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# Prenatal infection and schizophrenia: A decade of further progress

Keely Cheslack-Postava [a,*], Alan S. Brown [a,b]

[a] Department of Psychiatry, New York State Psychiatric Institute, Columbia University Irving Medical Center, New York, NY, USA
[b] Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY, USA

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ABSTRACT

Epidemiologic studies have provided evidence that prenatal exposure to maternal infection is associated with an increased risk of developing schizophrenia in the offspring. Research over the past decade has added further to our understanding of the role of prenatal infection in schizophrenia risk. These investigations include several well-powered designs, and like some earlier studies, measured maternal antibodies to specific infectious agents in stored serum samples and large registers to identify clinically diagnosed infections during pregnancy. Convergent findings from antibody studies suggest that prenatal maternal infection with *Toxoplasma gondii* is associated with increased schizophrenia risk in the offspring, while associations with HSV-2 infection are likely attributable to confounding. Maternal influenza infection remains a viable candidate for schizophrenia, based on an early serological study, though there has been only one attempt to replicate this finding, with a differing methodology. A prior association between maternal serologically confirmed cytomegalovirus infections require further study. Clinically diagnosed maternal infection, particularly bacterial infection, also appears to be associated with increased risk of offspring schizophrenia, and heterogeneity in these findings is likely due to methodological differences between studies. Further clarification may be provided by future studies that address the timing, type, and clinical features of infections. Important insight may be gained by examining the long-term offspring outcomes in emerging epidemics such as Zika virus and COVID-19, and by investigating the interaction between exposure to prenatal infection and other risk or protective factors.



## 1. Introduction

In this era of Covid-19, the devastating effects of the pandemic on populations worldwide have called new attention to the importance of infection on health. In this review, we focus on prenatal infection in regard to offspring schizophrenia, a poignant example of the potential lifelong consequences of infection, persisting even into the next generation. Although schizophrenia has a lifetime prevalence of less than 1% (McGrath et al., 2008), it is associated with cognitive deficits (Tandon et al., 2009), social and functional impairment (Mohr et al., 2014), and reduced life expectancy (Laursen et al., 2014), factors which contribute to a high burden of disease and disability globally (Charlson et al., 2018). While schizophrenia is highly heritable, non-genetic factors are also implicated in risk (Hilker et al., 2018). Prenatal infection represents one such risk factor which has been well established, beginning with ecologic studies of influenza epidemics in populations (i.e., Barr et al., 1990; Kendell and Kemp, 1989; Mednick et al., 1988). Although the epidemiologic research demonstrating this connection stretches back at least 35 years, the field continues to evolve, building on prior work while introducing methodological innovations and expanding the scope of inquiry. Thus, we take the opportunity to update a prior review (Brown and Derkits, 2010) by looking back over the past decade to describe the research contributions added over that time frame and to assess the current state of the evidence on prenatal infection and schizophrenia.

According to the neurodevelopmental model, the clinical manifestation of schizophrenia is the conclusion of abnormal processes in brain development that begin years or decades prior to the observed onset of the disorder (Rapoport et al., 2012). The prenatal time period is critical for brain development, with processes including neurulation, neurogenesis, and neuronal migration, reaching completion before birth, while others such as synaptogenesis, gliogenesis, and myelination, also begin during gestation (Schepanski et al., 2018). Evidence that the gestational environment constitutes an important risk factor for offspring development of schizophrenia includes the increased risk observed among those exposed in utero to nutritional deficiency (Brown and Susser, 2008) and obstetric complications (Clarke et al., 2006), as well as to maternal infection, the focus of this review. Infection has been consistently implicated in schizophrenia risk by epidemiologic studies (discussed below) and by animal models of maternal immune activation (Brown and Meyer, 2018). Importantly, maternal

* Corresponding author at: Department of Psychiatry, New York State Psychiatric Institute, 1051 Riverside Drive Unit 23, New York, NY 10032, USA.
*E-mail addresses:* kc2497@cumc.columbia.edu (K. Cheslack-Postava), asb11@cumc.columbia.edu (A.S. Brown).

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infection during pregnancy or its complications are potentially preventable exposures, for example through vaccination or screening (Al-Haddad et al., 2019).

The epidemiologic studies of prenatal infection and schizophrenia that were reported through March 2009 were previously reviewed (Brown and Derkits, 2010). Here, we focus on the more recent studies which have expanded our understanding of this phenomenon over the decade since. As the earlier literature has been well described in the noted review, here we give only a brief summary in order to contextualize the newer research. The recognition of prenatal infection as a possible risk factor for schizophrenia began in the 1980's with a series of ecological studies focusing on exposure to influenza epidemics and based primarily in Europe, with Australia (McGrath and Castle, 1995; Morgan et al., 1997) and Japan (Izumoto et al., 1999; Mino et al., 2000) also represented. Results were mixed, with some investigations finding evidence for increased risk of schizophrenia among the offspring of exposed pregnancies, particularly during the second trimester (i.e., Barr et al., 1990; Limosin et al., 2003; Mednick et al., 1988, 1994; Takei et al., 1996), while other failed to replicate these associations (i.e., Erlenmeyer-Kimling et al., 1994; Morgan et al., 1997; Takei et al., 1995; Westergaard et al., 1999). Meanwhile, a limited number of ecological studies looked at other infections, with associations between measles (Torrey et al., 1988), mumps (O'Callaghan et al., 1994), and varicella zoster infections (O'Callaghan et al., 1994; Torrey et al., 1988), among others, identified. However, consistency of the findings was limited, and studies simultaneously assessing risk related to several pathogens may have been impacted by false positive findings due to multiple comparisons. As ecological studies, these investigations defined exposure based on the timing and geographic location of pregnancy with respect to population-level prevalence of infections in question, rather than individually assessing subjects for actual evidence of infection. The result was potential misclassification of the exposure, a phenomenon expected to bias estimates of effect towards the null (Wacholder et al., 1995).

To ameliorate this issue, the next generation of studies, beginning in earnest around 2000 (though see (Cannon et al., 1996; Crow et al., 1991) as earlier exceptions), used cohort or case-control designs with individual exposure assessment, via either clinical records of diagnosis or serological biomarkers. In a birth cohort with clinically and serologically documented exposure to prenatal rubella, we found a five-fold elevated rate of non-affective psychosis, relative to a non-exposed cohort (Brown et al., 2000). Additional studies provided serological evidence, based on maternal antibody levels, for the association of prenatal influenza infection (Brown et al., 2004a) with schizophrenia. Findings for *Toxoplasma gondii* included studies that both showed (Brown et al., 2005) and did not show (Buka et al., 2001a) increased risk associated with elevated maternal antibody levels, and the evidence regarding herpes simplex virus type 2 (HSV-2) was also conflicting, including studies that both did (Buka et al., 2001a, 2008) and did not (Brown et al., 2006) support an association. The association with bacterial infections as a class was suggested by with a study using clinical exposure assessment (Sørensen et al., 2009). While these studies represented an important advancement over ecological designs, most involved modest case sample sizes, limiting power. Additionally, important sources of variation exist across studies, including in the case and exposure definitions.

As noted above, in this review we provide an update to this body of research by reviewing studies which have been added to the literature over the past decade. The scope of our description includes epidemiologic (human) studies examining the outcome of schizophrenia, or a broader group of psychosis outcomes that explicitly include diagnosed schizophrenia. We focus on studies that compare cases with schizophrenia to population or other controls; studies restricted solely to case populations and their characteristics or outcomes without reference to a control or non-affected group are excluded. Finally, we include studies that examined as an exposure prenatal infection during any time point in pregnancy. Evidence for maternal infection may be based on biomarkers (i.e. antibodies) or on clinical, administrative, or self-reported data, and may include evidence for infection with specific pathogens or general evidence for infection. However, for clarity of presentation, we limit the scope and do not include studies only examining broad measures of immunity/immunological markers or inflammation (i.e. cytokine or C-reactive protein levels, without focus on discerning evidence of current active infection). Further discussion of recent literature on the immune system or its markers more generally in relation to schizophrenia is well covered elsewhere (Allswede and Cannon, 2018; Zhang et al., 2018). A summary of the included studies can be found in Table 1.

## 2. Studies using antibodies for exposure assessment

A number of studies over the past decade continued the use of antibodies to obtain evidence of individual prenatal exposure to specific infections. These are discussed below, according to the pathogen examined.

### 2.1. Influenza

Despite its being a major focus of earlier work, recent investigation of prenatal influenza in schizophrenia risk has been limited. A case-control study (Ellman et al., 2009) based in the Collaborative Perinatal Project, a prospective birth cohort from the United States, measured IgG antibodies to influenza A and B in stored maternal serum samples which had been drawn at the end of pregnancy. In contrast to earlier serologic findings on influenza noted above (Brown et al., 2004a), the prevalence of elevated antibodies did not differ between the case and control groups. One possible explanation for the discrepant findings lies in the different timing of the serum samples during pregnancy of the respective studies, given that the earlier study showed the greatest elevation in risk for early to mid-pregnancy exposure. A second difference is that the earlier study utilized a measure of influenza that was validated based on seroconversion to the virus. The later study used a cut-off value at the 75th percentile to identify samples that were likely to have come from women with a recent active influenza infection, rather than being validated from seroconversion. Nonetheless, in the later study, influenza B exposure was associated with lower verbal IQ among cases, but not among controls, suggesting a possible role in verbal acquisition deficits in schizophrenia.

### 2.2. Toxoplasmosis

A second pathogen investigated in relation to schizophrenia is maternal exposure to *T. gondii*. In an earlier study, maternal exposure to antibody to this infectious agent was associated with schizophrenia among offspring (Brown et al., 2005). In a case-control study (Xiao et al., 2009), based on the Collaborative Perinatal Project, IgG antibodies to *T. gondii* in maternal pregnancy serum samples were measured. Cases with psychosis (about half of whom had schizophrenia diagnoses) and matched controls were included. This study was novel in separately assessing exposure to the three specific types of toxoplasma subtypes predominating in the U.S. (type I, type II, and type III). The investigators found that psychosis risk was nearly doubled among offspring whose mothers had antibodies to type I, the most virulent of the types in mice. Associations were not found for types II or III. However, the association with type I appeared to be mainly attributable to an increased risk of affective psychosis, as opposed to schizophrenia (Xiao et al., 2009). Association of *T. gondii* with schizophrenia and other non-affective psychosis was also assessed in a similarly sized case-control study (Blomström et al., 2012) of Swedish births. In that study, IgG antibodies were measured in archived dried neonatal blood samples. IgG antibodies cross the placenta during pregnancy (Malek et al., 1996) so that levels in newborns may be used to assess prenatal exposure. Here, *T. gondii* antibodies were associated with an approximate

**Table 1**
Recent epidemiologic studies on the association of prenatal maternal infection and risk of schizophrenia.

| First author, year | Location | Birth years of subjects | Number of cases and non-cases | Outcome definition | Exposure | Covariates (matched or adjusted) | Estimate of association | Notes |
|---|---|---|---|---|---|---|---|---|
| Studies using biomarker-based exposure assessment | | | | | | | | |
| Biomarkers in maternal serum during pregnancy | | | | | | | | |
| Ellman et al., 2009 | United States (Collaborative Perinatal Project, Philadelphia site), nested case--control study | 1959–1966 | 111 psychosis cases (70 with schizophrenia); 333 controls | DSM-IV diagnosis, confirmed using chart review | Influenza A and Influenza B IgG antibody levels >75th percentile, indicating probable recent infection; maternal serum samples at end of pregnancy | Matched on: sex, race, hospital, and date of birth. | Influenza A: 25% cases vs. 25% controls exposed, $p = 1.00$. Influenza B: 32% cases vs. 24% controls exposed, $p = 0.12$. | Influenza B exposure was associated with decreased verbal IQ at age 7 in cases but not controls. |
| Xiao et al., 2009 | United States (Collaborative Perinatal Project, Boston, Providence and Philadelphia sites), nested case-control study | 1959–1966 | 119 psychosis cases (including 106 schizophrenia); 618 controls | DSM-IV diagnosis, confirmed using structured clinical interview or medical chart review | *T. gondii* antibodies (types I, II, and III), maternal serum from end of pregnancy | Matched on: city, dated of birth, race/ethnicity, gender. | Type I: OR (95% CI) = 1.94 (1.08, 3.46); $p = 0.03$. Type II: OR (95% CI) = 1.37 (0.67, 2.79); $p = 0.38$. Type III: OR (95% CI) = 0.95 (0.32, 2.83); $p = 0.93$. | Association appears attributable to affective psychosis group. |
| Cheslack-Postava et al., 2015 | Finland, case-control study nested in a national birth cohort | 1983–1998 | 963 cases, 963 controls (207 cases/controls for *C. trachomatis*) | ICD-10 F20, F25 | HSV-2 and *Chlamydia trachomatis* antibodies, early to mid-pregnancy maternal serum | Matched on: sex, birth date, residence in Finland. Adjusted for: paternal age, birth locale, parental schizophrenia diagnosis. | HSV-2: OR (95% CI) = 1.22 (0.93, 1.60); $p = 0.14$ *C. trachomatis* (unadjusted): OR (95% CI) = 1.04 (0.59, 1.81); $p = 0.88$ | HSV-2: Unadj. OR (95% CI) = 1.33 (1.03, 1.72); $p = 0.03$ |
| Biomarkers in neonatal blood spots | | | | | | | | |
| Mortensen et al., 2010 | Denmark, case--control study nested in national birth cohort | 1981–1994 | 602 cases, 602 controls | ICD-10 F20 | HSV-2 antibodies, dried neonatal blood spots | Matched on: sex, birth date, residence in Denmark. Adjusted for: urbanicity at birth, parental age, immigrant status, 1st degree relative history of psychiatric disorder | IRR (95% CI) = 1.36 (0.99, 1.87); $p = 0.06$ | Unadj. IRR (95% CI) = 1.56 (1.17, 2.07); $p = 0.002$. Attenuation in adj model due primarily to paternal history of psychiatric disorder. |
| Blomström et al., 2012 | Sweden, case-control | 1975–1985 | 198 cases, 524 controls (including F20: 47 cases, 124 controls) | ICD-10 F20 (schizophrenia); ICD-10 F21–29 (other non-affective psychoses) | *T. gondii*, CMV, HSV-1, HSV-2 antibodies, dried neonatal blood spots | Matched on: sex, birth date, birth hospital. Adjusted for maternal age, migration. | For schizophrenia, (OR = 2.0, 95% CI 0.9–4.7); CMV (OR = 2.1, 95% CI 0.9–4.9); HSV-1 (OR = 0.8, 95% CI = 0.4, 1.6); HSV-2: OR (95% CI) = 0.5 (0.2, 1.4) | Evidence for dose-response relationship for *T. gondii* and CMV with schizophrenia. |
| Studies using clinical/registry based exposure assessment | | | | | | | | |
| Suvisaari et al., 2013 | Helsinki, Finland (Helsinki High Risk Study) | 1941–1977 | 29 cases, 242 non-cases; All children of mothers with schizophrenia spectrum diagnoses | DSM-IV schizophrenia spectrum psychosis (19 with schizophrenia) | Infections during pregnancy, from public hospital obstetric records. Recorded infections most often bacterial. | Adjusted for: sex, birth weight, maternal hypertension during pregnancy, placental abnormalities | HRR (95% CI) = 3.73 (1.27, 11.01); $p = 0.02$ | Study focused broadly on a range of obstetric complications. |

*(continued on next page)*

**Table 1** (*continued*)

| First author, year | Location | Birth years of subjects | Number of cases and non-cases | Outcome definition | Exposure | Covariates (matched or adjusted) | Estimate of association | Notes |
|---|---|---|---|---|---|---|---|---|
| Blomström et al., 2016 | Swedish national birth cohort | 1978–1997 | 8330 cases; 1,963,293 non-cases | ICD-10 F20–29/ICD-9 295, 297 and 298 except 298A and B | Registry inpatient diagnoses of infection during pregnancy based on ICD-8, 9 or 10 codes | Adjusted for: birth year, sex, parental psychiatric disorder, SES, parent inpatient care before or during pregnancy, urban birth, winter birth, parental age, parental immigrant status, SGA. | HR (95% CI) = 1.06 (0.88, 1.27) | Bacterial, viral, or other infections examined as separate categories were also not associated with outcome. |
| Nielsen et al., 2016 | Danish national birth cohort | 1977–2002 | 6729 cases; 1,396,454 non-cases | ICD-10 F20/ICD-8 295 | Register diagnosis of mother with infection during pregnancy | Adjusted for: calendar year, sex, sex X age interaction, urbanicity, parental history of psychiatric admission. | IRR (95% CI) = 1.16 (1.03, 1.31) | Also examined interaction with maternal diagnosis of anemia during pregnancy, finding independent effects. |
| Debost et al., 2017 | Danish national birth cohort | 1980–1998 | 9656 schizophrenia spectrum; 970,045 non-cases | ICD-8: 295, 295.x9, 296.89, 297. x9, 298.29–298.99, 299.04, 299.05, 299.09, 301.83; ICD-10: F20–F29 | Register record of mother admitted to hospital with infection during pregnancy, based on ICD-8 and ICD-10. | Adjusted for: calendar period, age, parental psychiatric history, parental education, childhood psychological trauma. | Without peripubertal psychological trauma: IRR (95% CI) = 1.05 (0.88–1.25); With trauma: IRR (95% CI) = 1.58 (1.33–1.88) | Interaction of prenatal infection with peripubertal psychological trauma was specific to males. |
| Lydholm et al., 2019 | Danish national birth cohort | 1996–2015 | 2186 schizophrenia disorder cases; 1,204,414 non-cases | ICD-10 F20–29 (secondary outcome) | Infections treated with prescription or requiring hospital contact during pregnancy. | Adjusted for: sex, birth year, concurrent infection in the other parent; and parental education, age, physical illnesses at childbirth, and psychiatric diagnoses. | Prescription: HR (95% CI) = 1.14 (1.00, 1.30); Hospital contact: HR (95% CI) = 1.29 (0.95, 1.77) | Primary study outcome was any mental disorder (ICD-10 F20–99); also examined infections before and after pregnancy, and paternal infections. |
| Al-Haddad et al., 2019 | Swedish national birth cohort | 1973–2014 | 4382 cases; 2,133,630 non-cases | ICD-10 F20–29 | Maternal hospitalization during pregnancy with infection (ICD-8, 9 or 10) | Adjusted for: maternal age, asthma, diabetes, premature rupture of membranes, and tobacco status, 10-year epoch of birth. | HR (95% CI) = 1.14 (0.83, 1.57) | Also examined autism, bipolar disorder, and depression as outcomes |
| Lee et al., 2020 | United States (Collaborative Perinatal Project, Boston and Providence sites) | 1959–1966 | 116 cases (52 schizophrenia and schizoaffective disorder, depressive type); 15,305 non-cases | DSM-IV diagnosis, confirmed using structured clinical interview or medical chart review | Any bacterial infection during pregnancy; identified through standardized maternal interviews, and physician record review | Adjusted for: sex, study site, year and season of birth, socioeconomic status; maternal education, race/ethnicity, and neurological/psychiatric conditions during pregnancy; parental history of mental illness, follow-up participation, and viral infection during pregnancy. | OR (95% CI) = 1.8 (1.2, 2.7); p = 0.002 | Association was stronger (OR = 2.9) for multisystemic infection and among males. |
| Pugliese et al., 2019 | Italy; clinically-based case-control study | age 18–65 between 2014 and 2016 | 91 cases; 85 controls | DSM-IV-TR schizophrenia spectrum disorder, treated as outpatients for at least 12 mos. | Maternal prenatal infection from medical records | Adjusted for: maternal stress, inadequate weight gain, asphyxia | OR (95% CI) = 7.67 (1.78, 33.1) | Study examined maternal prenatal psychological stress, obstetric complications, and medical illness including infection |

doubling in risk of schizophrenia. However, the association was no longer significant after adjustment for maternal age and migration, though it should be noted that this may be related to limited power, given that the sample size for schizophrenia specifically was rather low and that a dose-response relationship of higher risk with increasing antibody levels (Blomström et al., 2012) bolsters the evidence for a true association. Overall, the evidence provided by these newer studies strengthens the support for an association between prenatal exposure to *T. gondii* antibodies and risk of psychosis, although further clarification is warranted with respect to specific diagnostic categories.

### 2.3. Herpes simplex virus type 2

Several investigations addressed earlier conflicting reports regarding herpes simplex virus type 2 (HSV-2) by measuring antibodies to this virus. These included the Swedish case-control study using neonatal dried blood spots discussed above (Blomström et al., 2012), which did not find an association of schizophrenia with HSV-2 antibodies. A case-control study of schizophrenia and matched controls nested in a Danish national birth cohort (Mortensen et al., 2010) also measured IgG antibodies to HSV-2 in newborn dried blood samples. In a non-adjusted model, which accounted for the matching factors of sex, birth date, and residence in Denmark, but not other potential confounders, seropositivity for HSV-2 was associated with a modestly increased incidence rate. Upon further adjustment for urbanization of the place of birth, parental age, second generation immigration status, and history of psychiatric disorders in the first-degree relatives, the association was attenuated and no longer significant. Paternal history of psychiatric disorder was identified as the factor primarily contributing to the attenuation (Mortensen et al., 2010). Finally, our even larger study of nearly a thousand cases with schizophrenia and schizoaffective disorder, and their matched controls nested in a Finnish national birth cohort (Cheslack-Postava et al., 2015) measured IgG antibodies to HSV-2 in archived maternal serum samples from the first to early second trimesters of pregnancy. We found modest evidence for an association in analyses accounting for the matching factors (sex, birth date, residence in Finland at time of the case diagnosis) only. However, adjustment for paternal age, province of birth, and parental schizophrenia diagnosis resulted in an attenuated relationship that was no longer statistically significant (Cheslack-Postava et al., 2015). When added to the prior inconsistent evidence, these findings overall do not support a significant association between prenatal exposure to HSV-2 antibodies and risk of schizophrenia. Further, they highlight the apparent role of parental psychiatric disorder as a potential confounder of this relationship. As well as being as being associated with their offspring's psychiatric disorder risk, parental psychiatric illness may impact risk of infection through behavioral effects, confounding the observed associations between offspring infection exposure and schizophrenia. Thus, it is important that epidemiologic studies account for this covariate.

### 2.4. Other infections

Besides *T. gondii* and HSV-2, two of the studies described above contribute evidence regarding additional pathogens. Our study of archived maternal serum samples from a Finnish birth cohort also measured antibodies to *Chlamydia trachomatis* in a subsample of cases and matched controls, who were not found to differ in seropositivity to this pathogen (Cheslack-Postava et al., 2015). The smaller Swedish study using neonatal dried blood samples measured IgG antibodies to cytomegalovirus (CMV) and to herpes simplex virus type 1 (HSV-1; Blomström et al., 2012). HSV-1 antibodies were not associated with schizophrenia risk; however, CMV seropositivity was associated with a two-fold increased risk for schizophrenia, with evidence of a dose-response pattern between antibody levels and risk (Blomström et al., 2012).

## 3. Studies using clinical or records-based exposure assessment

Other studies, rather than using antibodies to measure the history of exposure to specific infectious agents, assessed clinical infection more generally based on records related to the pregnancy. For the most part, these take the form of register-based national birth cohorts or of prospective cohort studies.

### 3.1. National birth cohort studies

Large national birth cohort studies from Sweden and Denmark ascertained thousands of cases and provided mixed evidence regarding the association of diagnosed infections during pregnancy which were recorded in national registers with offspring schizophrenia diagnoses. Two studies of the Swedish population (Al-Haddad et al., 2019; Blomström et al., 2016) suggested against such an association. In the first study (Blomström et al., 2016), subjects were considered to be exposed if the mother was treated as an inpatient with an infection during pregnancy, based on ICD-8, 9, or 10 diagnostic codes; maternal exposure was not associated with schizophrenia/other psychoses. While diagnosed infections were also considered separately as bacterial, viral, or other, none of these categories were found to be associated with the outcome either. A second study based in Sweden (Al-Haddad et al., 2019) similarly evaluated exposure to infection, based on maternal hospitalization during pregnancy, which was also not significantly associated with an increased risk of schizophrenia and related disorders.

A Danish national birth cohort study used a similar design (Lydholm et al., 2019), with the exception that maternal infections treated with a prescription during pregnancy were also considered as exposures. Maternal infections defined by having had hospital contact were not associated with offspring schizophrenia, but risk of the outcome was modestly increased among those treated with prescription medications. In a separate Danish national birth cohort study (Nielsen et al., 2016), cases were restricted to those with narrow schizophrenia diagnoses (ICD-10 F20 or the equivalent). In this study, a register record of maternal diagnosis with infection during pregnancy was associated with a mildly increased risk of schizophrenia. In both of these studies, the effect sizes were small (under 20% increases in risk). In a third Danish birth cohort study and using a broad schizophrenia spectrum case definition (Debost et al., 2017), maternal hospitalization for infection during pregnancy was associated with an over 50% increased risk of offspring schizophrenia specifically among those who later experienced psychological trauma around the time of puberty. On the whole, while the evidence from the register-based birth cohort studies described above—all of which are amply powered with thousands of cases—is mixed, it is notable that the strongest findings were observed in the study that used a narrow case definition, possibly indicating specificity of the association.

### 3.2. Prospective cohort studies

While register-based studies of national birth cohorts facilitate very large population-wide studies, the exposure and outcome assessments, as well as the information about potential confounders are limited to the information that is included in these administrative sources. For instance, studies using registers of inpatient diagnoses will be limited in their assessment of prenatal infection to those most severe infections requiring hospitalization. Moreover, such studies may only be conducted in locations and during time periods where suitable administrative sources exist, limiting generalizability. Some studies instead used existing cohorts in which information about prenatal conditions was collected through record review and/or interview. In one, cases with confirmed DSM-IV diagnoses of schizophrenia and related psychoses were identified among the offspring of mothers enrolled in two sites

of the prospective U.S. Collaborative Perinatal Project (Lee et al., 2020). In this population, any bacterial infection during pregnancy, as identified through standardized maternal interviews and physician record review, was associated with an almost 2-fold increased risk of psychoses including schizophrenia. The association was even stronger for multisystemic infections, and among males (Lee et al., 2020). A relatively small study limited to the offspring of mothers with schizophrenia spectrum diagnoses themselves who were followed in the Finnish Helsinki High Risk Study, identified cases with DSM-IV schizophrenia spectrum psychoses and compared them to offspring without such diagnoses (Suvisaari et al., 2013). Infections during pregnancy, as recorded in hospital obstetric records, were primarily bacterial and were associated with an over 3-fold increased risk of offspring schizophrenia spectrum diagnoses. Taken together, the results of these two studies support an impact of bacterial infections, specifically, although the Swedish birth cohort study that examined bacterial infections separately did not report an association (Blomström et al., 2016).

Finally, a small study in Italy included clinically treated schizophrenia spectrum outpatients as cases and community controls (Pugliese et al., 2019). Medical record of maternal prenatal infection was strongly associated with schizophrenia spectrum disorder, after adjustment for maternal stress, inadequate weight gain, and asphyxia. While suggestive, given several methodological factors including the wide age range of subjects (age 18–65 at ascertainment), limited sample size, and potential selection bias in the identification of controls, the results of this study should be interpreted cautiously.

## 4. Conclusion

### 4.1. Summary of findings reviewed above

Research over the past decade has added substantially to our understanding of the role of prenatal infection in schizophrenia risk. Since our earlier finding that maternal influenza exposure during pregnancy is associated with increased schizophrenia risk, only one study has utilized an influenza antibody assay to assess the exposure (Ellman et al., 2009) and this finding may have been due to methodologic differences. Hence, further studies will be necessary to replicate the association. Based on convergent findings from antibody studies across multiple cohorts, the preponderance of evidence suggests that prenatal maternal infection with *T. gondii* is associated with increased schizophrenia risk in the offspring. HSV-2 infection, however, appears unlikely to increase risk, with observed associations attributable to confounding. Initial findings of increased risk associated with CMV seropositivity should be replicated before conclusions are drawn. Regarding maternal clinically diagnosed infection, the overall evidence suggests that this exposure, particularly bacterial infection, is associated with increased risk of offspring schizophrenia, with heterogeneity in the findings of individual studies likely due to methodological differences. Further clarification may be provided by studies that address the timing, type, and clinical features of these infections, as well as rigorously addressing potential confounding, for example using sibling comparison designs (Donovan and Susser, 2011). In the following sections, we first make note of several additional lines of evidence related to the association of prenatal infection with schizophrenia, but beyond the scope of our in-depth review. We then describe directions for future research.

### 4.2. Other relevant lines of evidence

As noted above, we focused this review specifically on studies that addressed diagnosed schizophrenia, included a comparison group without schizophrenia, and examined prenatal infection. Additional research directions over the past decade may provide valuable insight related to these associations. In the following section, we briefly summarize such categories of research, highlighting key examples.

First, some investigations have examined outcomes related to, but not inclusive of, diagnosed schizophrenia. Studies of such outcomes may provide information on the specificity of associations, including that with pre-morbid risk. These include a study which found that prenatal maternal antibodies indicating influenza exposure were associated with bipolar disorder, but only among the cases with psychotic features, a symptom overlapping with schizophrenia and related non-affective psychotic disorders (Canetta et al., 2014a). Others have examined as outcomes factor analysis-derived measures quantifying subjects' reported positive psychotic experiences (Betts et al., 2014) and psychotic-like experiences in 11-year olds (Dreier et al., 2018).

Second, studies examining the relationship of prenatal infection exposure to clinical characteristics within schizophrenia cases only (i.e., without comparison to a control group) can help to identify the neurocognitive functions involved in the disorder which may be susceptible to developmental disturbance by infection. This may in turn implicate specific brain regions as affected. An example is the finding that schizophrenia patients who had been exposed to maternal infection with either influenza or toxoplasmosis had impaired performance on tasks of executive function relative to non-exposed cases (Brown et al., 2009).

Third, infections occurring after birth—that is, from infancy through early adulthood–have been examined in relation to schizophrenia. In one study, for example, infections (particularly bacterial) occurring sometime after birth but prior to diagnosis, and resulting in hospital contact were associated with increased schizophrenia risk in a dose-response manner (Nielsen et al., 2014). In another study, serologically determined exposure to Epstein-Barr Virus by age 4 was associated with a five-fold increased risk of positive psychotic experiences in adolescence (Khandaker et al., 2014). These findings are suggestive of a "two-hit" model, whereby prenatal infection exposure "primes" the immune system, thereby increasing vulnerability to later postnatal insults (Giovanoli et al., 2013).

Finally, a number of studies including those from our group (Canetta et al., 2014b; Ellman et al., 2010) examined prenatal maternal cytokines, complement, or C-reactive protein, immune markers or markers of inflammation in general that are not specifically diagnostic of infection (reviewed in (Allswede and Cannon, 2018; Zhang et al., 2018)). This built on earlier findings by our group and others that higher prenatal maternal levels of the pro-inflammatory cytokines IL-8 (Brown et al., 2004b) and TNF-α (Buka et al., 2001b) increased schizophrenia risk. Recent meta-analyses suggest that elevated maternal levels of C-reactive protein, IL-8 (pro-inflammatory), and IL-10 (anti-inflammatory) are each associated with increased risk of offspring schizophrenia (Zhang et al., 2018). Meanwhile findings for other individual cytokines are more varied. For example, prenatal maternal IL-6 was higher in schizophrenia cases than in controls from the same cohort (Goldstein et al., 2014), inconsistent with a prior study that did not find this association (Buka et al., 2001b). One study took the approach of computing composite measures based on cytokine groupings and reported that higher levels of maternal anti-inflammatory Th2 cytokines (based on IL-4, IL-5, and IL-13 levels) were associated with lower odds of psychosis in offspring (Allswede et al., 2016). Lastly, in a single epidemiologic study examining the complement system, high maternal levels of the complement factor C1q were associated with significantly increased risk of psychotic disorders in the offspring, while the levels correlated with those of HSV-2 and adenovirus antibodies (Severance et al., 2014). Studies of these markers provide evidence regarding specific immune system pathways as potential mechanisms linking prenatal infection to schizophrenia risk in the offspring.

### 4.3. Future directions

Building on the work related to known neurodevelopmental teratogens such as prenatal rubella (Brown et al., 2000), examining population experiences with emerging infections may provide

novel insights about the long-term consequences for schizophrenia risk. In utero infection with Zika virus, which was relatively unknown until the 2015–2016 epidemic, is associated with congenital Zika virus syndrome, a severe condition involving complications such as microcephaly, brain and eye abnormalities, epilepsy, and motor, vision, and hearing impairments (Pomar et al., 2019). Findings on neurodevelopmental sequelae in offspring prenatally exposed to Zika virus who did not manifest the congenital syndrome, however, have been mixed. Some (Aguilar Ticona et al., 2021; Stringer et al., 2021), but not all (Grant et al., 2021) studies have reported developmental delays or deficits prior to age 3. These findings related to early childhood general neurodevelopmental decrements related to Zika virus are suggestive given that schizophrenia is also associated with pre-morbid general cognitive deficits (Sheffield et al., 2018).

In a U.S. national sample over 8 months of the pandemic in 2020, 1.6% of women hospitalized for childbirth had concurrent COVID-19 (Jering et al., 2021); the proportion affected at any time during pregnancy will be larger. Vertical transmission has been estimated to occur in approximately 3% of cases (Kotlyar et al., 2021) and maternal and infant complications are reported to be modestly increased among COVID-19 affected pregnancies (Jering et al., 2021); however, the long-term implications are still unknown. For both Zika virus and COVID-19, it will be decades before the long-term outcomes vis a vis offspring schizophrenia can be known. Large prospective birth cohorts with well-documented exposure information will enable determination of the impact of prenatal exposure to these infections on the developmental course preceding diagnosis.

Another issue is that most studies of specific infections to date have considered these infections individually. This may result in exposure misclassification, biasing results towards the null, if multiple different infections influence risk via the same pathway. The simultaneous consideration of multiple infections in future studies may be facilitated by the development of novel low-cost, efficient multiplex assays (i.e. Brenner et al., 2018).

Ultimately, understanding the role of prenatal infection in the etiology of schizophrenia will depend on understanding how exposure to infection interacts with other risk factors and exposures. Aspects of maternal and infant genetics and physiology may influence the susceptibility to the potential adverse impacts of prenatal infection. For example, a study reported that an increased risk of psychosis associated with maternal infection with *T. gondii* or CMV occurred only among neonates with low levels of acute phase proteins, a marker of innate immunity (Blomström et al., 2015). It also may be, as described above as the "two-hit" model, that multiple exposures over development act in concert, with a prenatal exposure increasing susceptibility to a later insult. The association of maternal prenatal hospitalization for infection specific to those with peripubertal trauma exposure (Debost et al., 2017) may be one example of such a phenomenon. Analyses of studies focusing on combined effects—whether of multiple infections or of infections and other environmental exposures–should carefully address issues including multiple comparisons, correlation between exposures, and the selection of appropriate models for the relationship of joint exposure patterns to outcome risk.

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### Declaration of competing interest

None.

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