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Associations Between Maternal Infection During Pregnancy, Childhood Infections, and the Risk of Subsequent Psychotic Disorder—A Swedish Cohort Study of Nearly 2 Million Individuals

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Objective: **Recent studies question whether the risk for psychotic disorder associated with prenatal exposure to infection are due to infections per se, or to shared susceptibility of both infections and psychiatric disorders. Moreover, the potential link between prenatal infection and serious infections during childhood, another alleged risk factor for psychotic disorder, remains unknown. The aim of this study was to investigate the role of maternal infections during pregnancy in context of parental psychiatric disorders and subsequent childhood infections.** ***Method:*** **All children born in Sweden 1978–1997 were linked to the National Patient Register. Hazard ratios of nonaffective psychosis were estimated in relation to maternal infection during pregnancy and odds ratios of childhood infection were calculated in relation to maternal infection during pregnancy. Relative excess risk due to interaction (RERI) estimated biological synergism between parental psychiatric disorder and maternal infection during pregnancy, and between maternal infection during pregnancy and childhood infection.** ***Results:*** **Maternal infection during pregnancy was not statistically significantly associated with offspring psychosis (adjusted hazard ratio: 1.06, 95% CI 0.88–1.27). However, maternal infection during pregnancy and maternal psychiatric disorders acted synergistically in offspring psychosis development (RERI 1.33, 95% CI 0.27–2.38). Maternal infection during pregnancy increased the risk of offspring childhood infections (OR 1.50, 95% CI 1.45–1.54). These 2 factors also interacted in psychosis development (RERI 0.63, 95% CI 0.12–1.14).** ***Conclusions:*** **Among mothers with a history of psychiatric disease, infection during pregnancy increases the risk of psychosis in offspring. Maternal infections during pregnancy appear to contribute to the risk of childhood infections, which together render the child more vulnerable to psychosis development.**

Key words: schizophrenia/psychosis/prenatal/fetal/interaction

Introduction

Numerous studies, with different designs, have examined the association between various types of maternal infections during pregnancy and offspring psychotic disorder. Some studies report an association while others do not, reviewed by Khandaker et al.[1]

Clarke et al,[2] found no significant association between maternal pyelonephritis during pregnancy and schizophrenia or psychotic disorder in the offspring. However, they did report a synergistic effect between a family history of psychosis and maternal pyelonephritis on the risk of schizophrenia, suggesting that those who have a familial liability of psychotic disorder are more sensitive to exposure to certain infections during fetal life than those without.

Nielsen et al[3] recently reported that any maternal hospitalization for infection during pregnancy was modestly associated with later development of schizophrenia in offspring. They also found equally strong associations between maternal and paternal infection before, during, or after pregnancy and schizophrenia development in the child and suggest a genetic propensity for infection as an explanation to their finding, rather than the maternal infection during pregnancy per se.

In addition to data from genetic studies implying a role for the immune system in the etiology of psychosis,[4] recent studies indicate that defects in innate immunity among individuals with nonaffective psychosis are present already at birth.[5,6] These findings, along with the observation that hospitalization for infection during both childhood and adult life are associated with psychotic

disorder,[7–10] not only supports the hypothesis of deficient immune responses in schizophrenia[11] but also hints at a "multiple-hit" scenario,[12] where exposure to maternal infection during fetal life may increase both susceptibility and neurodevelopmental vulnerability to infections later in life.

Current knowledge, however, leaves many questions unanswered: Are maternal infections during pregnancy associated with psychotic disorders in the offspring when important confounders have been taken into account? Is type of infection (bacteria or virus) or its timing (with regard to trimester) important? Are previously reported synergistic effects between parental history of psychosis and maternal infection observed in both mothers and fathers? Are maternal infections before or during pregnancy associated with infections during childhood (perhaps because of genetic vulnerability or fetal programming) and are such infections interacting in the causation of psychosis? In an attempt to address these outstanding questions, we here present findings from a longitudinal study using a large population-based cohort of nearly 2 million individuals and their parents. We investigate the role of maternal infections during pregnancy in the context of parental psychiatric disorder, familial susceptibility to infections, and subsequent childhood infections. We consider multiple confounding factors including factors related to the likelihoods of someone contracting infections and being admitted to a hospital, such as; socio economic position, urban birth, parental immigration as well as hospitalization for other causes, all of which are also associated with psychosis.

Methods

Registers

This study is based on Psychiatry Sweden, a linkage of several health and population registers created for studies of the etiology of psychiatric disorders). The National Patient Register (NPR) was used for identification of infection and nonaffective psychoses. The NPR includes virtually all inpatient care in Sweden since 1973, and psychiatric outpatient visits since 2001.[13] Data on perinatal variables was retrieved from the Medical Birth Register (MBR), initiated in 1973 and including data from the prenatal, delivery, and neonatal periods from almost all deliveries in Sweden.[14] We obtained data on single households from The Population and Housing Census, administered every 5 years and including, by law, all individuals registered and living in Sweden with information on demographic data.[15] Data on socioeconomic status in terms of disposable income adjusted for family size and highest education level among parents were retrieved from the Longitudinal Integration Database for Health Insurance and Labor market studies, updated annually since 1990 and integrating information from the labor market, educational and social sectors.[15] We used the Total Population Register, initiated 1968,[15] to determine year of emigration if any. Date of death was retrieved from the National Cause of Death Register.

Study Population

All children born in Sweden between 1978 and 1997 who were alive on their 13th birthday were identified in the MBR. Individuals without a registered biological mother and father, and those not living in Sweden at age 13 were excluded.

Assessment of Exposure

All diagnoses of infection were identified according to ICD-8, -9, and -10 codes (supplementary table S1). We omitted all codes including "sequel" and "post-", and extracted the primary diagnoses except when the pregnant women had been given a primary diagnosis of obstetric conditions (ICD-8 630–679, ICD-9 630–677, and ICD-10 Chapter O). In those cases, the first diagnosis of infection of the 7 secondary diagnoses was extracted. Pregnancy was defined as first day of last menstrual period (LMP) before pregnancy up until the day of delivery. "Trimesters" were defined as: zeroth: LMP-35days (before uteroplacental circulation is established), first: 36–97 days, second: 98–188 days, and third: 189 days-delivery.

Psychotic Disorder

Caseness was defined as receipt of in- or outpatient care with diagnoses of nonaffective psychosis, ICD-10 F20-29 and ICD-9 295, 297, and 298 except 298A and B.

Covariates

Based on the literature, the following covariates were considered as potential confounding factors: winter birth (ie, child born December–May[16]); urban birth (child born in municipality with ≥200 000 inhabitants in 1980)[17]; small for gestational age (SGA)[18]; mother or father ≥ 35 years at time of birth[19]; either parent born outside Sweden[20]; single-parent household[21]; disposable family income on individual level (in quintiles according to birth year using the highest quintile as reference)[21]; highest education among parents (<9 y, 9 y, 10–12 y, >12 y [reference], and missing ["missing" was given a value because of a rather large amount of missing information on this variable in the registers])[21]; and parental diagnoses of psychotic (ICD-10 F20-29) or other psychiatric disorders (ICD-10 F00-99) until December 31, 2011.[22] Family tendency of seeking hospital care or becoming hospitalized was parameterized as hospitalization of either parent with any diagnosis other than infection or a psychiatric disorder up to 5 years before or during pregnancy.[10]

Statistical Methods

We calculated hazard ratios (HR) and 95% CI for nonaffective psychosis using Cox regression. Children were followed from 13 years of age until diagnosis of nonaffective psychosis, death, emigration, or December 31, 2011, whichever came first. In the basic model, all HRs were adjusted for sex of child and birth year as a centered, quadratic term (in order to allow for potential nonlinear relationships between the diagnosis of psychosis and time). Adjusted models included the basic adjustment as well as the covariates described in the preceding section. In order to separate the potential effects of infections during pregnancy from a high familial liability to serious infections, the analyses examining the risk of psychosis in relation to maternal infections were repeated after excluding mothers with a hospital diagnosis of infection during the 5 years prior to the index pregnancy (referred to as the restricted analyses in figures 1A, 1B, and 2A). Conversely, in order to examine the potential influence of familial liability to infection separate from possible biological mechanisms that could occur with infection during pregnancy, mothers with infection during pregnancy were excluded in restricted analyses examining the risk of psychosis in relation to parental infections occurring prior to pregnancy (referred to as the restricted analyses in figures 1C, 1D, and 2B).

The association between maternal infection during pregnancy and childhood infection among offspring was calculated as an OR and 95% CI using logistic regression, adjusted as detailed above. We then stratified the population on the basis of a diagnosis of nonaffective psychosis and repeated the analyses. To test for interaction on the additive scale, implicating causal or biological interaction, the relative excess risk due to interaction (RERI = RR11 − RR10 − RR01 + 1) was calculated for the risks of offspring nonaffective psychosis associated with parental infection prior to or during pregnancy, and/or parental psychiatric disorders.[23] Both the point estimate and the 95% CI of RERIs were assessed using a method accounting for the asymmetric distribution of confidence limits for hazard ratios.[24] Likewise, a possible interaction between maternal infections prior to or during pregnancy and childhood infections in the development of nonaffective psychosis was calculated using RERI. RERI > 0 implies presence of positive additive interaction. Statistical analyses were made using IBM SPSS statistics 22.0 (IBM).

Approval

Ethical approval has been sought and granted from the Regional Ethics Committee of Stockholm, EPN. Dnr 2010/1185-31/5.

Results

A total of 1 971 623 children were followed up in the registers. Altogether, 8330 (0.4%) of the children were subsequently diagnosed with nonaffective psychosis between ages 13 and 33. As expected, children who later developed nonaffective psychosis tended to be male, have older parents and parental histories of immigration, psychiatric disorders and hospital admissions prior to the birth of the index child. These children were also more often born in urban environments, born small for gestational age and brought up in a family with low socio-economic status (table 1). Associations between the covariates and the exposures and the outcome can be found in supplementary table S2.

In the total population, there was a small but significantly increased risk of developing nonaffective psychosis among children whose mothers were hospitalized for infection during pregnancy, HR 1.26, 95% CI: 1.05, 1.52 (table 2). However, this association disappeared in the adjusted model. Adjustments for parental psychiatric disorder, previous parental hospital admission, and low socioeconomic status among parents attenuated the association the most. Risk for nonaffective psychosis did not vary by type of infection (bacterial or viral; table 2). Infection during the third trimester tended to increase risk of nonaffective psychosis in the offspring, (HR 1.23, 95% CI: 0.96, 1.58), whereas infections during other trimesters did not (table 2). Frequences of the most common diagnoses of infection among the pregnant women can be found in supplementary table S3. Maternal, but not paternal, admission for infection up to 5 years prior to pregnancy was weakly associated with offspring psychosis (HR 1.14, 95% CI: 1.05, 1.23) in the fully adjusted model (table 2).

In contrast, among individuals whose parents were diagnosed with a psychiatric disorder, exposure to maternal infection during pregnancy was significantly associated with psychosis development in the fully adjusted model, HR 1.30, 95% CI: 1.02, 1.66. Among individuals with parents without a psychiatric disorder there was no association, HR 0.84, 95% CI: 0.63, 1.11.

Further exploration of the role of psychiatric disorder in the family indicated an interaction between maternal psychiatric disorder and maternal infection during pregnancy on the child's risk of developing psychosis (RERI 0.79, 95% CI: −0.02, 1.60) (figure 1A), particularly among mothers who were not hospitalized for infections before pregnancy (RERI 1.33, 95% CI: 0.27, 2.39), and therefore not predisposed to inpatient care for infections. Interestingly, psychiatric disorders among fathers did not interact with maternal infection during pregnancy on the risk for psychoses in the offspring (RERI 0.14 95% CI: −0.59, 0.87, figure 1B). Moreover, maternal, but not paternal, infection during 5 years prior to pregnancy was weakly but significantly associated with psychosis development in offspring, irrespective of maternal psychiatric disorder (figures 1C and 1D). There was no indication of synergism between maternal psychiatric disorder and maternal infection prior to pregnancy (RERI −0.50, 95% CI: −0.82, −0.17) or between paternal psychiatric disorder

and paternal infection prior to pregnancy (RERI −0.08, 95% CI: −0.49, 0.32) on psychosis risk in the offspring.

We next investigated whether maternal infections during pregnancy per se or maternal predisposition for infections (ie, infections prior to pregnancy) were associated with increased risk of childhood infections. The odds of being hospitalized with infection during childhood increased following exposure to maternal infection during prenatal

Table 1. Characteristics of the Study Population

			All Children Born in Sweden 1978–1997[a], *N* = 1 971 623			
			No Diagnosis of Nonaffective Psychosis[b] (*n* =1 963 293, 99.6%)		Diagnosis of Nonaffective Psychosis[b] (*n* = 8330, 0.4%)	
			n	%	*n*	%
Male			1 007 074	51.3	4872	58.5
Urban birth[c]			303 258	15.4	1601	19.2
Born December–May			1 015 884	51.7	4306	51.7
Small for gestational age	With information		53 217	2.7	339	4.1
	Missing		49 120	2.5	191	2.3
Parent ≥35 y at time of birth	Mother		221 721	11.3	1065	12.8
	Father		525 930	26.8	2449	29.4
Parent born outside Sweden	Mother[i]		236 555	12.0	1443	17.3
	Father		250 346	12.8	1579	19.0
Parent psychotic disorder[d]	Mother		16 020	0.8	420	5.0
	Father		13 372	0.7	288	3.5
Parent psychiatric disorder[e]	Mother		160 795	8.2	1736	20.8
	Father		171 465	8.7	1636	19.6
Socioeconomic status	Any parent highest education	<9 y	37 501	1.9	331	4.0
		9 y	141 629	7.2	828	9.9
		10–12 y	959 081	48.9	3881	46.6
		>12 y	823 026	41.9	3272	39.3
		missing	2056	0.1	18	0.2
	Single-parent household		175 564	8.9	1397	16.8
	Disposable income[f]	First quintile (lowest)	392 659	20.0	1926	23.1
		Second quintile	392 659	20.0	1726	20.7
		Third quintile	392 658	20.0	1644	19.7
		Fourth quintile	392 658	20.0	1582	19.0
		Fifth quintile (highest)	392 659	20.0	1452	17.4
Maternal hospital admission with infection[g] during pregnancy			23 667	1.2	117	1.4
Hospital admission with infection[g] 5 y prior to pregnancy	Mother		130 532	6.6	706	8.5
	Father		64 894	3.3	283	3.4
Any inpatient care[h] up to 5 y before pregnancy	Mother		388 796	19.8	1830	22.0
	Father		267 522	13.6	1238	14.9
Any inpatient care[h] during pregnancy	Mother		118 972	6.1	691	8.3
	Father		50 055	2.5	270	3.2
Admission with infection[g] during childhood 0–13 y			460 416	23.5	2335	28.0

Note: [a]With information on biological parents and living in Sweden at 13 y of age. Individuals with missing information on variables were excluded, 1046 in total).
[b]ICD-10 F20-29.
[c]>200 000 habitants 1980.
[d]ICD-10 F20-29.
[e]ICD-10 F00-99.
[f]Per family member.
[g]See supplementary table S1.
[h]Except with diagnoses ICD-10 F00-99, or with infection.[g]
[i]67% Europe (40% from Finland), 20% Asia (60% from the Middle East), 6% Africa (22% from Etiopia), 5% South America (65% from Chile), 1% North America (86% from the United States).

Table 2. Associations Between Nonaffective Psychosis and Parental Hospital Admission With Infection Among Individuals Born in Sweden 1978–1997, Hazard Ratios (HR) and 95% CI

Mother Hospital Admitted With Infection During Pregnancy	*N*, Nonaffective Psychosis/ No Diagnosis of Nonaffective Psychosis	Basic Model[a]	Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Any infection	117/ 23 667	1.26 (1.05, 1.52)	1.23 (1.02, 1.48)	1.13 (0.94, 1.35)	1.07 (0.89, 1.28)	1.06 (0.88, 1.27)
Bacterial infection	66/ 13 018	1.31 (1.02, 1.66)	1.27 (1.00, 1.62)	1.15 (0.90, 1.47)	1.09 (0.85, 1.38)	1.08 (0.84, 1.37)
Viral infection	18/ 4041	1.04 (0.66, 1.66)	1.00 (0.63, 1.58)	0.91 (0.58, 1.45)	0.86 (0.54, 1.36)	0.85 (0.54, 1.36)
Other infection	32/ 6694	1.26 (0.89, 1.78)	1.23 (0.87, 1.74)	1.15 (0.81, 1.63)	1.11 (0.78, 1.57)	1.10 (0.78, 1.56)
Zeroth trimester	7/ 1424	1.10 (0.53, 2.32)	1.03 (0.49, 2.16)	0.92 (0.44, 1.93)	0.86 (0.41, 1.81)	0.85 (0.40, 1.79)
First trimester	12/ 3369	0.91 (0.52, 1.60)	0.88 (0.50, 1.55)	0.79 (0.45, 1.39)	0.74 (0.42, 1.30)	0.73 (0.41, 1.28)
Second trimester	38/ 8354	1.15 (0.84, 1.58)	1.11 (0.81, 1.53)	1.02 (0.74, 1.40)	0.96 (0.70, 1.32)	0.95 (0.69, 1.31)
Third trimester	61/ 11 164	1.42 (1.11, 1.83)	1.40 (1.09, 1.81)	1.29 (1.00, 1.66)	1.24 (0.96, 1.59)	1.23 (0.96, 1.58)
Mother hospitalized with infection sometime in the 5 y before pregnancy	706/ 130 532	1.33 (1.23, 1.44)	1.29 (1.19, 1.39)	1.19 (1.10, 1.28)	1.13 (1.05, 1.22)	1.14 (1.05, 1.23)
Father hospitalized with infection sometime in the 5 y before pregnancy	283/ 64 894	1.09 (0.97, 1.23)	1.06 (0.94, 1.19)	1.00 (0.89, 1.13)	0.97 (0.86, 1.09)	0.97 (0.86, 1.09)

Note: SES, socioeconomic status.
[a]Adjusted for year of birth and sex.
[b]Additionally adjusted for mother or father with psychotic disorder (ICD-10 F20-29).
[c]Additionally adjusted for mother or father with psychiatric disorder (ICD-10 F00-99).
[d]Additionally adjusted for SES, and any parent any inpatient care before or during pregnancy except for treatment of infection or psychiatric care.
[e]Additionally adjusted for urban birth, winter birth, parental age ≥ 35 y, small for gestational age, and parent born outside Sweden.

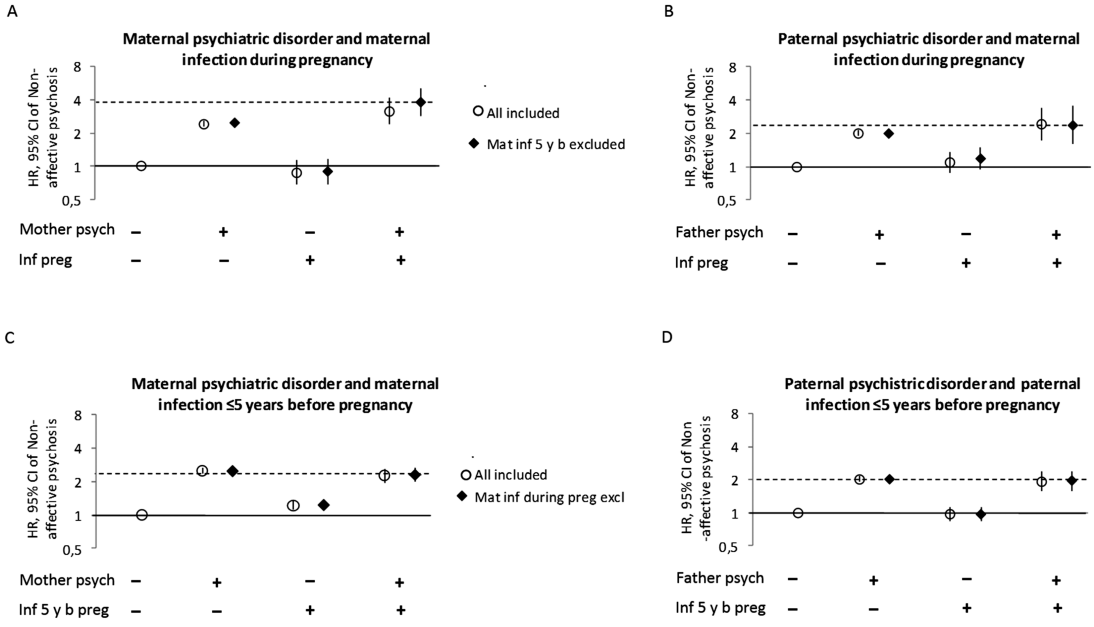

Fig. 1. Risk of nonaffective psychoses (hazard ratio and 95% CI) among individuals with and without maternal infection during pregnancy, parental infection sometime in the 5 y before pregnancy, and parental psychiatric disorder. Fully adjusted for birth year, sex, urban birth, winter birth, parental age ≥ 35 y, small for gestational age, parent born outside Sweden, low socioeconomic status, any parent any inpatient care before or during pregnancy except for treatment of infection or psychiatric care. Circles represent the general population and diamonds the restricted model.

life (OR 1.50, 95% CI: 1.45, 1.54), particularly among children who would later develop nonaffective psychosis (OR 2.12, 95% CI: 1.46, 3.07; table 3). Maternal infection prior to pregnancy increased the risk of childhood

infection, both in the general population (OR 1.37, 95% CI: 1.35, 1.38) and, to a similar extent, among individuals who later developed nonaffective psychosis (OR 1.29, 95% CI: 1.10, 1.53; table 3). Finally, we analyzed if the combination of maternal and childhood exposures to infections further increased the risk for psychoses in the child. We observed an interaction between maternal infection during pregnancy and childhood infection in terms of the risk of nonaffective psychosis (RERI 0.45, 95% CI: 0.03, 0.87) (figure 2A). The relationship was stronger when women who had been hospitalized for infections before pregnancy were excluded from the analysis (RERI 0.63, 95% CI: 0.12, 1.14). There was no evidence of interaction between maternal infection during 5 years prior to pregnancy and later childhood infection in terms of psychosis risk (RERI −0.07, 95% CI: −0.25, 0.11) (figure 2B).

Discussion

In this, the largest population-based cohort study to date, we found no evidence that hospitalization for infection during pregnancy was associated with nonaffective psychosis in the offspring overall. Consideration of the type of pathogen (bacteria, virus, or other) and timing of infection did not change this null association. Previous studies have found an association between schizophrenia or nonaffective psychoses in the offspring and specific groups of maternal infections and it is possible that specific maternal infections, not captured by our current approach, are more hazardous to the fetus than others. For example, acute infection with influenza during pregnancy[25] and chronic infection (where initial exposure can occur outside of pregnancy) with *Toxoplasma gondii*[26–28] have previously been associated with the development of psychoses in the offspring. Nielsen et al, who previously also investigated any maternal infection, did find a modest association with schizophrenia. However, they did not adjust for some of the confounders included here, which may explain the somewhat discrepant results between their study and ours. In particular, adjustment for parental psychiatric disorders (not only psychotic disorders), low socioeconomic status, and parental hospital care-seeking patterns attenuated the associations between maternal infection during pregnancy and nonaffective psychoses in the offspring in our study. Solely adjusting for parental psychotic disorders does not appear to fully account for confounding by familial mental and social disadvantages.

We found evidence for a modest familial susceptibility to be hospitalized for infection among individuals with nonaffective psychosis; admission with maternal infection during the 5 years prior to pregnancy was weakly associated with offspring psychosis, but the fact that paternal admission with infection before pregnancy was not associated speaks against a general parental liability for infections among patients with nonaffective psychoses, as reported for patients with schizophrenia by Nielsen et al.[3] Their study, however, included parental infections "after birth" of the index child, where familial transmission of infections can occur.[29,30]

A genetic predisposition to psychosis in conjunction with 1 or more environmental insults have been proposed in the etiology of psychosis.[31] We found evidence for synergism between maternal psychiatric disorder (a proxy marker of genetic predisposition in the mother as well as the child) and infection during pregnancy on psychosis risk in the offspring, which is in agreement with previous observations by Clarke et al[2] and Nielsen et al.[3] Importantly, exposure to maternal infection did not appear to interact with paternal

Table 3. Associations Between Maternal Infection During Pregnancy or Maternal Infection Sometime in the 5 y Before Pregnancy and Childhood Infection Among the Total Population and Among Individuals With Nonaffective Psychosis, OR and 95% CI

	Maternal Infection During Pregnancy	*N*, Childhood Infection/ No Childhood Infection	Basic Model[a] OR (95% CI)	Adjusted Model[b] OR (95% CI)	Maternal Infection ≤5 y Before Pregnancy	*N*, Childhood Infection/ No Childhood Infection	Basic Model[a] OR (95% CI)	Adjusted Model[b] OR (95% CI)
Total population	Unexposed	454 825/ 1 493 014	1 (reference)	1 (reference)	Unexposed	422 024/ 1 418 361	1 (reference)	1 (reference)
	Exposed	7926/ 15 858	1.66 (1.61, 1.70)	1.49 (1.45, 1.53)	Exposed	40 727/ 90 511	1.51 (1.49, 1.53)	1.37 (1.35, 1.38)
Individuals with nonaffective psychosis	Unexposed	2277/ 5936	1 (reference)	1 (reference)	Unexposed	2081/ 5543	1 (reference)	1 (reference)
	Exposed	58/ 59	2.58 (1.79, 3.72)	2.12 (1.46, 3.07)	Exposed	254/ 452	1.49 (1.27, 1.76)	1.29 (1.10, 1.53)

Note: [a]Adjusted for birth year and sex.
[b]Additionally adjusted for urban birth, winter birth, small for gestational age, parental age ≥ 35 y, parental history of psychiatric disorder, parent born outside Sweden, low SES, any parent any inpatient care before or during pregnancy except for treatment of infection or psychiatric care, and for the child during childhood (0–13 y).

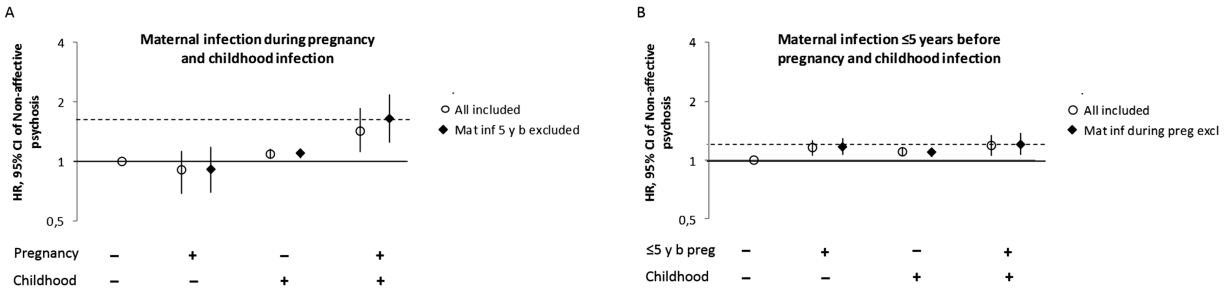

Fig. 2. Risk of nonaffective psychoses (hazard ratio and 95% CI) following exposure to maternal infection during pregnancy (A) or before pregnancy (B), and childhood infection. Fully adjusted for birth year, sex, urban birth, winter birth, parental age ≥ 35 y, small for gestational age, parental history of psychiatric disorder, parent born outside Sweden, low socioeconomic status, any parent any inpatient care before or during pregnancy except for treatment of infection or psychiatric care, and for the child during childhood (0–13 y). Circles represent the general population and diamonds the restricted model.

psychiatric disorder (a proxy for genetic predisposition in the father as well as the child). Neither did synergism occur between parental psychiatric disorder and parental infections prior to pregnancy, which would indeed be unlikely to influence a future pregnancy unless the infectious agent resulted in a persistent infection.[32] Taken together, these results indicate an effect of acute infections during pregnancy specific to vulnerable mothers on the risk for the offspring to later develop nonaffective psychosis.

Many of the genetic loci that so far have been associated with schizophrenia are located within the major histocompatibility (MHC) region on chromosome 6, a region dense with genes linked to both immunity and brain development.[4] Interestingly, genetic risk for schizophrenia, both within and outside the MHC-region, appears to overlap with risk for other psychiatric diagnoses,[33] which suggests that genetic variation in many regions, including the MHC region, may explain some of the interaction between maternal psychiatric disease and infection. Indeed both common and rare genetic variation in innate and adaptive immune response genes have been reported to contribute to both susceptibility and outcome of infectious disease with a major, but not exclusive, role for genes in the MHC region, reviewed in ref.[34] However, a number of environmental factors among mothers with psychiatric disease, such as medication, life-style or body mass index, can also potentially explain the observed interaction, only partially accounted for by our adjustments.

While there are no studies on acute maternal infections, some chronic maternal infections have been reported to have persistent effects on the child's innate immune system for years in the absence of transmission of the pathogen.[32] The biological mechanisms involved in the maternal-fetal interplay relating to the response to infection, and the specific role that the maternal environment might play, remain to be identified. One hypothesis posits that excessive maternal immune activation is the common effector mechanism linking exposure to a number of different agents to the pathogenesis of psychosis in the offspring. While strongly supported by experimental studies,[35,36] there is so far little clinical support for this hypothesis.[37–39]

Regardless of the mechanisms acting during gestation, there are indications of deficiencies relating to innate immunity both among neonates who will develop nonaffective psychosis[5] and among adults who have developed psychosis[6] suggesting that these individuals are more vulnerable to infections.

Brain development proceeds through early adulthood[40] and is therefore potentially continuously vulnerable to disruptive influences which may be more likely to occur in individuals with immune deficits. We and others have previously reported that there is indeed a weak association between hospitalization with infection during childhood or later in life and the later development of psychosis.[9,10,41] In our previous study,[10] this association was not confounded by parental psychiatric disorders or care seeking habits. The factors determining risk for such childhood infections were however not identified. Here we observed that individuals whose mothers were exposed to infections before and, particularly, during pregnancy were themselves more likely to be hospitalized for infections during childhood. Importantly, exposure to maternal infection during, but not before, pregnancy, and to a subsequent childhood infection acted synergistically on future psychosis risk. These observations indicate that maternal infection during pregnancy can modify, not only the future risk of the offspring to be hospitalized for infection, but also the long-term outcomes of such infections. Contrarily, Betts et al[42], previously reported on the influence of maternal vaginal infection on offspring psychotic experience being mediated through childhood illness liability rather than synergism between the 2. However, they used self-reported information on possible exposure to infection in terms of experienced symptoms of vaginal infection during pregnancy and medical attention or symptoms of infection during the child's first 6 months such as skin rashes, runny nose, and diarrhoea, which may explain our discrepant findings.

It is becoming increasingly apparent that a sensitization by multiple stressors eventually accumulate to the development of psychosis.[43] If our observations replicate

in independent data sets, they suggest that future studies of risk factors for nonaffective psychoses need to take on the challenging task of having to disentangle the complex interactions between gene variants and environmental exposures during pregnancy and during childhood. Moreover, we found many risk factors for psychosis to be associated with early infection. If their effect is mediated by infection or if there is a possible synergism between these risk factors and early infection in psychosis risk needs attention in future studies.

Limitations

The validity of infectious disease diagnoses in the NPR is high.[44] However, our exposure variable included hospital-treated infections only, and hence likely only severe infections. Presumably, the majority of infections do not require hospital care, resulting in misclassification and perhaps underestimation of the association. Our results are not likely generalizable to the wide range of infections a woman could experience during pregnancy, particularly those that are more minor, uncomplicated, and easily resolved.

The proportion of individuals with a diagnosis of nonaffective psychosis (0.4%) in this data set is probably underestimated, mainly because of 2 factors. Firstly, the youngest individuals were only 14 years at the end of follow-up and had not had time to develop and receive a diagnosis. Using Cox regression in the analyses partly accounts for this, because the risks are estimated based on number of individuals per population at risk per day. Second, registration of diagnoses from outpatient care started in 2001 and reached complete coverage in 2005 in Sweden. Since about 25% of individuals with nonaffective psychosis only receive outpatient care,[45] some individuals with nonaffective psychosis may not have been included as cases here.

Despite the large data set rather few mothers were hospital admitted for infection during pregnancy. However, the confidence intervals in the analyses are rather narrow, suggesting satisfying power.

Conclusions

In this largest population-based study to date, we report that infections during pregnancy among mothers with psychiatric disorders were associated with an increased risk for nonaffective psychosis in offspring. In contrast, no such association was seen in absence of a maternal psychiatric history.

Exposure to maternal infections before and during pregnancy was associated with subsequent childhood infections. Maternal infections during, but not before, pregnancy interacted with childhood infections in terms of the risk of later psychosis in the child. These findings imply that gestation may indeed be a critical period of exposure and support the "second hit" theory. The risk associated with maternal infections is probably not entirely attributable to familial liability to infections, as previously proposed. From a public health perspective, the implications of an interaction between maternal and childhood infections on future psychosis risk warrants further studies.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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