Prenatal exposure to maternal infections or immune response and the offspring's risk for mental disorders – a review

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Tiivistelmä – Referat – Abstract

The objective of this review is to summarize the current scientific evidence on the effect of prenatal exposure to maternal infection and immune response on the offspring's risk for mental disorders.

Studies were searched from PubMed database with the following keywords: Mental Disorders AND Prenatal Exposure Delayed Effects AND Infection AND Inflammation.

Prenatal exposure to maternal influenza appears to increase the offspring's risk for schizophrenia spectrum disorders, although the studies are not fully consistent. Prenatal exposure to maternal fever seems to be related with elevated autism risk in the offspring. No replicated findings of an association between prenatal infectious exposure and other mental disorders exist.

Evidence for the effect of prenatal exposure to maternal infection on risk for mental disorders exists for several different infections, and it is likely that the genetic liability to these disorders operate in conjunction with the exposure. Therefore, genetically sensitive study designs are needed.

Avainsanat – Nyckelord – Keywords
Schizophrenia, Autistic Disorder, Prenatal Exposure Delayed Effects, Infection, Mental Disorders

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Muita tietoja – Övriga uppgifter – Additional information

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1 Introduction

Over the last two decades, many studies have investigated the prenatal maternal exposure to different infectious agents and the offspring's risk for mental disorders, mostly for schizophrenia. In the beginning, most of the studies used an ecologic study design, estimating the timing of the exposure to infectious agents retrospectively by obtaining data on epidemics in populations from different registries. Some studies also collected exposure data by interviewing the mothers during or shortly after pregnancy or using their medical records. Thereafter many studies requited a more accurate way of estimating maternal exposure, by investigating prospectively collected maternal sera. These studies have not focused on the mechanism by which the infectious agents increase the risk for mental disorders. To reveal the mechanisms and site of action of the infectious agents, researchers have used animal models.

Several reviews of prenatal infectious agents as risk factors for different mental disorders in offspring exist so far. Most of these reviews have covered the effect of infectious agents and/or other prenatal exposures on the risk of schizophrenia. Some of them have chosen to focus on either human (1-3) or animal studies (4-7), whereas others have included both study designs (8-10). Two reviews have combined schizophrenia and autism as the main outcomes, one (11) including both human and animal studies and the other (12) focusing on epidemiological studies. One review (13) chose to focus on prenatal exposures and the risk of both schizophrenia and depression. Autism has been chosen to the subject of one review (14) including both human and animal studies. To the knowledge of the author, however, no reviews covering prenatal exposure to infectious agents and the risk of different mental disorders has been published. The aim of this review is to summarize the literature on prenatal maternal infection and immune response and explore their role in the development of schizophrenia spectrum disorders, autism spectrum disorders, and other mental and neurocognitive disorders.

2 Methods

Studies were searched from PubMed database with the following keywords: Mental Disorders AND Prenatal Exposure Delayed Effects AND Infection AND Inflammation. All reviewed studies are described in the tables.

3 Prenatal maternal infection and immune response and risk for mental disorders

3.1 Schizophrenia Spectrum Disorders

Human studies

Of all mental disorders, clearly most attention has been paid to Schizophrenia Spectrum Disorders' association with the exposure of prenatal maternal infection and immune response. A pioneer study by Mednick et al. was conducted in 1988 (15), using a Finnish birth cohort exposed to type A2 influenza epidemic in 1957. The authors found an association between second trimester exposure to influenza epidemic and increased risk for schizophrenia spectrum disorders. These results attracted attention of many researchers, and several replications of the results exist (16-17). Following studies have sought to overcome the methodological limitations of the study by requiting different study designs, as reviewed below.

Support to the findings described below were derived from a study (16) in which the researchers sought to investigate the effect of prenatal exposure to maternal influenza on schizophrenia risk by retrospectively obtaining the data on influenza prevalence from a Danish national register. This study found that influenza exposure 4 months prior to birth was associated with an increased schizophrenia risk in the offspring (RR 1.12, 95% CI 1.01-1.24). A French study (17) also found an association between exposure to maternal influenza and schizophrenia in the

offspring, as significantly more individuals with schizophrenia than controls had been exposed to the virus during the fifth month of pregnancy (individuals with schizophrenia: OR 2.24, 95% CI 1.49-3.35, controls: OR 1.61, 95% CI 1.04-2.49). The exposure to maternal influenza was estimated from the existence of national influenza epidemics.

In contrast to these replications, also negative findings exist. One study (18) used a similar study design as the studies reviewed above, estimating the exposure from influenza epidemics, and no association was found between prenatal exposure to maternal influenza three, four or five months prior to the month of birth (RR 0.96, 95% CI 0.88-1.04; RR 1.00, 95% CI 0.92-1.09; RR 1.01, 95% CI 0.93-1.10, respectively) and schizophrenia.

In addition to examining the effect of prenatal exposure to maternal influenza on schizophrenia risk, the relationship between 16 different infectious diseases and risk of schizophrenia in the offspring was determined (19). Exposure was estimated by obtaining the data on the number of deaths from these diseases from a national registry, and the sample consisted of two independent sets of birth dates of patients with schizophrenia. In both of them, bronchopneumonia deaths preceded births of those with schizophrenia by three and five months. However, no association with the remaining 15 infectious diseases was found.

The association between prenatal exposure to both maternal influenza and measles and risk of schizophrenia was studied in a study (20) in which the statewide exposure data was obtained from US statewide infectious disease tables. However, the retrospective study design did not able to determine whether the mother had actually been infected or not. Neither influenza nor measles exposure was found to be associated with schizophrenia risk in the offspring.

One group of researchers (21) took also seasonality into account, and sought to examine whether the prenatal exposure to maternal influenza is an independent risk factor for schizotypy, i.e. the presence of schizophrenic-like thought patterns in the absence of psychosis (22), or confounded with the effect of cold temperature. For this purpose, the study was conducted among Mauritian subjects, because Hong Kong influenza epidemic between 1968 and 1972 and cold temperature were not confounded in Mauritius. Schizotypy was measured by a two-factor scale, in which positive symptoms were labeled as schizophrenism (SZ) and negative symptoms as physical and social anhedonia (AH). Prenatal influenza exposure was found to be associated with elevated schizophrenism, whereas exposure to low temperatures was associated with elevated anhedonia in the offspring.

One limitation of all of the above reviewed studies was that they were not able to determine whether the mother actually was infected or not. To overcome this problem, Mednick et al 1994 (23) obtained data on maternal infection and its timing during pregnancy from prenatal clinic records. A significantly higher rate of definite influenza infections was found in patients with schizophrenia exposed during the second trimester (86.7%) than in those exposed during the rest of the pregnancy (20%). Another research group (24) used a similar study design, obtaining data on different maternal respiratory infections from the gravida's Health Plan charts. An association was found between second trimester exposure to respiratory infections and risk for schizophrenia spectrum disorders (RR 2.13, 95% CI 1.05-4.35), whereas exposure during first and third trimesters had no impact on the risk.

The relationship between prenatal exposure to maternal genital/reproductive infections and the offspring's risk of schizophrenia has also been studied (25). Exposure data were obtained from diagnoses made by physicians during obstetric and medical visits. Periconceptional exposure to genital/reproductive infections was related

to an increased risk of schizophrenia spectrum disorders (OR 5.03, 95% CI 2.00-12.64).

One study (26) obtained the data on prenatal exposure to maternal bacterial infections by interviewing the mothers five days after delivery and at their first antenatal clinic visit. The effect of the exposure on the risk for both ICD-8 and broadly defined (ICD-8 and ICD-10) schizophrenia in the offspring was examined. Exposure during the first trimester was associated with an increased risk for both of them (OR 2.53, 95% CI 1.07-5.96 and OR 2.14, 95% CI 1.06-4.31, respectively).

In contrast to other studies, positive family history of psychotic disorders was sought to be taken into account by calculating the biological synergism between it and prenatal infection exposure on affecting the offspring's risk for schizophrenia. Acute pyelonephritis leading to the hospitalization of the mother was chosen as the prenatal infectious exposure for the study. The exposure data, together with the data on the family history of psychiatric diseases, was obtained from national registries. The authors found that prenatal pyelonephritis exposure was five times greater in those individuals having positive family history of psychosis compared to those who did not. While no significant increase in the risk of schizophrenia after the exposure to maternal pyelonephritis alone was found, the synergy analysis suggested an estimated 38%-46% of the offspring with schizophrenia to have developed the disorder as a result of synergism between both of the factors.

One study (28) sought to determine whether the effect of prenatal exposure to different infections on the offspring's schizophrenia risk was different from that of prenatal exposure to paternal infections or parental infections in general. Infection data was obtained from national hospital register diagnoses. No significant differences between these different types of exposures were found (parental infection: incidence rate ratio IRR 1.23, 95% CI 1.04-1.44; paternal infection: IRR 1.31, 95% 0.87-1.88).

The relationship between different complications during pregnancy and delivery, and schizophrenia risk in a group of children with mothers having schizophrenia spectrum disorders was examined (29), using the obstetric records as the source of complication data. Prenatal exposure to maternal infections was associated with an elevated risk of schizophrenia spectrum disorders in the offspring of mothers having schizophrenia spectrum disorders (HRR 3.73, 95% CI 1.27-11.01). Also, mothers having schizophrenia spectrum disorder during pregnancy had a higher rate of infections during pregnancy compared to those developing the disorder after the pregnancy (19.0% vs 9.3%, respectively). Thus, prenatal maternal infections might be among the mechanisms by which the maternal history of schizophrenia spectrum disorders elevates the offspring's risk for developing schizophrenia spectrum disorders.

Majority of the more recent studies in humans have used a more accurate approach, determining the prenatal exposure to maternal infections and immune response by assaying maternal serum samples collected during pregnancy. Because prenatal exposure to several different infectious agents had been found to be associated with increased risk to schizophrenia spectrum disorders, the serum levels of four cytokines elevated in infectious and inflammatory processes during the second trimester were investigated (30). The authors found that serum levels of IL-8 were significantly elevated in mothers of subjects than controls during the second trimester, whereas no differences in the levels of IL-1β, IL-6, or TNF-α were detected.

Another study (31) studied the effect of prenatal exposure to maternal influenza on the risk for schizophrenia spectrum disorders in the offspring. The exposure was determined by assaying maternal sera for influenza antibody, and results showed a seven-fold increase (OR 7.0, 95% CI 0.7-75.3) in risk when exposed during the first trimester, whereas

no association to the risk was observed after second- or third-trimester exposures. However, this finding did not achieve statistical significance (p=.08). The risk was increased three-fold (OR 3.0, 95% CI 0.9-10.1, p=.52) when using a gestational period from early to mid-pregnancy.

Also the effect of prenatal exposure to maternal herpes simplex virus 2 (HSV-2) infections on the offspring's risk for schizophrenia spectrum disorder has been examined (32). The research group assayed maternal sera from late pregnancy for IgG antibody to HSV-2, but no association (OR 1.04, 95% CI 0.76-1.43) with schizophrenia spectrum disorder risk was found.

The aim of one study by Brown et al. (33) was to examine whether prenatal exposure to maternal influenza or toxoplasmosis was associated with executive dysfunction in schizophrenic offspring. Maternal sera were assayed to determine the prenatally exposed vs. non-exposed subjects, and a neurophysiological test battery was used as a measure of executive functions. The results showed decreased skills in executive functions in most of the conducted tests among the exposed (serologically documented exposure to either influenza or toxoplasmosis during the first half of the pregnancy) patients compared to the non-exposed group.

A recent study (34) examined the association between the early gestational level of C-reactive protein (CRP) in the maternal serum samples and the risk of schizophrenia in the offspring. A significant association was found between increasing maternal CRP levels and schizophrenia prevalence in the offspring (OR 1.31, 95% CI 1.10-1.56). According to the authors, their findings provide the most robust evidence to date that maternal inflammation may play a significant role in schizophrenia. This was rationalized with a large, prospectively collected sample (N= over 700 cases and 700 controls), ascertainment of the schizophrenia diagnoses from national Finnish registers, and quantification of CRP levels from maternal serum samples. In addition,

the findings were not confounded by maternal age or education, previous births, parental psychiatric disorders, urbanicity, province of birth, twin/singleton status, or gestational week of the blood draw.

Schizoprenia Spectrum Disorders (SSDs)					
Reference	Objective	Sample	Method	Diagnosis/symptomatology	Key findings
Mednick et al. 1994	To examine the association between maternal influenza infection during second trimester and the offspring's risk of schizophrenia.	N=25 participants with schizophrenia from Helsinki born 1957-1958.	Reading of prenatal clinic records to determine the timing of maternal infection noted by obstetrical nurse.		Participants with schizophrenia exposed during the second trimester had a significantly higher rate of definite influenza infection (86.7%) compared to those exposed during the first and third trimesters (20%).
O'Callaghan et al. 1994	To examine the relationship between deaths from 16 different infectious diseases and births of individuals with schizophrenia.	Two independent sets of birth dates; Sample 1: N=6982 patients with schizophrenia born between 1938 and 1965 in England and Wales. Sample 2: N=9585 persons born between 1938 and 1958 in England and Wales having a diagnosis of schizophrenia.	The association between deaths from 16 infectious diseases was obtained from the Registrar General's Annual Review of Statistics. Poisson regression model was used for data analysis.	Diagnosis of schizophrenia was based on ICD-8 or -9.	National deaths from bronchopneumonia preceded births of individuals with schizophrenia, by three and five months respectively, in both of the two data sets. No association was found with the 15 other infectious diseases.

Venables et al. 1996	To examine whether exposure to maternal influenza during the second trimester is an individual risk factor for schizotypy or confounded with the effect of cold temperature.	N=771 (405 male and 366 female) participants of the Mauritius Project.	Influenza exposure data were obtained from newspaper records and Mauritian Registrar General's Department death causes.	Schizotypy was measured by a scale having a two-factor structure, positive symptoms labeled as Schizophrenism (SZ) and negative symptoms defined as physical and social anhedonia (AH).	The results suggest that prenatal exposure to influenza is associated with an elevation of schizophrenism, whereas exposure to low temperatures is associated with an elevation of anhedonia scores in the offspring.
Takei et al. 1996	To examine the relationship between in utero exposure to influenza epidemics and schizophrenia.	N=9462 patients with schizophrenia born between 1915 and 1970 in Denmark.	Influenza exposure data was obtained from Serum Institute, Copenhagen. Poisson regression analysis was used for data analysis.	Diagnosis of schizophrenia was based on ICD-8 (code 295.0-9).	Influenza exposure four months prior to birth was associated with a significantly increased risk of schizophrenia (RR 1.12, 95% CI 1.01-1.24).
Battle et al. 1999	To examine seasonal and maternal infectious disease influences on schizophrenia prevalence.	N=11,736 participants with schizophrenia and N=734,879 participants without schizophrenia from Georgia Medicaid database.	Statewide infectious disease tables were used to identify correlations with births of individuals with schizophrenia. Multiple regression analyses were used.	Diagnosis of schizophrenia was based on ICD-9 (code 295.xx).	A significant relationship between winter season and schizophrenia incidence was found, whereas exposure to neither maternal influenza nor measles was predictive of schizophrenia prevalence.

Westergaard et al. 1999	To examine the possible influence on schizophrenia prevalence of sibship characteristics and ecological influenza exposure data.	N=1 746 366 persons' Danish population-based cohort, of which N=2669 participants with schizophrenia.	The monthly numbers of influenza cases was obtained from the National Board of Health (1950-1979) and Statens Serum Institut (1980-1988). Sibship characteristics were calculated from data obtained from the Civil Registration System.	Diagnosis of schizophrenia was based on ICD-8 (code 295).	No association between birth order or influenza prevalence and risk of schizophrenia. Risk for schizophrenia was increased in individuals coming from a large (4/5 or more) sibship (RR 1.26, 95% CI 1.11-1.44/RR 1.46, 95% CI 1.22-1.75, respectively) and short intervals (<2 years) to the nearest younger or older siblings (RR 1.15, 95% CI 1.03-1.28/RR 1.22, 95% CI 1.05-1.38, respectively).

Brown et al. 2000	To examine the relationship between maternal exposure to respiratory infections and the offspring's schizophrenia spectrum disorders.	N=58 individuals with SSD and N=7 725 without SSD of the Prenatal Determinants of Schizophrenia (PDS) Study cohort.	Data on maternal medical conditions were obtained from the gravidas' Health Plan charts. The data were analyzed using proportional hazards regression. Analyses were adjusted for maternal smoking, education and race.	SSD was defined as schizophrenia, delusional disorder, psychotic disorder not otherwise specified, schizoaffective disorder and schizotypal personality. Diagnoses were ascertained by a three-step procedure including 1) ascertainment of psychiatric treatment by Health Plan registries; 2) identifying potential SSD cases; 3) interviewing the potential cases with the Diagnostic Interview for Genetic Studies (DIGS)/diagnosis based on chart review.	Second trimester exposure to respiratory infections was associated with a significantly increased risk of SSDs (RR 2.13, 95% CI 1.05-4.35), no associations were shown for first and third trimester exposures.
Limosin et al. 2002	To examine the relationship between gestational influenza virus exposure and risk of schizophrenia.	N=974 adults with schizophrenia born between 1949 and 1981 and their siblings without schizophrenia born between 1949 and 1981 (N=1589). N=974 matched controls.	Risk of exposure to the influenza virus was determined using data from French National Health and Medical Research Institute (INSERM) and French National Institute for Statistics and Economic Studies.	Diagnosis of schizophrenia was based on DSM-IV criteria.	Significantly more participants with schizophrenia than controls had been exposed to the influenza virus during the fifth month of pregnancy (OR 2.24, 95% CI 1.49–3.35, and OR 1.61, 95% CI 1.04–2.49).

Brown et al. 2004	To examine the relationship between maternal levels of four cytokines (IL-8, IL-1β, IL-6 and TNF-α) during the second trimester and the offspring's risk for schizophrenia.	N=59 participants with SSD and N=105 controls from a birth cohort born between 1959 and 1967.	Cytokine levels were determined from maternal sera by sandwich enzyme-linked immunosorbent assay. Conditional logistic regression models were used to estimate the association between each cytokine and SSDs, adjusting for maternal age, maternal ethnicity, socioeconomic status, maternal smoking and gestational age of the sample.	SSD was defined as schizophrenia, delusional disorder, psychotic disorder not otherwise specified, schizoaffective disorder and schizotypal personality. Diagnoses were ascertained by a three-step procedure including 1) ascertainment of psychiatric treatment by inpatient, outpatient and pharmacy registries; 2) identifying potential SSD cases; 3) interviewing the potential cases with the Diagnostic Interview for Genetic Studies (DIGS)/diagnosis based on chart review.	The second-trimester IL-8 levels were significantly higher in mothers of individuals with SSD than in comparison subjects. No differences were found between individuals with SSD and controls with respect to maternal levels of IL-1β, IL-6 or TNF-α.

Brown et al. 2004	To examine whether serologically documented prenatal exposure to influenza increases the risk of schizophrenia spectrum disorders.	N=64 individuals with SSD and N=125 controls from a large birth cohort born between 1959 and 1966.	Influenza exposure was determined by assaying maternal sera for influenza antibody. Conditional regression models were used, adjusting for maternal education, maternal age, paternal age, race, sex and number of maternal serum samples drawn.	SSD was defined as schizophrenia, delusional disorder, psychotic disorder not otherwise specified, schizoaffective disorder and schizotypal personality. Diagnoses were ascertained by a three-step procedure including 1) ascertainment of psychiatric treatment by inpatient, outpatient and pharmacy registries; 2) identifying potential SSD cases; 3) interviewing the potential cases with the Diagnostic Interview for Genetic Studies (DIGS)/diagnosis based on chart review.	The risk of SSDs was increased sevenfold for first-trimester influenza exposure. No increased risk was found with influenza during the second or third trimesters. Using a broader gestational period - early to midpregnancy - the risk of SSDs was increased threefold.

Babulas et al. 2006	To examine the relationship between exposure to maternal genital/reproductive infections and SSDs in the offspring.	N=7 794 offspring of pregnancies with prospectively acquired data on maternal G/R infections from obstetric records of which N=71 individuals with SSD.	Data on maternal genital/reproductive infections were obtained from physician diagnoses made during obstetric and medical visits. Data were analyzed with Cox proportional hazards regression. Analyses were adjusted for maternal age, race, education and mental illness.	SSD was defined as schizophrenia, delusional disorder, psychotic disorder not otherwise specified, schizoaffective disorder and schizotypal personality. Diagnoses were ascertained by a three-step procedure including 1) ascertainment of psychiatric treatment by inpatient, outpatient and pharmacy registries; 2) identifying potential SSD cases; 3) interviewing the potential cases with the Diagnostic Interview for Genetic Studies (DIGS)/diagnosis based on chart review.	Exposure to genital/reproductive infections during the periconceptional period was associated with significantly increased risk for SSDs (RR 5.03, 95% CI 2.00-12.64).

Brown et al. 2006	To examine whether maternal exposure to Herpes Simplex Virus 2 is associated with risk for adult schizophrenia.	N=60 individuals with SSD and N=110 controls from a large birth cohort born between 1959 and 1967.	Archived maternal sera from late pregnancy were assayed by enzyme-linked immunosorbent assay for IgG antibody to HSV-2. Conditional logistic regression models were used for data analysis, adjusting for maternal ethnicity and maternal education.	SSD was defined as schizophrenia, delusional disorder, psychotic disorder not otherwise specified, schizoaffective disorder and schizotypal personality. Diagnoses were ascertained by a three-step procedure including 1) ascertainment of psychiatric treatment by inpatient, outpatient and pharmacy registries; 2) identifying potential SSD cases; 3) interviewing the potential cases with the Diagnostic Interview for Genetic Studies (DIGS)/diagnosis based on chart review.	No associations were found between maternal IgG seropositivity or antibody levels to HSV-2 and the offspring's risk of SSDs.

Sørensen et al. 2008	To examine the relationship between maternal bacterial infection and risk of schizophrenia in the offspring.	N=4030 males and N=3911 females from Copenhagen Prenatal Cohort with data on prenatal exposure to infection.	Data on prenatal bacterial infections were obtained by interviewing the mothers five days after delivery and 67% at their first visit to the antenatal clinic. Multivariate models were used for data analysis, adjusting for social status and exposure to analgesics during pregnancy.	Diagnoses were obtained from Danish Psychiatric Central Research Register which used ICD-8 until 1993 and ICD-10 since 1994 (codes 295/F20, respectively). ICD-8 diagnosis was defined as narrow, more broadly defined diagnosis included both ICD-8 and -10 systems.	First-trimester exposure conferred an elevated risk of both ICD-8 and broadly defined schizophrenia (OR 2.53, 95% CI 1.07-5.96 and OR 2.14, 95% CI 1.06-4.31, respectively).

Brown et al. 2009	To examine whether exposure to prenatal infection is associated with executive dysfunction in patients with SSD.	N=26 patients with SSD exposed to prenatal maternal infection and N=24 non-exposed controls with SSD from a large birth cohort.	Data on exposure to influenza and toxoplasmosis were obtained from maternal sera. Executive function was measured by a neuropsychological battery including several tests.	SSD was defined as schizophrenia, delusional disorder, psychotic disorder not otherwise specified, schizoaffective disorder and schizotypal personality. Diagnoses were ascertained by a three-step procedure including 1) ascertainment of psychiatric treatment by inpatient, outpatient and pharmacy registries; 2) identifying potential SSD cases; 3) interviewing the potential cases with the Diagnostic Interview for Genetic Studies (DIGS)/diagnosis based on chart review.	Patients exposed to infection in utero committed significantly more total errors on the Wisconsin Card Sorting Test and took significantly more time to complete the Trails B than unexposed patients. Exposed patients also exhibited deficits on figural fluency, letter-number sequencing and backward digit span.

Clarke et al. 2009	To examine whether prenatal exposure to infection and positive family history of psychotic disorders interact synergistically to increase the risk of later schizophrenia.	N=9 596 women who received hospital treatment during pregnancy for an upper urinary tract infection in Helsinki 1947-1990.	The Medical Birth Register and the Finnish Population Register were linked to identify all individuals whose mothers were hospitalized during pregnancy for acute pyelonephritis. An additive statistical interaction model was used to calculate the amount of biological synergism between positive family history and prenatal exposure to infection.	Schizophrenia diagnoses for exposed and their families were obtained from Finnish Hospital Discharge Register, which has used ICD-8 (before 1987), ICD-9 (1987-1995) and ICD-10 (since 1995), code 295 in ICD-8 and -9/F20 in ICD-10.	Prenatal exposure to pyelonephritis was five times greater in those who had a family history of psychosis compared to those who did not. Prenatal exposure to infection alone did not significantly increase the risk of schizophrenia. The synergy analysis suggested that an estimated 38%-46% of the offspring who developed schizophrenia did so as a result of the synergistic action of both risk factors.
Nielsen et al. 2011	To examine the relationship between maternal infections during pregnancy or parental infections in general and risk for schizophrenia in the offspring.	All singletons born in Denmark 1978-1998 who were alive at their 10th birthday and whose mothers were born in Denmark (N=1 115 752).	Data on infections were obtained from the Danish National Hospital Register, coded by ICD-8/ICD-10 systems. Poisson regression model was used for data analysis, adjusting relative risks for calendar year, age, sex and history of schizophrenia, schizophrenia-like psychosis or psychiatric hospital contact in a parent.	Schizophrenia diagnoses were obtained from the Danish Psychiatric Central Research Register, which used ICD-8/ICD-10 (codes 295 and F20, respectively).	A slightly increased risk of schizophrenia was found after prenatal infection exposure, but it was not significantly different from the effect of infection in general.

Suvisaari et al. 2013	To compare the occurrence of obstetric complications in children of mothers with SSD and control children, and to investigate whether obstetric complications predicted children's psychiatric morbidity.	N=271 HR (Helsinki High-Risk) Study offspring with mothers having SSD and N=242 control offspring.	Data on obstetric complications were obtained from obstetric records. A Cox regression model was used for data analysis.	Information on mental disorders was obtained from the Finnish Hospital Discharge Register. Diagnoses were based on DSM-IV criteria. For individuals with psychotic and mood disorders, also the Operational Criteria Checklist for Psychotic Illness and the Major Symptoms of Schizophrenia Scale was completed.	Infections (HRR 3.73, 95% CI 1.27–11.01), hypertension during pregnancy (HRR 4.10, 95% CI 1.15–14.58), and placental abnormalities (HRR 4.09, 95% CI 1.59–10.49) were associated with elevated risk of SSDs within the HR group.
Canetta et al. 2014	To examine the relationship between maternal early gestational C-reactive protein and schizophrenia.	N=777 individuals with schizophrenia and N=777 matched controls from the Finnish Prenatal Study of Schizophrenia cohort.	C-reactive protein levels from maternal serum specimens were assessed using a latex immunoassay. Analyses were adjusted for maternal and parental history of psychiatric disorders, twin/singleton birth, urbanicity, province of birth and maternal socioeconomic status.	Diagnoses of schizophrenia (code F20) or schizoaffective disorder (F25) were based on ICD-10.	Increasing maternal C-reactive protein levels were significantly associated with schizophrenia in the offspring (OR=1.31, 95% CI=1.10–1.56).
IL-1β, Interleukin 1β IL-4 Interleukin 4; IL-6, Interleukin 6; TNF-α, Tumor Necrosis Factor α					

Animal studies

The use of serological assays has increased the reliability of determination of the prenatal exposure to infectious agents and inflammatory processes. However, they do not provide information about the mechanisms by which the exposure elevates the risk for schizophrenia spectrum disorders. For this purpose, animal models have been used. To mimic viral infection, mostly synthetic double-strand RNA polyriboinosinic-polyribocytidilic acid (poly I:C) has been used due to its advantages compared to viral infection. Advantages include the elicited nonspecific immune response common to various viruses and no virus-specific organ diseases, which could affect embryonal brain development (35-36). The models mimicking bacterial infection use mostly lipopolysaccharide (37-38), an endotoxin present on the outer membrane of gram-negative bacteria, to initiate the bacterial immune response.

Fatemi et al 1999 (39) focused on a finding from postmortem human brains of patients with schizophrenia (40) by investigating the reduced expression of reelin protein in the cells of layer I of neocortex. The offspring of mice prenatally infected with influenza virus showed significant reductions in reelin expression in neocortical layer I and also other cortical and hippocampal layers compared to non-exposed controls (39). Additionally, the thicknesses of the neocortex and hippocampus were reduced in the exposed offspring.

In human studies, loss of dendrites and spines (41-42) in the prefrontal cortex has been observed in patients with schizophrenia. A rat study (43) examined whether prenatal exposure to three cytokines - IL-1β, TNF-α, IL-6 - affected the number of primary dendrites, nodes and total dendrite length in the offspring of exposed rats. TNF-α and the combination of IL-1β and TNF-α both significantly reduced the total dendritic length (14% and 30%, respectively) and the number of nodes (27% and 32%,

respectively). In addition, IL-1β + TNF-α reduced the number of primary dendrites (17%).

The aim of one study (44) was to elucidate the site of action of exposure to prenatal maternal lipopolysaccharide challenge in increasing the schizophrenia risk in the offspring. For this purpose, lipopolysaccharide was iodinated and injected into pregnant rats. Its distribution, together with the measurement of the induction of IL-1β, TNF-α and IL-6 cytokines, was assessed in both maternal and fetal rat tissues. Lipopolysaccharide, as well as increases in IL-1β, IL-6 and TNF-α, was detected in maternal plasma and placenta, but not the fetal brain or liver. However, significant increase in IL-1β was detected in fetal plasma. Thus, the authors suggested that the actions of lipopolysaccharide in increasing the schizophrenia risk act indirectly.

In one study (45), the effect of prenatal poly (I:C) injection into pregnant mice on the offspring's the dopaminergic function was examined. Dopaminergic neurotransmitter function has been found to be impaired in patients with schizophrenia (46-47). Because cognitive dysfunction (48-49) and deficits in sensory motor gating (50) have been found in schizophrenic patients, also these were evaluated. In the juvenile stage, no differences were observed between the exposed and control offspring, whereas in adult offspring, the cognitive impairment and increased subcortical dopamine function were detected. Dopaminergic function in the offspring after poly (I:C) injection into pregnant mice was determined in another study (51). Dopaminergic maldevelopment starting in the fetal stages of life and depending on postnatal maturational processes was found in the exposed offspring.

Evidence for an involvement of oligodendrocytes and abnormal myelination in the prefrontal cortex and hippocampus in the pathophysiology of schizophrenia has been reported (52-57). Therefore, the effect of poly (I:C) injection into pregnant mice on these two factors in the offspring was the focus of an animal study (58). At early postnatal

periods, a significant decrease of myelin basic protein mRNA and protein was detected in the exposed offspring, but no significant loss of oligodendrocytes was observed. However, at the adult stages of life, these abnormalities were reverted to normal levels.

Postmortem studies on human brains of individuals with schizophrenia have showed impairments in the GABAergic function in the hippocampus (59-61). Therefore, the effect of poly (I:C) injection into pregnant mice on the hippocampal GABAergic neurotransmission in the offspring was determined (62), and abnormalities in the exposed subjects' hippocampal area CA1 was found.

It has been shown that patients with schizophrenia exhibit impairments in prepulse inhibition (63) and HPA-axis function (64). A group of researchers (65) aimed to determine the relationship between prenatal poly (I:C) injection into pregnant rats and these two factors in the offspring. Part of the pregnant rats were pretreated with the neurosteroid dehydroepiandrosterone (DHEA), which modulates the neuronal activity of several receptors in the brain (66) and appear to attenuate the severity of psychosis (67). The results showed alterations in prepulse inhibition and reduced HPA-axis response to stress in the exposed offspring. However, DHEA pretreatment reversed the effect of poly (I:C) treatment on prepulse inhibition in female offspring, and abnormal HPA-axis stress response was normalized in all offspring pretreated with DHEA.

Multiple metabolic abnormalities have been detected in drug-naive patients with schizophrenia, indicating a possible developmental origin. These abnormalities include impaired glucose tolerance (68), increased visceral and subcutaneous fat deposition (69), abnormal ingestive behavior (70) and increased peripheral corticosterone release (64). Therefore, the effect of prenatal poly (I:C) injection to pregnant mice on these metabolic abnormalities in the offspring was investigated (71). All the four were found in the exposed offspring either in periadolesence or in adulthood. Additionally, decreased release of proinflammatory IL-6 and

TNF-α and T-cell related IL-2 and IFN-γ cytokines, possibly underlying the excessive food and fluid intake, were detected.

The impact of maternal immune activation induced in mice by poly (I:C), influenza virus and IL-6 at day 9.5 on the fetal brain transcriptome was studied (72), specifically looking at the crystallin genes related to schizophrenia (73-75) and autism (76) risk. An acute and transient upregulation of the α, β and γ crystallin gene family was detected, and the levels of their expression were associated with the severity of maternal immune activation.

Using both a set of behavioral tests and brain investigation of neonatal rats, the potential effects of prenatal exposure to maternal LPS challenge at gestational days 15 and 16 on early neurophenotypic presentations seen in schizophrenia and autism were examined (77). The lipopolysaccharide exposed pups showed a significant decrease in the number and duration of ultrasonic vocalizations at 3rd and 5th postnatal days P3 and P5, as well as impairments in nest-seeking behaviors and odor-stroke associative learning at 8th and 9th postnatal days. In the brain investigation, significant decrease in the 5-HT1A and 5-HT1B expression at 3rd postnatal day was found. All these findings suggest a role of prenatal exposure to an immune activator in increasing the risk for schizophrenia and autism.

3.2 Autism Spectrum Disorders

Like schizophrenia, also autism spectrum disorders have attracted researchers' attention regarding prenatal exposure to maternal infection and immune response as risk factors. Both human and animal studies have been conducted to investigate the topic.

Human studies

The effect of prenatal exposure to maternal infections requiring hospitalization on the risk for autism spectrum disorders was examined by Atladóttir et al 2010 (78). They assessed at both viral and bacterial exposures. First-trimester hospitalization due to maternal viral infection was associated with an increased risk of autism spectrum disorders in offspring (HR 2.98, 95% CI 1.29-7.15), as was second-trimester hospitalization due to maternal bacterial infection (HR 1.42, 95% CI 1.08-1.87). However, when the pregnancy was assessed as a whole, no associations were found with either exposure. Because pathogens underlying different viral and bacterial infections were not separated in these analyses, the findings suggest a role of maternal immune activation rather than the pathogen itself in elevating the offspring's risk for autism spectrum disorders.

Maternal influenza and fever were chosen as exposures in another study (79). They sought to determine their potential effect on autism spectrum disorder risk in offspring. Influenza and fever exposures were obtained by telephone interviews. The results showed no association between prenatal exposure to maternal influenza and risk for autism spectrum disorders in the offspring, but exposure to maternal fever was associated with an elevated risk (OR 2.12, 95% CI 1.17-3.84). This risk was attenuated if the mother had taken antipyretic medication (OR 1.30, 95% CI 0.59-2.84), but remained elevated for the offspring of those mothers who did not (OR 2.55, 95% CI 1.30-4.99), indicating that exposure to maternal infections and inflammation acts through an indirect pathway in elevating the risk for autism in the offspring, i.e. the pathogen itself does not affect the developing nervous system but the symptom it causes, fever, does.

In another study by Atladóttir et al 2012 (80), the impact of prenatal exposure to common infections, febrile episodes and use of antibiotics on autism spectrum disorder and infantile autism risk in the offspring was

determined. Exposure data were obtained by telephone interviews with the mother during pregnancy and early postpartum. Results showed only little evidence for an association between mild infections or short febrile episodes and risk for autism spectrum disorders or infantile autism. However, exposure to maternal influenza elevated the risk significantly (HR 2.3, 95% CI 1.0-5.3). Moreover, prolonged febrile episodes were associated with an increased risk of infantile autism (HR 3.2, 95% CI 1.8-5.6) and use of antibiotics during pregnancy was a potential risk factor for both autism spectrum disorders and infantile autism. However, due to multiple testing, the authors emphasized that the significant findings may be due to a chance and the negative findings need to be further investigated.

Maternal serum samples have been utilized in a study (81), which increases the reliability of exposure data. The levels of C-reactive protein (CRP) were assessed from maternal serum specimens and categorized in quintiles for the examination of the relationship between prenatal exposure to maternal CRP and risk of childhood autism in the offspring. When comparing the risks between the quintiles, an increased risk was found between the highest and lowest quintiles (OR 1.43, 95% CI 1.02-2.01). Thus, elevated CRP levels seemed to be associated with an increased risk of autism in the offspring, suggesting a common pathway by which various maternal infectious and inflammatory exposures elevate the risk of autism.

Autism Spectrum Disorders (ASDs)					
Reference	Objective	Sample	Method	Diagnosis/symptomatology	Key findings
Atladóttir et al. 2010	To examine the relationship between maternal infections requiring hospitalization during pregnancy and autism spectrum disorders in the offspring.	All children born in Denmark 1980-2005 (N= 1 612 342).	Exposure data were obtained from Danish National Hospital Register. Analyses were adjusted for sex, paternal age, parity and parental history of psychiatric disorder.	ASD diagnoses were obtained from the Danish Psychiatric Central Register, which used ICD-8 1969-1993 and ICD-10 since 1994 (ICD-8 codes: 299.00, 299.01, 299.02, 299.03 and ICD-10 codes: F84.0, F84.1, F84.5, F84.8, and F84.9).	Admission to hospital due to maternal viral infection during the first trimester and maternal bacterial infection during the second trimester were found to be associated with ASDs in the offspring. No associations were found when the total period of pregnancy was used (HR 2.98, 95% CI 1.29–7.15 and HR 1.42, CI 1.08–1.87, respectively).
Zerbo et al. 2012	To examine the relationship between maternal influenza or fever during pregnancy and the offspring's risk for ASDs or developmental delays.	N=538 children with ASD, N=163 with developmental delay and N=421 typically developing children.	Exposure data were obtained by telephone interviews. Multivariate regression models were used for data analysis, adjusting for maternal age, maternal education, place of residence, maternal smoking, periconceptional vitamin supplementation, parity, type of health insurance coverage, sex and race.	ASD/developmental delay diagnoses were clinically confirmed by the Mullen Scales of Early Learning, Vineland Adaptive Behavior Scales, Autism Diagnostic Interview-Revised and -Generic.	Neither ASDs nor developmental delay were associated with influenza, but both were associated with maternal fever (OR 2.12, 95% CI 1.17-3.84 and OR 2.50, 95% CI 1.20-5.20, respectively). The fever-associated risk of ASDs was attenuated among mothers who reported taking antipyretic medications (OR 1.30, 95% CI 0.59-2.84), but remained elevated for those who did not (OR 2.55, 95% CI 1.30-4.99).

Atladóttir et al. 2012	To determine the occurrence of common infections, febrile episodes, and use of antibiotics reported by the mother during pregnancy and the risk of ASDs and infantile autism in the offspring.	N=96 736 participants from a population-based cohort consisting of children aged 8-14 years and born 1997-2003 in Denmark.	Information on infection, febrile episodes and use of antibiotics was self-reported trough telephone interviews during pregnancy and early postpartum. Cox proportional hazards regression model was used for data analysis, adjusting for sex, maternal age, parity, maternal smoking, paternal age, parental psychiatric history and parents' educational status.	Diagnoses of ASDs and infantile autism were retrieved from the Danish Psychiatric Central Register using ICD-10 (codes F84.0, F84.1, F84.5, F84.8 and F84.9).	Little evidence was found that various mild infections or febrile episodes were associated with ASDs/infantile autism. Maternal influenza infection was however associated with a twofold increased risk of infantile autism (HR 2.3, 95% CI 1.0-5.3), prolonged febrile episodes with a threefold increased risk of infantile autism (HR 3.2, 95% CI 1.8-5.6) and use of various antibiotics during pregnancy were potential risk factors for ASDs/infantile autism.
Brown et al. 2013	To examine the relationship between maternal early gestational C-reactive protein and childhood autism.	N=677 individuals with autism and N=677 matched controls from a cohort of all offspring born in Finland 1987-2005.	C-reactive protein levels from maternal serum specimens were assessed using a latex immunoassay and categorized in quintiles. The analyses were adjusted for gestational age of the blood draw, number of previous births and maternal lifetime history of depression.	Childhood autism diagnoses were based on ICD-10 (code F84.0).	Increasing maternal C-reactive protein levels were significantly associated with autism in the offspring when comparing the risk of the highest and lowest quintiles (OR 1.43, 95% CI 1.02-2.01).

Animal studies

Animal models have also been used to determine the possible mechanisms by which prenatal exposure to maternal infections and immune response increase the risk of autism spectrum disorders in the offspring. One study (82) chose the three core symptoms of autism for a closer investigation: social interaction and language deficits and repetitive/stereotyped behaviors. These were modeled in mice by different tests: ultrasonic vocalization analyses in pups' isolation test and in response to female and male stimuli in adult male mice, the three chamber social test, scent marking test, marble burying test, self-grooming test and olfactory sensitivity test. The offspring of mice injected with poly (I:C) at gestational day 10.5 showed autism-related changes in all the previously mentioned tests suggesting a role of exposure to prenatal maternal infections in increasing the offspring's risk for autism spectrum disorders.

The object of another animal study (83) was to determine the autism-related immunological, molecular and behavioral effects of maternal immune activation exposure in the offspring. A rat model was used, injecting pregnant rats at gestational day 15 with lipopolysaccharide and collecting maternal serum, amniotic fluid and fetal brain for investigation. Also behavioral tests were conducted, to determine social preference, exploration and olfaction. A three-chamber test was used to model social preference, measuring the ratio of time the rat spent in the social and home boxes. Exploration was determined by measuring the number of nose-hole pokes and total movement in a box with 16 holes. Olfaction was assessed by measuring the time that the rats needed to find a buried cookie. After maternal lipopolysaccharide exposure, the results showed elevated pro-inflammatory cytokine levels in maternal serum, amniotic fluid and fetal brain at 4h, and the levels decreased but remained elevated at 24h. In the behavioral tests, decreased social preference and exploration behaviors were detected in offspring as juveniles and young adults. Additionally, dysregulation of 3285 genes

was observed, with increased expression of cell death and cellular stress genes and decreased expression of developmentally-regulated and brain-specific genes, similarly to previously observed expression changes in autism. The authors concluded that maternal immune activation induces a maternal cytokine response and selectively targets the fetal expression of neuronal migration and hypoxia-inducing genes.

3.3 Other Mental Disorders

In the recent years, also other mental disorders have been investigated with regard to prenatal exposure to maternal infection and immune response. The number of studies is still small, and they are reviewed below.

3.3.1 Attention-Deficit Hyperactivity Disorder (ADHD)

The relationship between exposure to prenatal maternal infection and risk of attention-deficit hyperactivity disorder (ADHD) has been examined in one study (84). The researchers focused on maternal genitourinary infection and pre-eclampsia as exposures potentially affecting the offspring's ADHD risk. Exposure data were based on diagnoses made during pregnancy. An increased risk for ADHD was detected after both maternal genitourinary infection and pre-eclampsia exposure (OR 1.29, 95% CI 1.23-1.35 and OR 1.19, 95% CI 1.07-1.32, respectively). Additionally, 53% (OR 1.53, 95% CI 1.32-1.77) increase in ADHD risk was found among children with both exposures compared to those without either of them. The sex and race of the child, birth weight, maternal age, education, alcohol and tobacco use were adjusted for in the analyses.

3.3.2 Anorexia Nervosa

To date, only one study (85) has investigated the exposure to prenatal maternal infection and anorexia nervosa risk in offspring. Exposure to

chickenpox, influenza, measles and rubella infections in the neurodevelopmentally most crucial, third to sixth months of pregnancy, were investigated. Researchers used an ecological study design, collecting data on numbers of monthly cases of each infection and the total living population in every year included in the study from national registries. To obtain the incidence rates, numbers of monthly infection cases were divided for the total living population in that year.

The results showed an increased risk for anorexia nervosa in subjects exposed to peaks of chickenpox (OR 1.6, 95% CI 1.2-2.0) and rubella (OR 1.5, 95% CI 1.1-2.0) infections during the sixth month of pregnancy, which is later than what has been seen in studies concentrating on schizophrenia. The authors suggested that this could underlie the characteristic of anorexia nervosa patients that, unlike schizophrenic patients, they usually have normal intelligence quotient levels, as infection-associated events early in fetal life have been observed to have a stronger impact on neurodevelopment compared with infections later in fetal life. Additionally, exposure to the peak of chickenpox was associated with a lower age of onset of AN (17.0 ± 3.3 vs 18.5 ± years, $p < 0.001$). No association was found between prenatal measles or influenza exposure and anorexia nervosa risk (OR 1.0, 95% CI 0.7-1.3 and OR 1.0, 95% CI 0.7-1.4, respectively).

3.3.3 Bipolar Disorder

Parboosing et al. 2013 (86) studied the relationship between prenatal exposure to maternal influenza and offspring's risk for bipolar disorder. Exposure data was obtained from maternal medical records. They found a significantly increased bipolar disorder risk (OR 3.82, 95% CI 1.58-9.24) in offspring exposed to maternal influenza at any time during pregnancy. If replicated in future studies, this finding might provide important information for prevention of the disorder.

3.3.4 Depression

One study (87) has been published examining the potential effect of prenatal exposure to maternal viral infections on risk for depression in the offspring. Two large cohorts were compared, one known to have been exposed to prenatal maternal infection, the other not known to have exposed (N= over 3000 in both cohorts). The data on depression among the offspring were obtained by sending morbidity questionnaires to the primary care physicians of the subjects. The results showed no association (RR 1.0, 95% CI 0.8-1.2) between in-utero viral exposure and depression risk. Furthermore, the authors concluded that given the even distribution of effects around the unity with an overall RR of one, their study provided no evidence for an association with any antenatal virus exposure.

Other mental disorders					
Reference	Objective	Sample	Method	Diagnosis/symptomatology	Key findings
Pang et al. 2009	To examine whether in-utero viral infections result increased risk of depression later in life.	N=3076 participants born 1946-1980 whose mothers suffered known viral infections in pregnancy and N=3076 non-exposed controls.		Morbidity questionnaires were sent to the participants' primary care physicians including several items all coded according to the IDC-9.	No overall association between in-utero viral exposure and risk of depression was found.

Favaro et al. 2011	To examine the role of prenatal viral infections in the development of anorexia nervosa.	All female individuals born in the Veneto region 1970-1984 residing in the urban and suburban area of Padua (N=27 682).	The monthly viral exposure data were obtained from the Italian Statistical Annals of Demographics and Public Health. Logistic regression analyses were used, adjusting for socioeconomic status, population density and month of birth.	The anorexia nervosa diagnoses were obtained by consulting three registries: Register of the Eating Disorders Unit of the area, the Public Mental Health Database and the Register of Hospital Admissions. DSM-IV criteria were used, waiving the single criterion of amenorrhea for three consecutive months.	Exposures to the peaks of chickenpox and rubella infections (OR 1.6, 95% CI 1.2–2.0 and OR 1.5, 95% CI 1.1–2.0) during the sixth month of pregnancy were significantly associated with an increased risk of anorexia nervosa.
Mann et al. 2011	To examine the relationship between maternal genitourinary infection or pre-eclampsia and risk of ADHD.	N=84 721 children born 1996-2002 from Medicaid billing data for pregnant women.	Maternal genitourinary infections and pre-eclampsia were identified on the basis of diagnoses made during pregnancy coded by ICD-9. Multivariable logistic regression model was used for data analysis, adjusting for sex, race, maternal education, maternal age, birth weight, alcohol use and tobacco use.	ADHD diagnoses were obtained from the children's Medicaid files, based on ICD-9 (codes 314.00, 314.01).	Maternal genitourinary infection and pre-eclampsia were both associated with increased risk of ADHD (OR 1.29, 95% CI 1.23-1.35 and OR 1.19, 95% CI 1.07-1.32, respectively), and children with both exposures were 53% more likely to have ADHD compared to children with neither exposure.

Parboosing et al 2013	To examine whether maternal influenza during pregnancy is associated with bipolar disorder in the offspring.	N=92 individuals with bipolar disorder and N=722 controls from Child Health and Development Study born 1959-1966.	Data on exposure to influenza was obtained from maternal medical records using ICD-9. Conditional logistic regression models were used for data analysis, adjusting for maternal age, race, education, and psychiatric history and gestational age at birth.	BD diagnoses were made by using Structured Clinical Interview for DSM-IV.	A significant, nearly fourfold (OR 3.82, 95% CI 1.58-9.24) increase in the risk of bipolar disorder after exposure to maternal influenza infection at any time during pregnancy was found.

3.3.5 Developmental Delay

The same study mentioned above when discussing autism spectrum disorders (79), also explored the relationship between prenatal exposure to maternal influenza and fever and developmental delay risk in offspring. The exposure data were obtained by telephone interviews. As was the case for autism spectrum disorders, no association between maternal influenza exposure and offspring's risk for developmental delay was found (OR 1.15, 95% CI 0.54-2.47). However, maternal fever was associated with an increased risk for developmental delay in the offspring (OR 2.50, 95% CI 1.20-5.20), suggesting that different infectious pathogens may act indirectly, via the teratogenic effect on developing nervous system of the fever they cause, in elevating the offspring's risk for developmental delay.

3.4 Other Neurocognitive Deficits

In addition to mental disorders, neurocognitive deficits have also been studied with regard to prenatal exposure to maternal infection and immune response. These studies are reviewed here.

In one study (88), the potential association between in-utero exposure to acute inflammation and long-term major neurodevelopmental disability at age of 6 years was determined among offspring who were born preterm. Data on inflammation exposure were collected by trained research nurses. Major neurodevelopmental disability was defined as one or more of the following: IQ <70, cerebral palsy (CP), blindness, deafness, or other severe neurological motor deficit. Several psychometric measures were used to assess IQ of the children. In this study, no association was found between in-utero inflammation exposure and major neurodevelopmental disability.

To examine the possible effect of prenatal exposure to maternal influenza on adulthood intelligence in the offspring, another research group (89) conducted intelligence tests among boys born in Norway between 1967 and 1973. While the mean intelligence score tends to increase from one birth year to another, an inverse association was found with birth year 1970, when an influenza pandemic named as the Hong Kong flu haunted Europe. Thereby, men born 6 to 9 months after the epidemic had lower intelligence scores compared to the men born in the same months a few years before or after.

Cytomegalovirus (CMV) infection -associated sequelae (deafness, hearing loss, auditory damage, neurodevelopmental delay) after serologically documented prenatal exposure to maternal CMV infection in pregnancies with and without abnormal findings on ultrasound examination and MRI have also been investigated (90). Significantly

more sequelae were observed in first-trimester than second-trimester exposed offspring (19.7% vs. 5.6%, P = 0.01). Additionally, abnormal findings on prenatal ultrasound examination were associated with an increased risk of sequelae, whereas abnormal MRI findings were not. Having both normal ultrasound and MRI findings decreased the sequelae risk in first- and second-trimester exposed infants to 15.6% and 2.0%, respectively.

A few animal studies have also been conducted on neurocognitive deficits. The effect of lipopolysaccharide challenge in pregnant rats at gestational days 8, 10 and 12 on the offspring's spatial learning and memory performances at different stages of life have been observed (91). The structure of hippocampal CA1 region and the expression of synaptophysin and glial fibrillary acidic protein were also determined in the offspring. The spatial learning and memory abilities were significantly reduced in the offspring of lipopolysaccharide exposed rats, and a significant neuron loss, decreased expression of synaptophysin and increased expression of glial fibrillary acidic protein in the hippocampal CA1 region were found. All findings except the increased expression of glial fibrillary acidic protein, which was seen in all three age stages, were more significant with age increasing. The authors suggested that this might reflect the effect of prenatal maternal inflammation in making spatial learning and memory abilities more sensitive to the age increasing.

To examine the anxiety and stress responses and neurophysiological changes following prenatal lipopolysaccharide exposure, a rat model was used (92). Pregnant rats were injected with lipopolysaccharide at gestational day 10.5, and several tests assessing anxiety and stress responses, together with brain dopamine and serotonin (5-HT) determination, were conducted in the offspring. The results showed more anxiety-like behaviors and heightened stress response in lipopolysaccharide exposed rats, as well as reduction of the dopamine levels in the nucleus accumbens and serotonin levels the medial

prefrontal cortex and hippocampus. Additionally, glucocorticoid receptors in the dorsal hippocampus and the 5-HT1A- receptors in the dorsal and ventral hippocampus were reduced in the exposed offspring. These molecular level findings may be associated with the observed increases in stress-response and anxiety like behaviors of the offspring.

Other Neurocognitive Deficits					
Reference	Objective	Sample	Method	Diagnosis/symptomatology	Key findings
Andrews et al. 2008	To determine the association between in utero exposures to acute inflammation and long-term major neurodevelopmental disability at age of six years among children born prior to the 32nd gestation week.	A cohort of N=424 consecutive single pregnancies delivered between 23 and <32 weeks.	Pregnancy and neonatal data were collected by trained research nurses. Analyses were adjusted for gestational age and ethnicity.	To assess intelligence quotient (IQ), a wide range of psychometric measures including the Wechsler Intelligence Scale for Children-IV or the Differential Ability Scales, was used. Major neurodevelopmental disability was defined using a composite that included one or more of the following: IQ <70, CP, blindness, deafness, or other severe neurological motor deficit such as abnormal balance, impaired coordination, dystonia, or a seizure disorder that affected function.	Delivery gestational age, neonatal complications and caregiver IQ were significantly associated with increased risk of severe neurodevelopment outcomes, whereas in utero exposure to acute inflammation was not.

Eriksen et al. 2009	To examine the hypothesis that prenatal exposure to an influenza pandemic was associated with reduced intelligence in adulthood.	All boys born alive in single birth 37-43 weeks' gestation in Norway 1967-1973 (N=205 634).	Statistical analyses were adjusted for the continuous birth year variable, birth order, being born small for gestational age, maternal age, maternal education, marital status, paternal age and paternal education.	The intelligence test data were obtained by conducting three subtests: 1) the Arithmetic Test; 2) the Word Similarities Test; and 3) the Figures Test.	An inverse association between the birth months July, August, September and October in 1970 and intelligence score was found. Thus, the intelligence scores of the men born six to nine months after the epidemic were lower than the mean values for the men born in the same months a few years before or after.
Lipitz et al 2013	To determine the outcome of pregnancies with documented cytomegalovirus (CMV) infection with and without abnormal findings on ultrasound examination and MRI.	N=71 first-trimester and N=74 second-trimester CMV-infected individuals in Israel.	CMV infection data was obtained from serial screening.	Patients underwent serial prenatal ultrasound scans and fetal MRI. All neonates underwent ocular fundus examination, ultrasound brain scan and hearing evaluation, and were followed by a pediatrician.	Patients with first-trimester CMV infection had infants with significantly more sequelae (auditory damage or neurodevelopmental disabilities) than second-trimester infected patients (19.7% vs. 5.6%). Abnormal prenatal ultrasound findings were associated with increased risk of sequelae, and having both normal MRI and ultrasound findings decreased the risk associated with infections (to 15.6% and 2.0%, respectively).

4 Discussion

According to the accumulating data from the human studies in the field, there seems to be an association between prenatal exposure to maternal influenza and risk for schizophrenia spectrum disorders and schizotypy in the offspring, as this finding has been replicated in several studies (15-17, 21, 23, 31). However, also negative findings exist (18-20). For the

other maternal infections having been studied, replications exist for HSV-2 (93-94) and toxoplasma gondii (95-96). Researchers have tried to elucidate the underlying mechanisms by which the infections increase the risk of offspring's schizophrenia-related structural and behavioral abnormalities in animal studies, but the variation in the investigated mechanisms and structures has not lead to replications for any specific mechanism. For autism spectrum disorders, replications in human studies exist for the relationship between prenatal exposure to maternal febrile episodes (79,80) as well as cytokines IL-4 and IL-5 in amniotic fluid (97-98), and elevated autism risk in the offspring. Of other mental disorders, there are no replicated findings.

It seems likely that the timing of the prenatal exposure has an effect on the outcome, resulting in different disorders according to the time of maternal infection during the pregnancy. As an example, exposure to maternal infection during early to mid-pregnancy has been related to elevated risk of schizophrenia, whereas exposure during the sixth month of pregnancy seems to be associated with an increased risk for anorexia nervosa. This might be due to the different effects in different times on neurodevelopment in the pathogenesis of these two disorders.

For schizophrenia spectrum disorders and influenza, the existing data is not fully consistent, as both positive and negative findings exist. However, it is possible that some negative findings reflect power issues rather than a true lack of association. To overcome this problem, it would be important to use large data sets. Additionally, different studies have used slightly different outcomes (schizophrenia, schizophrenia spectrum disorders, schizotypy), which may have affected the results. As many of the reviewed studies relied on epidemiological exposure data, it is impossible to determine the number of mothers actually infected and the exact timing of the exposure. This aspect is reflected in the different timings of the infection between epidemiological and serologic studies: as the epidemiological studies show that second trimester exposure would be the most critical, Brown et al. 2004 (31) found in their serologic

study that first-trimester influenza exposure significantly elevated the risk of schizophrenia spectrum disorders. This might be due the earlier infection diagnosis when assaying the serum samples.

Because of the smaller number of studies investigating the effect of prenatal exposure to maternal infections on the offspring's risk for autism spectrum disorders, replications of findings are more rare. Maternal fever and elevated levels of IL-4 and IL-5 in the amniotic fluid have been found to be related with an elevated risk, suggesting an indirect mechanism by which the infections might increase the risk for autism spectrum disorders, i.e. the infectious agent itself does not cause the elevation in the risk for autism spectrum disorders but the teratogenic effect of hyperthermia or cytokines might underlie the elevation. However, in the case of maternal fever, the studies with positive findings relied on telephone interviews in collecting the exposure data, which may have affected the results, as the mothers of children with autism spectrum disorders may have remembered better whether they had had fever during pregnancy (recall bias).

In most of the reviewed studies, one common caveat is the lack of controlling for the genetic liability to the disorder. As it is significant in many mental disorders, this may have affected the results in a way that the increased risk may not be due to the infectious exposure alone but the synergism between both of the factors. The synergism hypothesis was tested by Clarke et al. (27), and they found that risk for schizophrenia after prenatal exposure to pyelonephritis was five times greater in the individuals having a family history of psychosis compared to those who did not. There are also some studies (25, 28, 34) adjusting the analyses for parental history of psychiatric disorder. This increases the independency of the findings of an effect of infections, because psychiatric disorders have been found to be associated with increased number of infections (99). Also, not all the studies have adjusted for potential confounding factors (e.g. maternal age, education, urbanicity), which should be taken into account when looking at the results.

Considering the findings from the reviewed studies, it seems that the mechanism underlying the elevation of risk for different mental disorders after prenatal exposure to maternal infections may act trough an indirect and common pathway for different infections. Rather than specific infectious agents, some factors acting in the immune response and inflammation (cytokines or acute phase proteins, for example) common to various infections might be the critical key factors behind the findings. Intriguing findings already exist, as elevated maternal levels of IL-8 and CRP have been found to be associated with an increased risk for schizophrenia spectrum disorders (30, 34). Similar findings of an association between CRP and childhood autism also exist (81). However, replications of these two findings are needed and, as discussed above, the genetic liability and potential confounding factors should be taken into account. In addition to schizophrenia and autism, other mental disorders would also need more investigation in terms of prenatal exposure to maternal infections and risk for these disorders.

In conclusion, there seems to be an association between prenatal exposure to maternal infections and immune response and the offspring's risk for different mental disorders. To yield stronger evidence for these findings, future studies should ideally use larger study samples with prospectively collected maternal serum samples and genetically sensitive study designs (e.g. sibling design, twin design, novel designs with genetically unrelated offspring), as well as adjust for various potential confounding factors.

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Supplements

Supplementary table 1.
Summary of the included animal studies covering possible mechanisms underlying the effect of prenatal exposure to infection or maternal immune response on the offerings risk for mental disorders.
CMV, Cytomegalovirus; DA, Dopamine; DHEA, Dehydroepiandrosterone; GABA, Gamma-Aminobutyric Acid; GFAP, Glial Fibrillary Acidic Protein; IL-1β, Interleukin 1β; IL-2 Interleukin 2; IL-4 Interleukin 4; IL-6, Interleukin 6; INF-γ, Interferon γ; LPS, Lipopolysaccharide; SYP, Synaptophysin; TNF-α, Tumor Necrosis Factor α; 5-HT, Hydroxytryptamine,
ASR, Acoustic Startle Response; MIA, Maternal Immune Activation; PPI, Prepulse Inhibition; USV, Ultrasonic vocalizations

Reference	Objective	Method	Key findings
Schizophrenia Spectrum Disorders (SSDs)			
Fatemi et al. 1999	To examine whether human influenza infection in pregnant mice would alter the expression of reelin in neonatal brains.	Pregnant mice were infected with human influenza virus in the ninth day of pregnancy. The brains of the offspring were then investigated in postnatal day zero.	Prenatally-infected brains showed significant reductions in reelin-positive cell counts in layer I of neocortex and other cortical and hippocampal layers when compared to controls. Moreover, viral infection caused decreases in neocortical and hippocampal thickness.

Gilmore et al. 2004	To study the effect of infection-related cytokines on the dendritic development of cortical neurons.	Primary mixed neuronal cultures from embryonic day 18 rats were obtained and exposed to 0, 100 or 1000 units (U)/ml of IL-1β, TNF-α, IL-6 or IL-1β + TNF-α for 44 h. Number of primary dendrites, nodes and total dendrite length was determined.	100 U of TNF-α significantly reduced the number of nodes (27%) and total dendritic length (14%), and 100 U of IL-1β + TNF-α significantly reduced the number of primary dendrites (17%), nodes (32%) and total dendritic length (30%), but these did not affect the overall neuron survival. At 1000 U, each cytokine significantly reduced the number of primary dendrites (14-24%), nodes (28-37%), total dendritic length (25-30%) and neuron survival was reduced (14-21%). These findings are consistent with the neuropathology of schizophrenia.
Ashdown et al. 2006	To elucidate the site of action of LPS in increasing the risk of schizophrenia.	Pregnant rats received i.p. 5 Ci of iodinated LPS at gestational day 18, and its distribution was assessed in maternal/fetal tissues. Additionally, induction of the inflammatory cytokines IL-1β, IL-6 and TNF-α was measured in maternal/fetal tissues after LPS challenge.	LPS was detected in maternal tissues and placenta, but not the fetus. Significant increases in IL-1β, IL-6 and TNF-α were detected in maternal plasma and placenta, but not in fetal liver or brain. A significant increase in IL-1β was detected in fetal plasma. These findings suggest indirect actions of LPS in increasing the risk of schizophrenia.
Ozawa et al. 2006	To examine whether maternal immune response to viruses influenced fetal brain development leading to schizophrenia.	Poly (I:C) was administered into pregnant mice. Behavioral evaluations, sensorimotor gating and biochemical evaluation of the dopaminergic function in the offspring of saline- or poly (I:C) - treated dams were conducted.	In juveniles, no difference was found between the two groups. In adults, poly (I:C) administration caused increased subcortical DA function and cognitive impairment.

Makinodan et al. 2008	To examine the relationship between maternal infection and schizophrenia in the offspring by examining the infection's effect on previously found abnormalities in human brains of individuals with schizophrenia.	Poly (I:C) or saline was injected into pregnant mice at embryonic day 9.5. The brains of their offspring were examined for biochemical end histological abnormalities with special reference to oligodendrocytes.	A significant decrease of myelin basic protein mRNA and protein was detected at early postnatal periods in poly (I:C) mice. The hippocampus of juvenile poly (I:C) mice was less myelinated and axonal diameters were significantly smaller than in control mice, but there was no significant loss of oligodendrocytes. These abnormalities reverted to normal levels at the adult stage.
Vuillermot et al. 2010	To examine the hypothesis that prenatal immune challenge has an impact on structural and functional dopaminergic development.	Pregnant mice were injected with either poly (I:C) or vehicle at gestational day nine. The dopaminergic structural and functional development was then evaluated from fetal to adult stages of life in the offspring.	The prenatal immune challenge led to dopaminergic maldevelopment starting in the fetal stages of life and dependent on postnatal maturational processes.
Ducharme et al. 2012	To examine the effects of prenatal infection on the GABAergic neurotransmission in the brain of the offspring, which has been found to be impaired in patients with schizophrenia.	At gestational day nine, mice received a tail vein injection of either poly (I:C) or saline. The brains of the offspring were investigated by immunohistochemistry.	Prenatal infection reduced the density of parvalbumin- but not somatostatin-positive interneurons in the CA1 area of the hippocampus and strongly reduced the strength of inhibition early during postnatal development. Additionally, reduced theta oscillation generated in the CA1 area was found.
Maayan et al. 2012	To examine the effect of poly (I:C) treatment on schizophrenia-like behavioral, neurochemical and neuorophysiological abnormalities in rodent offspring.	Pregnant rats at gestational day 15 were injected with either poly (I:C) or saline. In both groups, there were rats with and without pretreatment with DHEA. Acoustic startle response test, prepulse inhibition test and corticosterone level tests were used to evaluate the possible schizophrenia-related changes caused by poly (I:C) treatment.	Poly (I:C) prenatal administration was associated with alterations in the ASR/PPI and the HPA-axis stress response in rat offspring on postnatal day 90. We show that pretreatment with DHEA reverses poly (I:C)-related ASR/PPI disruption in female rats and normalizes HPA-axis stress response in a united group of male and female rats.

Pacheco-Lopez et al. 2013	To test the hypothesis that metabolic alterations pertinent to SSDs can be primed by an environmental risk factor associated with the disorder, namely prenatal exposure to immune challenge.	Pregnant mice on gestational day nine received either a single injection of poly (I:C) or vehicle. Metabolic effects in the offspring were studied using high-resolution computed tomography and fully automated indirect calorimetry system, along with an oral glucose tolerance test and plasma cytokine and corticosterone measurements.	Prenatal immune activation caused altered glycemic regulation and abnormal ingestive behavior in periadolescence and led to an adult onset of excess visceral and subcutaneous fat deposition. These effects were accompanied by age-dependent changes in peripheral secretion of proinflammatory IL-6 and TNF-α and T cell–related IL-2 and IFN- γ cytokines and by increased release of the stress hormone corticosterone in periadolescence.
Scizophrenia and Autism			
Garbett et al. 2012	To examine the immediate effects of MIA induced by influenza virus, poly (I:C) and IL-6 on the fetal brain transcriptome to determine the mechanisms by which maternal infection increases the risk for schizophrenia and autism in the offspring.	MIA was induced in pregnant mice by influenza virus, poly (I:C) and IL-6 at embryonic day 9.5. The transcriptomes from the embryonic brains were investigated.	All three MIA treatments lead to strong and common gene expression changes in the embryonic brain. Most notably, there is an acute and transient upregulation of the α, β and γ crystallin gene family. Furthermore, levels of crystallin gene expression are correlated with the severity of MIA as assessed by placental weight.

Baharnoori et al. 2012	To investigate the potential effects of prenatal immune activation on early neurophenotypic presentations using a set of behavioral test battery.	Pregnant rats were administered with 100 µg/kg LPS i.p. at gestational days 15 and 16. Behavioral test battery was used to investigate the neurophenotypic presentations. The offspring's brains were investigated by quantitative real-time polymerase chain reaction.	No significant effect on maternal behavior or mother-pup interaction by this treatment during the first postnatal week. No major changes in physical developmental milestones of pups were noted from postnatal days six to sixteen. Importantly, prenatal LPS-exposed pups had a significant decrease in the number and duration of ultrasonic vocalization calls at 3rd and 5th postnatal days. Prenatal LPS treatment also led to impairments in nest-seeking behavior and odor-stroke associative learning in neonatal rats at 8th and 9th postnatal days. At the molecular level, significant decrease in the expression of cortical 5HT1A and 5HT1B messenger RNA at 3rd postnatal day was detected. These findings suggest a role of prenatal exposure to an immune activator in impairing the social/communicative behavior reported in individuals with autism and schizophrenia.
Autism Spectrum Disorders (ASD)			

Malkova et al. 2012	To examine the effect of MIA on three core symptoms of autism in the offspring.	Pregnant mice were injected with either poly (I:C) or saline at day 10.5 of pregnancy. Pups' USVs in the isolation test, adult male USV responses to female and male stimuli and USV analysis were conducted, along with the three chamber social-, scent marking-, marble burying-, self-grooming- and olfactory sensitivity tests. These were used as mouse models of the three core symptoms of autism: social interaction and language deficits, and repetitive/stereotyped behaviors.	Compared to pups born to saline-injected mothers, pups born to MIA mothers produce a lower rate of USVs in the isolation test starting at day eight. The quality of the vocalizations is also different; analysis of sound spectrograms of ten day-old pups shows that male pups from MIA mothers emit significantly fewer harmonic and more complex and short syllables. These communication differences are also apparent in adult offspring. Compared to controls, adult MIA males emit significantly fewer USVs in response to social encounters with females or males, and display reduced scent marking in response to female urine. Regarding a second autism symptom, MIA males display decreased sociability. In a third test of characteristic autism behaviors, MIA offspring exhibit increased repetitive/stereotyped behavior in both marble burying and self-grooming tests.

Oskvig et al. 2012	To investigate the immunological, molecular, and behavioral effects of MIA in the offspring.	Pregnant rats were given an i.p. injection of LPS or saline on gestational day 15. Maternal serum, amniotic fluid, and fetal brain were collected for investigation and chip-based immunoaffinity capillary electrophoresis with laser-induced fluorescence detection was used for analysis. Microarray, quantitative real-time polymerase chain reaction and behavioral tests were also conducted.	LPS significantly elevated pro-inflammatory cytokine levels in maternal serum, amniotic fluid, and fetal brain at 4 h, and levels decreased but remained elevated at 24 h. Offspring born to LPS-treated dams exhibited reduced social preference and exploration behaviors as juveniles and young adults. In the microarray analysis, dysregulation of 3,285 genes in restricted functional categories, with increased mRNA expression of cellular stress and cell death genes and reduced expression of developmentally-regulated and brain-specific genes, were observed. These results provide a novel mechanism by which MIA induces the widespread down-regulation of critical neurodevelopmental genes, including those previously associated with autism.
Other Neurocognitive Deficits			
Hao et al. 2010	To examine the effects of prenatal exposure to LPS repeatedly on spatial learning and memory performances in rat offspring's lifetime.	Sixteen pregnant rats were divided into two groups treated with either LPS or saline at gestational days eight, ten and twelve. After delivery, the rat offspring's spatial learning and memory abilities were tested by Morris water maze at the age of three (young), ten (adult) and twenty (aged) months. The structure of hippocampal CA1 region was observed by light microscopy, and the expression of SYP and GFAP in CA1 region were measured by	LPS offspring needed longer escape latency and path-length in the Morris water maze and presented a significant neuron loss, decreased expression of SYP and increased expression of GFAP in CA1 region. All these findings were more significant with age increasing.

		immunochemistry.	
Lin et al. 2012	To examine the anxiety and stress responses and neurophysiological changes after prenatal exposure to LPS challenge.	Pregnant mice were injected with either LPS or saline at embryonic day 10.5. The stress and anxiety-like responses in the offspring were evaluated by open field-, elevated plus maze-, novelty-induced hypophagia-, restraint stress-, dexamethasone challenge- and corticotrophin-releasing hormone challenge tests. Brain DA- and 5-HT biochemical studies were also conducted.	LPS rats displayed more anxiety-like behaviors and heightened stress responses. DA in the nucleus accumbens and 5-HT in the medial prefrontal cortex and the hippocampus were significantly reduced in LPS rats. Their glucocorticoid receptors in the dorsal hippocampus and the 5-HT1A receptors in the dorsal and ventral hippocampus were also reduced. In addition, chronic but not acute fluoxetine treatment reversed the behavioral changes and increased hippocampal 5-HT1A receptor expression. These alterations may be associated with the increases in stress response and anxiety-like behaviors in the offspring.