of the autoimmune diseases have been associated with, for instance, different markers in the HLA 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 (Eaton et al. 1992; Benros et al. 2012; Vinogradov et al. 1991). However, ascertainment bias or anti-inflammatory and analgesic effects of antipsychotics might also be involved in this negative association (Mors et al. 1999; Sellgren et al. 2014; Torrey and Yolken 2001).

## **Influence of Maternal Factors**

Infections during pregnancy might permanently alter the peripheral immune system of the fetus, and thereby change the response and vulnerability to future infections (Patterson 2009). Early-life exposure to infection and/or immune activation may induce sensitizing or preconditioning effects that can cause the organism to exacerbate reactions to subsequent immunological challenges in later life (Meyer et al. 2011a). This could be an alternative explanation for the increased incidence of infections prior to a diagnosis of schizophrenia and depression. Furthermore, epigenetic modifications after exposures to infections or other environmental factors could also induce dysregulation of the immune system.

## **The Influence of Psychological Stress**

Psychological stress can affect the immune system functioning and might increase the risk of acquiring infections and enhancing immunological responses in the individual (Pedersen et al. 2010; Ader et al. 1995). Both schizophrenia and depression are associated with psychological stress particularly preceding the onset of the diagnosis. Thus, the inflammatory response might simply be a parallel finding and not a causal relationship. The relationship might also be bidirectional with immune responses leading to psychological stress preceding the more severe psychiatric symptoms. The psychological effects of having an infection or autoimmune disease may also affect the associations with schizophrenia and depression. However, several of the chronic autoimmune diseases did not by themselves increase the risk, which indicates that the associations are not only due to the psychological stress of living with a chronic disease or being hospitalized.

## **The Influence of Medical Treatment**

An iatrogenic effect of medical treatment seems unlikely to explain the major associations, since only some of the autoimmune diseases would be treated with, for instance, steroids or interferon, which may increase the risk of psychosis and depression. Additionally, a decreased risk of psychosis associated with the use of steroids has also been reported (Laan et al. 2009), and newer biological treatment of autoimmune diseases has been shown to decrease the risk of mood disorders (Tyring et al. 2006). Furthermore, anti-inflammatory agents have been suggested to improve depression symptoms in patients with inflammatory disorders and enhance responsiveness to antidepressants (Tyring et al. 2006; Miller 2010; Meyer et al. 2011b; Henry et al. 2008). Antibiotics have not been associated with an increased risk of schizophrenia or depression. However, one could speculate that certain types of antibiotics might alter, for instance, the gut microflora, and thereby have positive or

negative effects on the immune system, and possibly also on psychiatric disorders (Cryan and Dinan 2012). Additionally, some antipsychotics can also affect immune responses possibly affecting the risk of subsequent autoimmune diseases and infections (Goldsmith and Rogers 2008).

## **The Influence of Social and Lifestyle Factors**

Social and lifestyle factors of persons not yet diagnosed with psychiatric disorders may increase the probability of smoking and alcohol and drug abuse, which can suppress the immune system and thereby increase the vulnerability to infection or have immune-activating effects resulting in autoimmunity (Margutti et al. 2006; Sperner-Unterweger 2005; Sopori 2002). Furthermore, social and lifestyle factors may affect the way individuals seek help in the health care system, and decreased compliance of treatment initiated by the general practitioner might lead to hospital treatment for autoimmune diseases and infections. Nevertheless, the added risk from infections or autoimmune diseases was not more pronounced in persons with a psychiatric family history or a personal history with substance abuse, which could be used as proxy variables for social and lifestyle factors (Benros et al. 2011, 2013).

## **Views on the Role of Infections and Autoimmunity in Association with Schizophrenia and Depression**

The underlying etiological mechanisms of the associations between infections and autoimmune diseases with schizophrenia and depression may be numerous and speculative, but not necessarily mutually exclusive and may in fact be interconnected. Both innate and adaptive immune responses might be involved, and there are many different routes of communication between the periphery and the brain (Dantzer et al. 2008). The psychiatric symptoms can be directly triggered by immune components, such as brain-reactive antibodies and cytokines, or infections reaching the CNS, possibly through increased permeability of the blood–brain barrier, or be secondary to systemic inflammation indirectly affecting the brain (Muller and Schwarz 2010; Dantzer et al. 2008; Diamond et al. 2009; Kayser et al. 2010; Bechter 2013). The associations with a range of autoimmune diseases and infections may reflect inflammation as a common pathway to schizophrenia and depression. Increased inflammation may increase the blood–brain barrier permeability, making the brain vulnerable to immune components such as autoantibodies and cytokines, or possibly the effect of specific T-cell subsets that are involved in immune surveillance of the brain (Goverman 2009). Furthermore, an imbalance between the Th1 and Th2 systems has also been proposed as an etiological component (Muller and Schwarz 2010), which would fit with the increased prevalence of autoimmune diseases and atopic disorders in people with schizophrenia

(Eaton et al. 2006; Pedersen et al. 2012). Inflammation can additionally affect the brain without passing the blood–brain barrier through stimulation of peripheral nerves (Dantzer et al. 2008) or proinflammatory cytokines activating the tryptophan–kynurenine pathway involved in regulation of the glutamate and serotonin system (Dantzer et al. 2008), and probably also indirectly the dopamine system (Muller and Schwarz 2010). Low-grade brain inflammation has also been proposed as an underlying causal mechanism of subgroups of patients with schizophrenia and severe depression, which could be triggered by infections and autoimmune diseases (Bechter et al. 2010; Bechter 2013). Additionally, inflammation might act as a priming event on microglia, inducing a long-term development of abnormal signal patterns (Hickie et al. 2009). The inflammation associated with severe infections and autoimmune diseases may also reactivate less severe infections that have been associated with schizophrenia and depression, such as herpes virus and *toxoplasma* infections. Some infectious agents escape surveillance by the immune system, but after an acute infection or inflammation, symptoms may flare up from the latent infection (Fellerhoff and Wank 2011). Additionally, alterations of the gut microbiota can also influence brain function and behavior possibly through neural, endocrine, and immune pathways (Cryan and Dinan 2012).

## Implications from Large-Scale Epidemiological Studies

The observed associations in the population-based register studies support a possible immunological contribution in subgroups of patients with schizophrenia and depression. However, whether it is a causal relationship or an epiphenomenon due to, for instance, other environmental factors or common genetic vulnerability remains to be proven. Register-based studies cannot identify specific etiological pathways; nonetheless, the observed associations seem robust. Additionally, there is a temporal and a dose–response relationship particularly for infections, which could indicate causal associations. Furthermore, the associations seem biologically plausible based on experimental animal and human studies. However, the associations between several somatic diseases seem to be of a bidirectional nature with increased incidence both before and after the psychiatric diagnosis. Additionally, new studies indicate that an even broader range of hospital contacts for somatic diseases than previously described seem to be associated with an elevated risk of psychiatric disorders. Even though most people with infections or autoimmune diseases do not develop psychiatric symptoms, immune exposures are rather common, and, in particular, infections might prove to be an important risk factor that is very common.

Schizophrenia and depression have complex, multifactorial, and to a large extent unknown etiologies (Yirmiya and Goshen 2011). A main contributing risk factor in population-based studies is a psychiatric family history that is, however, unlikely to be a sufficient cause and probably increases the risk of psychiatric disorders through interaction with environmental risk factors (Agerbo et al. 2012; Mortensen et al. 2010). Genetically vulnerable individuals might be at a particular risk of developing

psychiatric disorders like schizophrenia and depression as a consequence of inflammation and immune components affecting the brain. Subgroups of people with schizophrenia and depression 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 (Eaton et al. 2006; Wright et al. 1996; Benros et al. 2014). Additionally, it is interesting that etiological mechanisms similar to those of schizophrenia and depression are hypothesized to be involved in the initiation of autoimmunity where genetic susceptibility is required along with triggering events such as infections (Goldsmith and Rogers 2008).

## Perspectives

Diagnostic delay and under-treatment of somatic co-morbidity is a general problem for psychiatric patients (Laurson et al. 2007; Goldman 1999; Harris and Barraclough 1998), and possibly explains the increased mortality (Laurson et al. 2007, 2011). The increased mortality in psychiatric patients is actually mainly due to somatic diseases, even though suicide has received the most attention (Laurson et al. 2011; Laurson 2011). Hence, a thorough clinical examination and frequent somatic check-ups also seem of the utmost importance in patients with schizophrenia and depression. Screening for somatic diseases affecting the brain, such as autoimmune diseases and infections, preferentially with material closer to the brain, such as CSF in addition to sera, could in the near future prove to be helpful in diagnosing and treatment planning for persons with first-onset symptoms of schizophrenia and depression. However, the CNS is well protected and still difficult to access in vivo with regard to investigating signs of inflammation or relevant immune components.

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 3.2–6 % of patients with schizophrenia (Bechter et al. 2010; Kranaster et al. 2011). Furthermore, an increasing number of previously unknown antibodies with reactivity against the CNS are being reported in recent years (Steiner et al. 2012; Graus et al. 2010). Some of the strongest evidence for the potential for autoimmunity and immune components to cause psychiatric symptoms comes from the NMDA antibody-induced limbic encephalitis where psychiatric symptoms are often dominant in the initial and the remission phase of the disorder in up to 70 % of the cases (Kayser and Dalmau 2011), and which has been demonstrated to be treatable with immune therapies (Graus et al. 2010; Kayser and Dalmau 2011).

Potentially, immune and autoimmune processes could be involved in the prodrome and perhaps etiology of a non-negligible proportion of individuals with schizophrenia and depression. Symptom manifestations of autoimmune conditions might particularly resemble the subtype of psychosis and depression with chronic relapsing remitting illness, for instance (Yum et al. 2009). Subgroups of schizophrenia and depression could prove to be of a more systemic character, with inflammation as a common etiological mechanism that, besides the neuropsychiatric symptoms, includes physical

diseases such as autoimmune disease, cardiovascular disease, diabetes, and cancer (Dantzer et al. 2008; Leboyer et al. 2012). In addition, some psychiatric disorders and somatic diseases might have shared causes and be manifestations of the same underlying disease process or be exacerbated by each other. Whether or not the co-occurrence of somatic diseases in people with psychiatric symptoms is causally related to the psychiatric symptoms, the individuals would benefit from treatment for their somatic co-morbidity to reduce mortality and improve quality of life.

## Conclusion

In summary, experimental animal studies as well as human studies indicate that many diverse immune challenges can induce symptoms of schizophrenia and depression. There seems to be a solid association between autoimmune diseases and infections with both schizophrenia and depression based on large-scale nationwide studies. A prior autoimmune disease is associated with an increased risk of schizophrenia by 29 % and depression by 45 %. Any history of hospitalization with infection is associated with an increased risk of schizophrenia with 60 % and depression by 62 %. The combined effect of having had hospital contacts with both autoimmune diseases and infections increased the risk of schizophrenia by 2.3 times and the risk of depression by 2.4 times. Particularly the number of infections requiring hospitalization increases the risk of developing schizophrenia and depression in a dose–response relationship. Hospital contact because of infections was the most common risk factor, occurring in nearly 24 % of all patients before a schizophrenia diagnosis and in nearly 32 % of all patients before a depression diagnosis. Hospital contacts because of autoimmune diseases had occurred in 2.4 % of the patients before a schizophrenia diagnosis and in 5 % before a mood disorder diagnosis. After the diagnosis with schizophrenia the subsequent risk of autoimmune diseases is increased by 53 %, and in individuals with schizophrenia and hospital contacts for infections the risk is increased by 2.7 times. Autoimmune diseases occurred in 3.6 % after the schizophrenia diagnosis.

## References

- Abraham AL, Focaccia R, Gattaz WF. Childhood meningitis increases the risk for adult schizophrenia. *World J Biol Psychiatry*. 2005;6 Suppl 2:44–8.
- Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. *Lancet*. 1995;345(8942):99–103.
- Agerbo E, Mortensen PB, Wiuf C, et al. Modelling the contribution of family history and variation in single nucleotide polymorphisms to risk of schizophrenia: a Danish national birth cohort-based study. *Schizophr Res*. 2012;134(2–3):246–52.
- Arias I, Sorlozano A, Villegas E, et al. Infectious agents associated with schizophrenia: a meta-analysis. *Schizophr Res*. 2012;136(1–3):128–36.

- Balok DA. Neuroimmunopathology in a murine model of neuropsychiatric lupus. *Brain Res Rev.* 2007;54(1):67–79.
- Bartova L, Rajcani J, Pogady J. Herpes simplex virus antibodies in the cerebrospinal fluid of schizophrenic patients. *Acta Virol.* 1987;31(5):443–6.
- Bechter K. Updating the mild encephalitis hypothesis of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013;42:71–91.
- Bechter K, Reiber H, Herzog S, Fuchs D, Tuman H, Maxeiner HG. Cerebrospinal fluid analysis in affective and schizophrenic spectrum disorders: identification of subgroups with immune responses and blood–CSF barrier dysfunction. *J Psychiatr Res.* 2010;44(5):321–30.
- Bender L. Childhood schizophrenia. *Psychiatr Q.* 1953;27:663–81.
- Benros ME, Laursen TM, Dalton SO, Mortensen PB. Psychiatric disorder as a first manifestation of cancer: a 10-year population-based study. *Int J Cancer.* 2009;124(12):2917–22.
- Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *Am J Psychiatry.* 2011;168(12):1303–10.
- Benros ME, Mortensen PB, Eaton WW. Autoimmune diseases and infections as risk factors for schizophrenia. *Ann NY Acad Sci.* 2012;1262(1):56–66.
- Benros ME, Waltoft BL, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. *JAMA Psychiatry.* 2013;70(8):812–20.
- Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB. A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. *Am J Psychiatry.* 2014;171(2):218–26.
- Blomstrom A, Karlsson H, Svensson A, et al. Hospital admission with infection during childhood and risk for psychotic illness—a population-based cohort study. *Schizophr Bull.* 2014;40(6):1518–25.
- Bode L, Reckwald P, Severus WE, et al. Borna disease virus-specific circulating immune complexes, antigenemia, and free antibodies—the key marker triplet determining infection and prevailing in severe mood disorders. *Mol Psychiatry.* 2001;6(4):481–91.
- Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry.* 2010;167(3):261–80.
- Brown AS, Schaefer CA, Quesenberry Jr CP, Liu L, Babulas VP, Susser ES. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry.* 2005;162(4):767–73.
- Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry.* 2001;58(11):1032–7.
- Butterworth RF. Hepatic encephalopathy: a central neuroinflammatory disorder? *Hepatology.* 2011;53(4):1372–6.
- Carta MG, Angst J, Moro MF, et al. Association of chronic hepatitis C with recurrent brief depression. *J Affect Disord.* 2012;141(2–3):361–6.
- Cascella NG, Kryszak D, Bhatti B, et al. Prevalence of celiac disease and gluten sensitivity in the United States clinical antipsychotic trials of intervention effectiveness study population. *Schizophr Bull.* 2011;37(1):94–100.
- Chen CH, Chiu YL, Wei FC, et al. High seroprevalence of Borna virus infection in schizophrenic patients, family members and mental health workers in Taiwan. *Mol Psychiatry.* 1999;4(1):33–8.
- Chen P, Jiang T, Ouyang J, Chen Y. Depression, another autoimmune disease from the view of autoantibodies. *Med Hypotheses.* 2009;73(4):508–9.
- Chen SJ, Chao YL, Chen CY, et al. Prevalence of autoimmune diseases in in-patients with schizophrenia: nationwide population-based study. *Br J Psychiatry.* 2012;200(5):374–80.
- Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA Psychiatry.* 2013a;70(9):931–9.
- Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. *Am J Psychiatry.* 2013b;170(3):324–33.
- Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci.* 2012;13(10):701–12.

- Dalman C, Allebeck P, Gunnell D, et al. Infections in the CNS during childhood and the risk of subsequent psychotic illness: a cohort study of more than one million Swedish subjects. *Am J Psychiatry*. 2008;165(1):59–65.
- Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46–56.
- Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N Engl J Med*. 2003;349(16):1543–54.
- Davidson A, Diamond B. Autoimmune diseases. *N Engl J Med*. 2001;345(5):340–50.
- Diamond B, Huerta PT, Mina-Osorio P, Kowal C, Volpe BT. Losing your nerves? Maybe it's the antibodies. *Nat Rev Immunol*. 2009;9(6):449–56.
- Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom Med*. 2002;64(1):52–60.
- Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Ruslanova I, Yolken RH. Association of serum antibodies to herpes simplex virus 1 with cognitive deficits in individuals with schizophrenia. *Arch Gen Psychiatry*. 2003;60(5):466–72.
- Dickerson F, Stallings C, Origoni A, et al. Markers of gluten sensitivity and celiac disease in recent-onset psychosis and multi-episode schizophrenia. *Biol Psychiatry*. 2010;68(1):100–4.
- Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446–57.
- Drexhage RC, Weigelt K, van Beveren N, et al. Immune and neuroimmune alterations in mood disorders and schizophrenia. *Int Rev Neurobiol*. 2011;101:169–201.
- Eaton WW, Hayward C, Ram R. Schizophrenia and rheumatoid arthritis: a review. *Schizophr Res*. 1992;6(3):181–92.
- Eaton WW, Byrne M, Ewald H, et al. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. *Am J Psychiatry*. 2006;163(3):521–8.
- Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar disorder, and non-affective psychosis. *Bipolar Disord*. 2010;12(6):638–46.
- Fellerhoff B, Wank R. Increased prevalence of *Chlamydomphila* DNA in post-mortem brain frontal cortex from patients with schizophrenia. *Schizophr Res*. 2011;129(2–3):191–5.
- Fellerhoff B, Laumbacher B, Mueller N, Gu S, Wank R. Associations between *Chlamydomphila* infections, schizophrenia and risk of HLA-A10. *Mol Psychiatry*. 2007;12(3):264–72.
- Fessel WJ. Autoimmunity and mental illness. A preliminary report. *Arch Gen Psychiatry*. 1962;6:320–3.
- Fishman SL, Murray JM, Eng FJ, Walewski JL, Morgello S, Branch AD. Molecular and bioinformatic evidence of hepatitis C virus evolution in brain. *J Infect Dis*. 2008;197(4):597–607.
- Gilvarry CM, Sham PC, Jones PB, et al. Family history of autoimmune diseases in psychosis. *Schizophr Res*. 1996;19(1):33–40.
- Gold SM, Irwin MR. Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. *Immunol Allergy Clin North Am*. 2009;29(2):309–20.
- Goldman LS. Medical illness in patients with schizophrenia. *J Clin Psychiatry*. 1999;60 Suppl 21:10–5.
- Goldsmith CA, Rogers DP. The case for autoimmunity in the etiology of schizophrenia. *Pharmacotherapy*. 2008;28(6):730–41.
- Goodwin RD. Association between infection early in life and mental disorders among youth in the community: a cross-sectional study. *BMC Public Health*. 2011;11:878.
- Goverman J. Autoimmune T, cell responses in the central nervous system. *Nat Rev Immunol*. 2009;9(6):393–407.
- Graff H, Handford A. Celiac syndrome in the case histories of five schizophrenics. *Psychiatr Q*. 1961;35:306–13.
- Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. *J Neurol*. 2010;257(4):509–17.
- Hadjivassiliou M, Sanders DSGRA, Woodroffe N, Boscolo S, Aeschlimann D. Gluten sensitivity: from gut to brain. *Lancet Neurol*. 2010;9(3):318–30.



- Harris EC, Barraclough B. Excess mortality of mental disorder. *Br J Psychiatry*. 1998;173:11–53.
- Hart DJ, Heath RG, Sautter Jr FJ, et al. Antiretroviral antibodies: implications for schizophrenia, schizophrenia spectrum disorders, and bipolar disorder. *Biol Psychiatry*. 1999;45(6):704–14.
- Heath RG, Krupp IM. Schizophrenia as an immunologic disorder. I. Demonstration of antibrain globulins by fluorescent antibody techniques. *Arch Gen Psychiatry*. 1967a;16(1):1–9.
- Heath RG, Krupp IM. Catatonia induced in monkeys by antibrain antibody. *Am J Psychiatry*. 1967b;123(12):1499–504.
- Henry CJ, Huang Y, Wynne A, et al. Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. *J Neuroinflammation*. 2008;5:15.
- Hickie IB, Banati R, Stewart CH, Lloyd AR. Are common childhood or adolescent infections risk factors for schizophrenia and other psychotic disorders? *Med J Aust*. 2009;190(4 Suppl):S17–21.
- Hornig M, Briese T, Licinio J, et al. Absence of evidence for bornavirus infection in schizophrenia, bipolar disorder and major depressive disorder. *Mol Psychiatry*. 2012;17(5):486–93.
- Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171–86.
- Irani S, Lang B. Autoantibody-mediated disorders of the central nervous system. *Autoimmunity*. 2008;41(1):55–65.
- Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL. Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. *Psychiatr Q*. 2012;83(1):91–102.
- Jin SZ, Wu N, Xu Q, et al. A study of circulating gliadin antibodies in schizophrenia among a Chinese population. *Schizophr Bull*. 2012;38(3):514–8.
- Jones AL, Mowry BJ, Pender MP, Greer JM. Immune dysregulation and self-reactivity in schizophrenia: do some cases of schizophrenia have an autoimmune basis? *Immunol Cell Biol*. 2005;83(1):9–17.
- Kalaydjian AE, Eaton W, Cascella N, Fasano A. The gluten connection: the association between schizophrenia and celiac disease. *Acta Psychiatr Scand*. 2006;113(2):82–90.
- Karlsson H, Bachmann S, Schroder J, McArthur J, Torrey EF, Yolken RH. Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. *Proc Natl Acad Sci U S A*. 2001;98(8):4634–9.
- Katzav A, Solodeev I, Brodsky O, et al. Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. *Arthritis Rheum*. 2007;56(3):938–48.
- Kayser MS, Dalmau J. Anti-NMDA receptor encephalitis in psychiatry. *Curr Psychiatry Rev*. 2011;7:189–93.
- Kayser MS, Kohler CG, Dalmau J. Psychiatric manifestations of paraneoplastic disorders. *Am J Psychiatry*. 2010;167(9):1039–50.
- Khandaker GM, Zimbron J, Dalman C, Lewis G, Jones PB. Childhood infection and adult schizophrenia: a meta-analysis of population-based studies. *Schizophr Res*. 2012;139(1–3):161–8.
- Kim KS. Mechanisms of microbial traversal of the blood–brain barrier. *Nat Rev Microbiol*. 2008;6(8):625–34.
- Kimura A, Sakurai T, Koumura A, et al. High prevalence of autoantibodies against phosphoglycerate mutase 1 in patients with autoimmune central nervous system diseases. *J Neuroimmunol*. 2010;219(1–2):105–8.
- Koponen H, Rantakallio P, Veijola J, Jones P, Jokelainen J, Isohanni M. Childhood central nervous system infections and risk for schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2004;254(1):9–13.
- Korczak DJ, Pereira S, Koulajian K, Matejcek A, Giacca A. Type 1 diabetes mellitus and major depressive disorder: evidence for a biological link. *Diabetologia*. 2011;54(10):2483–93.
- Kowal C, Degiorgio LA, Nakaoka T, et al. Cognition and immunity; antibody impairs memory. *Immunity*. 2004;21(2):179–88.
- Kranaster L, Koethe D, Hoyer C, Meyer-Lindenberg A, Leweke FM. Cerebrospinal fluid diagnostics in first-episode schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2011;261(7):529–30.
- Laan W, Smeets H, de Wit NJ, Kahn RS, Grobbee DE, Burger H. Glucocorticosteroids associated with a decreased risk of psychosis. *J Clin Psychopharmacol*. 2009;29(3):288–90.
- Laske C, Zank M, Klein R, et al. Autoantibody reactivity in serum of patients with major depression, schizophrenia and healthy controls. *Psychiatry Res*. 2008;158(1):83–6.

- Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophr Res*. 2011;131(1–3):101–4.
- Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry*. 2007;68(6):899–907.
- Laursen TM, Munk-Olsen T, Gasse C. Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. *PLoS One*. 2011;6(9):e24597.
- Leboyer M, Soreca I, Scott J, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord*. 2012;141(1):1–10.
- Leweke FM, Gerth CW, Koethe D, et al. Antibodies to infectious agents in individuals with recent onset schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2004;254(1):4–8.
- Liang W, Chikritzhs T. Early childhood infections and risk of schizophrenia. *Psychiatry Res*. 2012;200(2–3):214–7.
- Maj M. When does depression become a mental disorder? *Br J Psychiatry*. 2011;199(2):85–6.
- Marballi K, Quinones MP, Jimenez F, et al. In vivo and in vitro genetic evidence of involvement of neuregulin 1 in immune system dysregulation. *J Mol Med (Berl)*. 2010;88(11):1133–41.
- Margutti P, Delunardo F, Ortona E. Autoantibodies associated with psychiatric disorders. *Curr Neurovasc Res*. 2006;3(2):149–57.
- Mednick SA, Machon RA, Huttunen MO, Bonett D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry*. 1988;45(2):189–92.
- Meyer U, Feldon J, Dammann O. Schizophrenia and autism: both shared and disorder-specific pathogenesis via perinatal inflammation? *Pediatr Res*. 2011a;69(5 Pt 2):26R–33.
- Meyer U, Schwarz MJ, Muller N. Inflammatory processes in schizophrenia: a promising immunological target for the treatment of negative/cognitive symptoms and beyond. *Pharmacol Ther*. 2011b;132(1):96–110.
- Miller AH. Depression and immunity: a role for T cells? *Brain Behav Immun*. 2010;24(1):1–8.
- Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 2009;65(9):732–41.
- Mors O, Mortensen PB, Ewald H. A population-based register study of the association between schizophrenia and rheumatoid arthritis. *Schizophr Res*. 1999;40(1):67–74.
- Mortensen PB, Norgaard-Pedersen B, Waltoft BL, et al. *Toxoplasma gondii* as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. *Biol Psychiatry*. 2007;61(5):688–93.
- Mortensen PB, Pedersen MG, Pedersen CB. Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? *Psychol Med*. 2010;40(2):201–10.
- Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 2007;370(9590):851–8.
- Muller N, Schwarz MJ. Immune system and schizophrenia. *Curr Immunol Rev*. 2010;6(3):213–20.
- Niebuhr DW, Millikan AM, Cowan DN, Yolken R, Li Y, Weber NS. Selected infectious agents and risk of schizophrenia among U.S. military personnel. *Am J Psychiatry*. 2008a;165(1):99–106.
- Niebuhr DW, Millikan AM, Yolken R, Li Y, Weber NS. Results from a hypothesis generating case-control study: herpes family viruses and schizophrenia among military personnel. *Schizophr Bull*. 2008b;34(6):1182–8.
- Nielsen PR, Laursen TM, Mortensen PB. Association between parental hospital-treated infection and the risk of schizophrenia in adolescence and early adulthood. *Schizophr Bull*. 2013;39(1):230–7.
- Nielsen PR, Benros ME, Mortensen PB. Hospital contacts with infection and risk of schizophrenia: a population-based cohort study with linkage of Danish national registers. *Schizophr Bull*. 2014;40(6):1526–32.
- Nikkila HV, Muller K, Ahokas A, Rimon R, Andersson LC. Increased frequency of activated lymphocytes in the cerebrospinal fluid of patients with acute schizophrenia. *Schizophr Res*. 2001;49(1–2):99–105.

- Noll R. Kraepelin's 'lost biological psychiatry'? Autointoxication, organotherapy and surgery for dementia praecox. *Hist Psychiatry*. 2007;18(71 Pt 3):301–20.
- Okusaga O, Yolken RH, Langenberg P, et al. Association of seropositivity for influenza and coronaviruses with history of mood disorders and suicide attempts. *J Affect Disord*. 2011;130(1–2):220–5.
- Ozawa K, Hashimoto K, Kishimoto T, Shimizu E, Ishikura H, Iyo M. Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: a neurodevelopmental animal model of schizophrenia. *Biol Psychiatry*. 2006;59(6):546–54.
- Padmos RC, Bekris L, Knijff EM, et al. A high prevalence of organ-specific autoimmunity in patients with bipolar disorder. *Biol Psychiatry*. 2004;56(7):476–82.
- Patterson PH. Immune involvement in schizophrenia and autism: etiology, pathology and animal models. *Behav Brain Res*. 2009;204(2):313–21.
- Pedersen CB, Mortensen PB. Evidence of a dose–response relationship between urbanicity during upbringing and schizophrenia risk. *Arch Gen Psychiatry*. 2001;58(11):1039–46.
- Pedersen A, Zachariae R, Bovbjerg DH. Influence of psychological stress on upper respiratory infection—a meta-analysis of prospective studies. *Psychosom Med*. 2010;72(8):823–32.
- Pedersen MG, Stevens H, Pedersen CB, Norgaard-Pedersen B, Mortensen PB. Toxoplasma infection and later development of schizophrenia in mothers. *Am J Psychiatry*. 2011;168(8):814–21.
- Pedersen MS, Benros ME, Agerbo E, Borglum AD, Mortensen PB. Schizophrenia in patients with atopic disorders with particular emphasis on asthma: a Danish population-based study. *Schizophr Res*. 2012;138(1):58–62.
- Pilkington T. The coincidence of rheumatoid arthritis and schizophrenia. *J Nerv Ment Dis*. 1955;124:604–6.
- Pop VJ, Maartens LH, Leusink G, et al. Are autoimmune thyroid dysfunction and depression related? *J Clin Endocrinol Metab*. 1998;83(9):3194–7.
- Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biol Psychiatry*. 2008;63(8):801–8.
- Reichelt KL, Landmark J. Specific IgA antibody increases in schizophrenia. *Biol Psychiatry*. 1995;37(6):410–3.
- Rice JS, Kowal C, Volpe BT, Degiorgio LA, Diamond B. Molecular mimicry: anti-DNA antibodies bind microbial and nonnucleic acid self-antigens. *Curr Top Microbiol Immunol*. 2005;296:137–51.
- Ripke S, Sanders AR, Kendler KS, et al. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet*. 2011;43(10):969–76.
- Rivest S. Interactions between the immune and neuroendocrine systems. *Prog Brain Res*. 2010;181:43–53.
- Rose NR. The role of infection in the pathogenesis of autoimmune disease. *Semin Immunol*. 1998;10(1):5–13.
- Samaroo D, Dickerson F, Kasarda DD, et al. Novel immune response to gluten in individuals with schizophrenia. *Schizophr Res*. 2010;118(1–3):248–55.
- Sellgren C, Frisell T, Lichtenstein P, Landen M, Askling J. The association between schizophrenia and rheumatoid arthritis: a nationwide population-based Swedish study on intraindividual and familial risks. *Schizophr Bull*. 2014;40(6):1552–9.
- Seminog OO, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. *Thorax*. 2013;68(2):171–6.
- Shankar V, Kao M, Hamir AN, Sheng H, Koprowski H, Dietzschold B. Kinetics of virus spread and changes in levels of several cytokine mRNAs in the brain after intranasal infection of rats with Borna disease virus. *J Virol*. 1992;66(2):992–8.
- Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, et al. Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. *Mol Psychiatry*. 2011;16(7):751–62.
- Smith DJ, Langan J, McLean G, Guthrie B, Mercer SW. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. *BMJ Open*. 2013;3(4).

- Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol.* 2002;2(5):372–7.
- Sperner-Unterweger B. Immunological aetiology of major psychiatric disorders: evidence and therapeutic implications. *Drugs.* 2005;65(11):1493–520.
- Stefansson H, Ophoff RA, Steinberg S, et al. Common variants conferring risk of schizophrenia. *Nature.* 2009;460(7256):744–7.
- Steiner J, Bogerts B, Sarnyai Z, et al. Bridging the gap between the immune and glutamate hypotheses of schizophrenia and major depression: potential role of glial NMDA receptor modulators and impaired blood–brain barrier integrity. *World J Biol Psychiatry.* 2012;13(7):482–92.
- Strous RD, Shoenfeld Y. Behavioral changes in systemic lupus erythematosus are of an autoimmune nature. *Nat Clin Pract Rheumatol.* 2007;3(11):592–3.
- Sullivan PF, Daly MJ, O’Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nat Rev Genet.* 2012;13(8):537–51.
- Sundquist K, Li X, Hemminki K, Sundquist J. Subsequent risk of hospitalization for neuropsychiatric disorders in patients with rheumatic diseases: a nationwide study from Sweden. *Arch Gen Psychiatry.* 2008;65(5):501–7.
- Suvisaari J, Mautemps N, Haukka J, Hovi T, Lonnqvist J. Childhood central nervous system viral infections and adult schizophrenia. *Am J Psychiatry.* 2003;160(6):1183–5.
- Tanaka S, Matsunaga H, Kimura M, et al. Autoantibodies against four kinds of neurotransmitter receptors in psychiatric disorders. *J Neuroimmunol.* 2003;141(1–2):155–64.
- Terayama H, Nishino Y, Kishi M, Ikuta K, Itoh M, Iwahashi K. Detection of anti-Borna disease virus (BDV) antibodies from patients with schizophrenia and mood disorders in Japan. *Psychiatry Res.* 2003;120(2):201–6.
- Torrey EF, Yolken RH. The schizophrenia-rheumatoid arthritis connection: infectious, immune, or both? *Brain Behav Immun.* 2001;15(4):401–10.
- Torrey EF, Yolken RH, Winfrey CJ. Cytomegalovirus antibody in cerebrospinal fluid of schizophrenic patients detected by enzyme immunoassay. *Science.* 1982;216(4548):892–4.
- Torrey EF, Leweke MF, Schwarz MJ, et al. Cytomegalovirus and schizophrenia. *CNS Drugs.* 2006;20(11):879–85.
- Torrey EF, Bartko JJ, Lun ZR, Yolken RH. Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. *Schizophr Bull.* 2007;33(3):729–36.
- Trevathan R, Tatum JC. Rarity of concurrence of psychosis and rheumatoid arthritis in individual patients. *J Nerv Ment Dis.* 1953;120:83–4.
- Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet.* 2006;367(9504):29–35.
- Uranova NA, Zimina IS, Vikhrevva OV, Krukov NO, Rachmanova VI, Orlovskaya DD. Ultrastructural damage of capillaries in the neocortex in schizophrenia. *World J Biol Psychiatry.* 2010;11(3):567–78.
- Vinogradov S, Gottesman II, Moises HW, Nicol S. Negative association between schizophrenia and rheumatoid arthritis. *Schizophr Bull.* 1991;17(4):669–78.
- Vonk R, van der Schot AC, Kahn RS, Nolen WA, Drexhage HA. Is autoimmune thyroiditis part of the genetic vulnerability (or an endophenotype) for bipolar disorder? *Biol Psychiatry.* 2007;62(2):135–40.
- Weiser M, Werbeloff N, Levine A, et al. CNS infection in childhood does not confer risk for later schizophrenia: a case–control study. *Schizophr Res.* 2010;124(1–3):231–5.
- Wilkinson J, Radkowski M, Eschbacher JM, Laskus T. Activation of brain macrophages/microglia cells in hepatitis C infection. *Gut.* 2010;59(10):1394–400.
- Wium-Andersen MK, Orsted DD, Nielsen SF, Nordestgaard BG. Elevated C-reactive protein levels, psychological distress, and depression in 73 131 individuals. *JAMA Psychiatry.* 2013;70(2):176–84.

- Wium-Andersen MK, Orsted DD, Nordestgaard BG. Elevated C-reactive protein associated with late- and very-late-onset schizophrenia in the general population: a prospective study. *Schizophr Bull.* 2014;40(5):1117–27.
- Wright P, Sham PC, Gilvarry CM, et al. Autoimmune diseases in the pedigrees of schizophrenic and control subjects. *Schizophr Res.* 1996;20(3):261–7.
- Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain Behav Immun.* 2011;25(2):181–213.
- Yolken RH, Torrey EF. Are some cases of psychosis caused by microbial agents? A review of the evidence. *Mol Psychiatry.* 2008;13(5):470–9.
- Yum SY, Yum SK, Kim T, Hwang MY. Clinical perspectives on autoimmune processes in schizophrenia. *Psychiatr Clin North Am.* 2009;32(4):795–808.