Epidemiological Studies of Prenatal and Childhood Infection and Schizophrenia

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Contents

Abstract Certain infectious agents can target the brain and interfere with its growth, development, and/or function. A number of studies indicate that exposure to common infectious agents during fetal and postnatal life may also contribute to the later development of schizophrenia and other non-affective psychoses. Epidemiological studies of maternal infections during pregnancy have provided somewhat contradictory results with regard to infections in general but have reported surprisingly consistent associations with specific maternal exposures such as *Toxoplasma gondii*. Childhood is also beginning to emerge as a sensitive period for the influence of infections including infectious agents not known to target the brain. Recent studies have associated childhood infections not only with a later diagnosis of schizophrenia but also with impaired cognitive function. Importantly, independent studies indicate that the associations between early life infection and the later development of schizophrenia are not explained by factors shared between related individuals or by genetic liability for schizophrenia.

Keywords Childhood · Cognition · Infection · Pregnancy · Schizophrenia

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1 Introduction

Some infections of the mother during pregnancy are recognized to target the fetus or newborn to interfere with its growth or development, including that of the brain. The most well-recognized agents with such teratogenic properties are *Toxoplasma gondii*, rubella virus, cytomegalovirus (CMV), and herpes simplex viruses, commonly referred to as the TORCH agents (Bale 2009). Congenital infections by these agents are fortunately rare even among infected mothers without pre-existing immunity. Moreover, the recent Zika virus epidemic in South America illustrates that emerging infections are a severe threat to human health (Alvarado and Schwartz 2017). Maternal infections can also be passed on to the offspring during or after birth (e.g., during breastfeeding) (Bale 2009). After birth, the neonate is increasingly exposed to not only its mother's infections but the infectious agents prevalent in the child's environment, which is likely to vary greatly across time, geographic regions, and socioeconomic groups.

1.1 The Timing of an Infection Affects the Outcome

Among children exposed to infection, the outcome can vary depending on the timing of the exposure in relation to their developmental stage. Whereas infections early in gestation may cause severe CNS malformations, later infections may cause more subtle symptoms (e.g., impairments in hearing or cognition), comprehensively reviewed in Bale (2009). In terms of neurodevelopmental processes, neurogenesis and neuronal migration in the developing cortex are largely complete by birth. The postnatal period is characterized by a very rapid growth, primarily involving glial cell proliferation and differentiation, synapse formation, and myelination, and the human brain reaches 90–95% of its adult volume by age 6. While regional gray matter volumes tend to decrease during adolescence, in part due to synaptic pruning, the formation of myelin sheaths around nerve fibers begins during fetal life and continues through the first few decades of life. Postnatal neurodevelopmental processes occur at different time points and rates in different cortical and subcortical regions, and all contribute to the changes in cognitive abilities and processing of social interactions and emotions that occur during the first decades of life (Semple et al. 2013; Houston et al. 2014).

Not only the brain but also the immune system undergoes development from fetal life through neonatal life, childhood, adolescence to adulthood. For the purpose of infections, the developmental stage of the immune system will also determine the outcome of an exposure. Many infections, primarily of viral origin such as hepatitis B virus (HBV), are largely asymptomatic when occurring during early life in part due to an inability of the neonate to mount an adequate response to eradicate the infections, which can lead to persistence and chronic infection to cause symptoms only later on in life. Older children and adults infected with HBV, on the other hand,

often develop acute disease symptoms (e.g., jaundice) due to an efficient destruction of infected (liver) cells and clearance of the infection. Other agents can cause life-threatening conditions in neonates, e.g., herpes simplex virus, but are usually asymptomatic in older children or adults. The developmental processes occurring both in the immune system and in the brain throughout childhood thus may have a substantial influence on the short- and long-term outcomes of an infection (Prendergast et al. 2012).

1.2 Other Factors Affecting the Outcome

In addition to the age of the child at infection, other host characteristics will influence the outcome of an exposure to an infection. These include pre-existing immunity, due to, e.g., vaccination or passive immunization by maternally derived antibodies, and genetic variation. Genetic variation, primarily in the MHC region on chromosome 6 (dense with genes encoding proteins involved in immune recognition and functioning, e.g., HLA molecules), is documented to influence susceptibility, progression, and recovery during infections in adult individuals and will likely also influence the outcome of infections occurring during early life (Dendrou et al. 2018; McLaren et al. 2013). In addition, genetic variation not only in the host but also in the infectious agent itself is a likely determinant of the outcome of an infection. Variation between strains of influenza A virus is well known (Petrova and Russell 2018) and can correlate with differences in cellular tropism and neuro-invasive properties (Ward 1996). In Sweden, the prevalence of different strains of mumps virus has varied with more neurovirulent strains being prevalent during the 1970s and early 1980s as compared to later years (Tecle et al. 1998).

It is established that some known infections during fetal life can interfere with brain growth and development. Whether infections during infancy and early childhood can also affect neurodevelopmental processes or even contribute to risk of schizophrenia or other severe mental illnesses with onsets decades later have been the focus of many investigations (see below).

The fact that still no specific agent or developmental stage has been conclusively linked to schizophrenia has prompted an epidemiological approach to the study of the role of infections in the development of schizophrenia. This approach has during the last four decades provided invaluable information using increasingly sophisticated methods and designs to address issues regarding reverse causality, misclassification, and confounding by socioeconomic conditions, other familial factors, or even genetic variation. Using population-based registers and biobanks with long follow-up times, available in countries like Denmark, Finland, and Sweden, researchers are beginning to dissect the various factors and their potential interactions involved in the etiology of schizophrenia as well as other severe and increasingly prevalent neuropsychiatric illnesses, such as autism spectrum disorder and attention-deficit hyperactivity disorder.

2 Epidemiological Studies of Infections During Pregnancy

In their seminal article published in 1988, Mednick et al. (1988) reported that offspring to pregnant women exposed to the 1957 epidemic of influenza A virus in Helsinki were at increased risk to develop schizophrenia as compared to offspring to women who were pregnant during preceding years when the same flu strain was not present in the population. The study had a purely ecological design and hence no information on if case mothers were actually infected during pregnancy, only that they were pregnant when the virus was prevalent in the population. Subsequent studies with information on maternal exposure at the individual level have, taken together, albeit not convincingly, supported this original observation; see Munk-Jorgensen and Ewald (2001), Selten et al. (2010) and references therein. Brown et al. (2004) reported a weak association between maternal influenza during pregnancy and the later development of schizophrenia in the offspring. This group of researchers used a large US birth cohort (born 1959–1966) to identify cases and controls and accessed stored maternal serum samples collected prospectively during pregnancy. They subsequently investigated these sera for the presence of antibodies to the relevant strains of the virus. A recent meta-analysis including this, and subsequent serological studies (Canetta et al. 2014; Ellman et al. 2009), did not support a significant effect of maternal influenza during pregnancy on schizophrenia risk in the offspring (Selten and Termorshuizen 2017).

Similar population-based approaches with nested case-control comparisons have been used in Denmark and Sweden to identify patients and comparison subjects along with prospectively collected blood samples from the neonatal period. Studies employing prospectively collected maternal serum samples during pregnancy with a nested case-control design based on large prospective cohort studies have, in addition to the United States, also been conducted in Finland. Antibodies of class G (IgG) are actively transported across the placenta during pregnancy to allow passive immunization of the newborn during the first months of life. Detection of IgG directed at specific infectious agents either in neonatal blood or in maternal serum samples allows researchers to determine maternal exposures to various agents at some time point (well) before sampling. These studies have mainly focused on the "usual suspects," i.e., infectious agents with affinity to the nervous system and the ability to establish chronic infections such as herpes viruses and *Toxoplasma gondii*. Using neonatal dried blood spots, schizophrenia or psychosis risk associated with maternal exposure to *T. gondii* has been reported from both Denmark (Mortensen et al. 2007) and Sweden (Blomstrom et al. 2012), whereas risk associated with maternal infections with herpes simplex type 2 virus (HSV-2) and CMV has been reported separately from Denmark (Mortensen et al. 2010) and Sweden (Blomstrom et al. 2012). Some, but not all, studies of maternal sera from the United States reported associations with HSV-2 (Buka et al. 2001, 2008; Brown et al. 2006), whereas risk for psychotic illness in the offspring has been consistently reported also for maternal exposure to *T. gondii* (Brown et al. 2005; Xiao et al. 2009). A more recent study from Finland failed to detect a significant association with HSV-2

(Cheslack-Postava et al. 2015). In summary, the current literature appear consistent with regard to the association between maternal *T. gondii* exposure and risk for psychotic illness in the offspring, but far less so with regard to the risk associated with herpesviruses.

Purely register-based studies examining potential association between maternal infections during pregnancy and the later development of schizophrenia and other non-affective psychoses in large populations have also been conducted. Such studies rely on prospective clinical ascertainments and registration of psychiatric diagnosis in regional or national health-care registers and on the clinical ascertainment/diagnosis of infections in clinical in- and/or outpatient settings during the time of exposure studied.

These kinds of register-based studies of maternal infections during pregnancy have been conducted in cohorts ranging in size from 8,000 to entire national populations with up to two million individuals and have explored maternal infections ranging from genital/reproductive infections (Babulas et al. 2006) and respiratory infections (Brown et al. 2000) to viral, bacterial, or any type of infection (Blomstrom et al. 2015; Nielsen et al. 2013; Sorensen et al. 2009). According to the larger population-based studies, maternal infections during pregnancy recorded in the in- and outpatient care system are rare. In the Swedish patient register, only slightly more than 1% of pregnant women are hospitalized for any type of infection during pregnancy, which likely results in a misclassification of the exposure. While a study in the Danish population reported a slight risk associated with any type of infection (RR 1.2, 95% CI 1.0–1.4), the effect appeared to be larger among mothers with a history of psychiatric disorders suggestive of an interaction between infections and genetic vulnerability for psychiatric diseases (Nielsen et al. 2013). Similar observations were made by Clarke et al. (2009) regarding pyelonephritis during pregnancy and also in another study of a large Swedish population of almost two million individuals (Blomstrom et al. 2015). In our study (Blomstrom et al. 2015), we observed no major risk of infections during pregnancy after taking potential confounding by parental psychiatric history and health-care seeking behaviors into account. Intriguingly, maternal infections during, but not before, pregnancy interacted significantly with maternal, but not paternal, psychiatric history. These observations suggest that additional risk for psychotic illness in the offspring is contributed by the intrauterine environment of women with psychiatric illness and infection. Suvisaari et al. (2013) made a similar observation in their Finnish high-risk cohort where the incidence of maternal infections during pregnancy was similar among mothers with schizophrenia spectrum disorders and comparison mothers but still appeared to significantly contribute to the development of schizophrenia spectrum disorders in the offspring to the affected mothers. In their study of the Mater University Study of Pregnancy pre-birth cohort, Betts et al. (2014) identified those who experienced psychotic symptoms by age 21. They studied the potential association with vaginal infections during pregnancy, based on maternal recall rather than a clinically ascertained diagnosis. They did not find a clear effect of such infections on subsequent psychotic symptoms in the offspring but did observe that maternal vaginal infections during pregnancy conferred increased susceptibility to childhood

diseases (including infections) in the offspring, which were, in turn, associated with psychotic symptoms in the offspring. These investigators were not able to consider the influence of a family history of psychiatric illness on these associations. We have briefly examined the association between maternal infection during pregnancy and the occurrence of diagnosed infections during childhood in the offspring (Blomstrom et al. 2015). We indeed observed that maternal infections, both during and before pregnancy, increased the odds of childhood infections in the offspring. Interestingly, we also observed a significant interaction between maternal infections during, but not before, pregnancy and childhood infections in the risk for non-affective psychosis in the offspring.

In conclusion, maternal infections in general during pregnancy appear to be only weakly associated with schizophrenia or other psychotic illnesses in the offspring. Further studies are needed to understand the mechanisms underlying the risks associated with specific agents and the interaction between infections during pregnancy and maternal psychiatric disorders.

3 Epidemiological Studies of Infections During Childhood

As described in the introduction, the postnatal period, from the time of birth to young adulthood, or even up to the time of the appearance of the first psychotic symptoms, entails developmental processes, which, if disturbed or delayed, would arguably be relevant for studies aiming at identifying environmental factors contributing to the pathogenesis of schizophrenia. For example, cannabis use in this period appears to be a true risk factor for chronic psychotic disorders, including schizophrenia, and not only a consequence of premorbid behaviors determined by genetic liability to disease (Marconi et al. 2016).

For natural reasons, many of the published studies of childhood infections have focused on those involving the central nervous system (CNS). Rantakallio et al. (1997) explored the association between registered infections involving the CNS up to age 14 and subsequent risk for a registered diagnosis of schizophrenia up to age 27 in the 1966 Northern Finland birth cohort with >11,000 births. An OR of 4.8 (95% CI 1.6–14.0) of schizophrenia for those exposed to viral CNS infections was reported but based on only four exposed cases illustrating the rarity of such diagnoses in medical registers. A subsequent follow-up study of this cohort with additional later onset cases resulted in a weaker and no longer significant association between infections during childhood and schizophrenia (Koponen et al. 2004). Using data from the UK National Child Development Study, a prospective population-based cohort of >17,000 children born in 1958, Leask et al. (2002) reported a strong association (OR 7.8) between meningitis during childhood and schizophrenia with a very wide CI 1.0–59.0 due to the detection of only a single exposed case. To examine rare exposures properly, we explored the Swedish population born 1973–1985 (>1.1 million individuals) followed until the end of 2002 with regard to the development of psychotic illness (Dalman et al. 2008). Registered diagnoses

involving CNS infections before age 12 were rare in this population (<0.8%) with the majority involving viruses. A weak association between viral CNS infections and non-affective psychoses was observed (OR 1.3, 95% CI 0.8–2.0) following adjustment for differences in sex, age, urban living, season of birth, and parental psychotic disorders (Dalman et al. 2008). In their subsequent report, Weiser et al. (2010) did not detect any significant association between meningitis infection up to age 16 and later hospitalization for schizophrenia using the Israeli National Psychiatric Hospitalization Registry. In their case-control design, they however used children with a registered diagnosis of gastroenteritis as a comparison group. Whether this group may also have been at increased risk for developing schizophrenia in comparison to children never hospitalized for infections during childhood was not investigated. A meta-analysis published in 2012 concluded that viral CNS infections during childhood confer increased risk of adult psychotic illness and that mechanisms may include both direct effects of pathogens and the effects of inflammatory response on the developing brain (Khandaker et al. 2012).

To address whether infections in general, and not only CNS infections, during childhood confer schizophrenia or non-affective psychosis risk, Liang and Chikritzhs (2012) investigated the potential association between all registered infections during the first 3 years of life and subsequent schizophrenia among males born 1980–1984 in Western Australia (>51,000 individuals). They reported a significant association with two or more hospitalizations for any infections or with one hospitalization for intestinal or respiratory infections (Liang and Chikritzhs 2012). At the time, two large population-based register studies were conducted in Denmark and Sweden. In our Swedish study, a large number of potential confounders such as male sex, birth in an urban environment, parental migration, parental age at birth of the child, parental psychiatric illness, parental socioeconomic status, and inpatient care during childhood for reasons other than psychiatric or infectious disease were identified and taken into account (Blomstrom et al. 2013). A weak risk associated with any type of infection during the period between birth and age 13 was observed, HR 1.10 (95% CI 1.03–1.18). The fairly narrow confidence interval reflects the fact that 1,114 exposed cases were identified in this the largest population studied to date. A somewhat stronger association between any type of infection and schizophrenia was observed in the Danish population (843,390 individuals born 1981–1996) after adjustments for essentially the same covariates as included in the Swedish study except parental socioeconomic status and hospitalization for "other" reasons, RR 1.41 (95% CI 1.32–1.51) (Nielsen et al. 2014). None of these studies observed an overall significant risk for psychotic illness associated with CNS infections, perhaps due to a lack of power despite the considerable sizes of the two study populations.

Population-based serological studies of specific infections among individuals who will later develop schizophrenia or other non-affective disorders have not been performed due to a general lack of prospectively collected samples during childhood. Khandaker et al. however investigated the potential association between serological evidence of Epstein-Barr virus (EBV) infections (by age 4) and psychotic experiences (by age 13 and reported by 15% of participants) in 400 individuals sampled from the longitudinal ALSPAC birth cohort (Khandaker et al. 2014). EBV

is a member of the herpesvirus family that causes usually asymptomatic infection among young individuals after which the virus establishes a latent state and lifelong persistence. These investigators reported that those infected with EBV were more likely to experience psychotic symptoms than the unexposed comparison group (Khandaker et al. 2014).

3.1 Childhood Infections and Development of Cognitive Abilities in Psychotic Illness

Low premorbid cognitive ability is a well-established risk factor for schizophrenia and other non-affective psychoses with an estimated 3.7% risk increase in schizophrenia risk for every point decrease in IQ (Khandaker et al. 2011). With regard to cognitive abilities, hospitalizations for infections have been associated with slightly poorer performance on scales measuring childhood emotional and cognitive development (Kariuki et al. 2016) as well as on cognitive tests at age 18 (Benros et al. 2015) in large population-based studies. In light of recent reports indicating that the low premorbid cognitive function observed in schizophrenia does not appear to be fully explained by shared familial factors (Kendler et al. 2015, 2016), we recently investigated the potential association between registered hospitalizations for infections during childhood, IQ at age 18, and the later development of schizophrenia and other non-affective psychoses in approximately 650,000 Swedish males (Khandaker et al. 2018). We observed that infections before age 5, but not later, were associated with slight but significant reductions in IQ at age 18, see Fig. 1, and with increased risk for the later development of non-affective psychoses. These relations were similar between individuals in the general population and in a comparison between full siblings suggesting that the associations were not fully explained by shared familial factors. IQ appeared to both mediate and moderate the effects of early childhood infections (Khandaker et al. 2018). This study thus suggests that early childhood infection may increase the risk of non-affective psychosis, not only by interfering with cognitive development but also by exaggerating the effects of cognitive vulnerability to psychosis. Both CNS infections and non-CNS infections were associated with cognitive deficits at age 18, in agreement with observations in the previous Danish study (Benros et al. 2015). This study included only males conscripted by the Swedish military and can thus not be generalized to females and individuals not eligible for mandatory screening by the Swedish military. The potential genetic confounding of the association between prior infections and schizophrenia was recently directly addressed in a case-control study nested in the population born since 1981 in Denmark (Benros et al. 2016). Benros et al. reported that polygenetic risk for schizophrenia and infections both conferred risk for schizophrenia, independent of each other suggesting that common genetic variation associated with schizophrenia risk is not explaining the association between infections and schizophrenia (Benros et al. 2016).

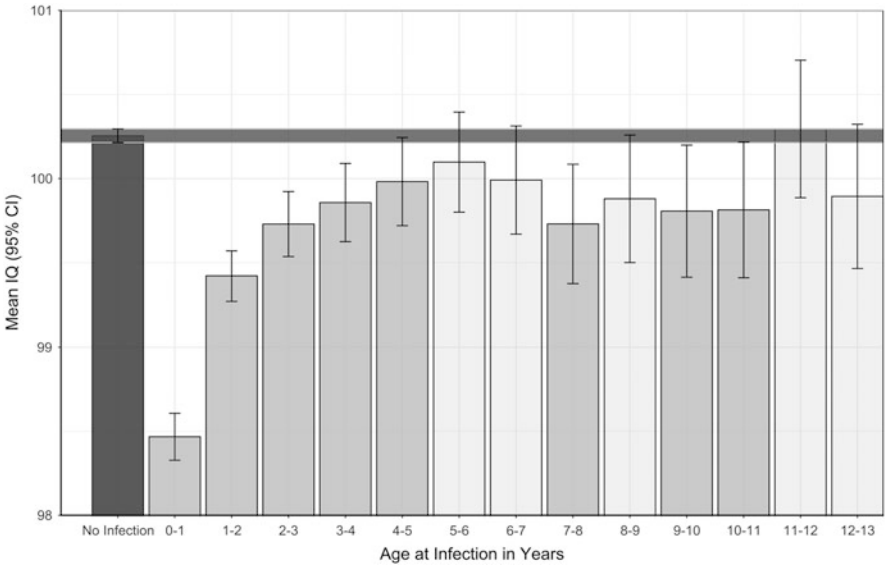

Fig. 1 Mean IQ (95% CI) at conscription for participants exposed to infection in childhood grouped by age at infection. The black bar indicates mean IQ for the unexposed group (i.e., no infection at any age). The gray bars indicate mean IQ for participants exposed to infection grouped by age at infection. Dark gray bars indicate a statistically significant difference in mean IQ for exposure to infection in that particular age compared with unexposed group. Reprinted from Khandaker et al. (2018)

In conclusion, studies of hospitalization for a wide range of infections after birth appear to be consistently associated with a later diagnosis of schizophrenia. Contrary to earlier reports, more recent studies indicate that risk does not appear to be limited to infections targeting the central nervous system. Recent studies are also beginning to address the important issue of familial or genetic confounding of these associations and thus far indicate that the risk conferred by infections is independent of both familial and genetic risk for schizophrenia.

4 Final Remarks

While family and twin studies clearly indicate a high heritability of schizophrenia, they also support important roles for shared and non-shared environmental factors (Lichtenstein et al. 2009; Sullivan et al. 2003). To move forward with regard to the risk for schizophrenia associated with maternal infections during pregnancy, we need to conduct large studies with objective measures of genetic risk among parents and comprehensive assessments of acute infectious exposures occurring during pregnancy. Moreover, we need to further understand the potential role played by chronic maternal infections, particularly those infections established before pregnancy that can be reactivated during pregnancy. Recent studies also indicate that the

role of infections occurring after birth needs to be further investigated. The studies suggesting that the reported associations between postnatal infections and schizophrenia are not fully explained by familial or genetic confounding tentatively suggest that infections can in fact be involved in the etiology of schizophrenia and other non-affective psychoses. We, however, need a far better understanding of "when, what, and who" before these observations will be useful to devise preventive strategies for psychotic disorders.

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