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Association Between Prenatal Exposure to Bacterial Infection and Risk of Schizophrenia

Holger J. Sørensen[2,3], Erik L. Mortensen[1,2,4], June M. Reinisch[2,5], and Sarnoff A. Mednick[6]

[2]Danish Epidemiology Science Center, Institute of Preventive Medicine, Copenhagen University Hospital; [3]Department of Psychiatry, Amager Hospital, Copenhagen University Hospital, Denmark; [4]Department of Environmental Health, Institute of Public Health, University of Copenhagen, Øster Farimagsgade 5, PO Box 2099, DK-1014 Copenhagen K, Denmark; [5]The Kinsey Institute for Research in Sex, Gender, and Reproduction, Indiana University, Bloomington, IN; [6]Social Science Research Center, University of Southern California

Recent research suggests that prenatal exposure to nonviral infection may be associated with increased risk of schizophrenia, and we hypothesized an association between maternal bacterial infection during pregnancy and elevated offspring risk of schizophrenia. Data on maternal infections from the Copenhagen Perinatal Cohort were linked with the Danish National Psychiatric Register. Offspring cases of narrowly defined schizophrenia (*International Classification of Diseases, Eighth Revision* [*ICD-8*]) and more broadly defined schizophrenia (*ICD-8* and *ICD-10*) were identified before the ages of 32–34 and 45–47 years, respectively. The effect of prenatal exposure to bacterial infections was adjusted for prenatal exposure to analgesics and parental social status. In a risk set of 7941 individuals, 85 cases (1.1%) of *ICD-8* schizophrenia were identified by the age of 32–34 years and 153 cases (1.9%) of more broadly defined schizophrenia by the age of 45–47 years. First-trimester exposure conferred an elevated risk of *ICD-8* schizophrenia (odds ratio 2.53; 95% confidence interval [CI] 1.07–5.96) and also of broadly defined schizophrenia (odds ratio 2.14; 95% CI 1.06–4.31). Second-trimester exposure also conferred a significantly elevated risk of schizophrenia but only in unadjusted analyses. These findings suggest a relationship between maternal bacterial infection in pregnancy and offspring risk of schizophrenia, and this effect was somewhat stronger for *ICD-8* schizophrenia with earlier onset. Post hoc analyses showed that upper respiratory tract and gonococcal infections were associated with elevated risk of the disease. An association between risk of schizophrenia and prenatal exposure to bacterial infections might be mediated through transplacental passage of maternally produced cytokines in response to bacterial infections.

Key words: schizophrenia/bacterial infections/viral infections/prenatal infections

Introduction

The hypothesis that viral infection during pregnancy may increase the risk of adult schizophrenia received much attention after the demonstration that people who were exposed to the 1957 type A2 influenza in Helsinki were at elevated risk of being admitted with schizophrenia.[1] This association was replicated in several studies,[2–7] and although not all studies point in the same direction,[8–10] it seems plausible that viruses play a role in the etiology of chronic diseases such as schizophrenia due to their potential for neurotropism and latency.[11] Recent studies have also explored the risk of schizophrenia associated with childhood infections,[12,13] and the largest of these investigations has found associations between serious viral central nervous system infections during childhood and later schizophrenia.[14]

Less is known about the possible relationship between early-life exposure to other infectious agents than viruses and risk of schizophrenia. Recently, studies have addressed the possible associations of in utero or perinatal exposure to *Toxoplasma gondii*, a protozoan parasite, and the development of schizophrenia; one study included maternal sera drawn before birth[15] and one used sera from infants.[16] Both studies found associations between risk of schizophrenia (or schizophrenia spectrum disorder) and increased levels of immunoglobulin G (IgG) antibodies to *T gondii*. Increased risk of schizophrenia has also been linked with respiratory infections[17] and periconceptual maternal genital infections.[18]

It is important to further examine prospective relationships between early exposures to viral and nonviral infectious agents and risk of schizophrenia. The Copenhagen Perinatal Cohort contains data on maternal viral and bacterial infection during pregnancy. The use of

[1]To whom correspondence should be addressed; tel: +45-3532-7839, fax: +45-3532-7748, e-mail: e.l.mortensen@pubhealth.ku.dk.

these baseline data and access to psychiatric outcome data enabled us to examine associations between maternal viral and bacterial infection during pregnancy and offspring risk of schizophrenia. We hypothesized a relationship between maternal viral infection and offspring schizophrenia but possibly also between maternal bacterial infection and schizophrenia in the offspring.

Methods

The methods of the data collection in the Copenhagen Perinatal Cohort are described in detail elsewhere.[19–21] Briefly, the cohort comprises 9125 individuals delivered by 8949 women between September 1, 1959, and December 31, 1961 at Rigshospitalet in Copenhagen. The mothers were mainly residents in Copenhagen, but some were admitted with obstetrical indications or due to their status as single mothers.[19]

The study sample of the present analyses comprised 7941 individuals, 4030 males and 3911 females. Included were all cohort members with data on prenatal exposure to infection and personal identification number (required for checking in the Danish Psychiatric Central Research Register).

Prenatal Infection

When the perinatal cohort was established, Aage Villumsen was responsible for collecting information on the mother's background and the course of pregnancy.[19] He interviewed all mothers 5 days after delivery and about 67% of the mothers at their first visit to the antenatal clinic (these mothers received a form for recording all illness, including common colds, during the remaining part of pregnancy). For all mothers, data collection was completed 5 days after delivery and included information about infections during different periods of pregnancy. A bacterial infection was coded as present if a medical diagnosis had been made and medical treatment instituted, for instance, by a general practitioner, a gynaecologist/obstetrician, or acute treatment at a hospital (a diagnosis of a bacterial infection did not necessarily include paraclinical verification). The following categories of bacterial infection were recorded: sinusitis, tonsillitis, pneumonia, cystitis, pyelonephritis, bacterial venereal infection, and any other bacterial infection. A viral infection was judged to be present if (1) a medical diagnosis had been made (commonly by the general practitioner) or (2) if symptoms consistent with minor respiratory illnesses or influenza had been present and the mother had been confined to bed and had a rise in temperature to at least 38°C.[19]

Potential Confounders

Data about parental social status were obtained from an interview with the mother when the child was 1 year old. The 1- to 8-point social status scale was based on breadwinner's occupation, breadwinner's education, type of income, and quality of housing.[20] Parental social status was categorized in 3 groups: low (status categories 1–4), high (categories 5–8), and missing data (the missing data rate for parental social status was 20.7%).

Findings from this cohort indicate a relatively strong relationship between the second-trimester exposure to analgesics and risk of schizophrenia.[22] Consequently, prenatal exposure to analgesics was considered a potential confounder of a relationship between maternal infection during pregnancy and offspring risk of schizophrenia.

Psychiatric Follow-up

Written approval to conduct a registry-based psychiatric follow-up was obtained from the regional scientific and ethics committee. The Danish Psychiatric Central Research Register has been computerized since April 1, 1969.[23] It contains data on all admissions to Danish psychiatric inpatient facilities. The period of follow-up was from April 1, 1969, until May 7, 2007. The diagnostic system in use when the Danish Psychiatric Central Research Register was computerized was the *International Classification of Diseases, Eighth Revision* (*ICD-8*). In *ICD-8*, schizophrenia is defined by prototypic descriptions of symptoms, such as bizarre delusions, delusions of control, abnormal affect, autism, hallucinations, and disorganized thinking. In 1994, the more operational *ICD-10* criteria were implemented (the *ICD-9* classification was never implemented in Denmark). The cohort and their parents were followed in the Danish Psychiatric Central Research Register to identify all admissions with a diagnosis of schizophrenia (*ICD-8* code 295 or *ICD-10* code F20). Cohort members were categorized as cases if they had been admitted with schizophrenia according to *ICD-8* (narrow definition) or *ICD-8* and/or *ICD-10* (broad definition).

Data Analysis

Binary variables were used to indicate the presence or absence of bacterial or viral infection in each trimester of pregnancy and to indicate any analgesics exposure during pregnancy. As described, social status was coded into 3 categories (high, low, and missing) with low social status as the reference category.

We examined the effect of prenatal exposure to infection in relation to schizophrenia according to *ICD-8* (until age 32–34 years) and to lifetime schizophrenia according to (*ICD-8* or *ICD-10*) (until age 45–47 years). The unadjusted effects of being exposed to viral or bacterial infection in each trimester were estimated, and indicator variables for bacterial infections in all 3 trimesters were included in multivariate models that also adjusted

Table 1. Multiple Logistic Regression Analysis of Lifetime *ICD-8* Schizophrenia Until Age 32–34 y and *ICD-8*/*ICD-10* Schizophrenia Until Age 45–47 y

	Odds Ratio (95% Confidence Interval)			
	Schizophrenia (*ICD-8*), $n = 85$		Schizophrenia (*ICD-8*/*ICD-10*), $n = 153$	
Exposure	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Infection				
First-trimester bacterial infection	2.91 (1.25–6.75)	2.53 (1.07–5.96)	2.41 (1.21–4.79)	2.14 (1.06–4.31)
Second-trimester bacterial infection	2.31 (1.15–4.35)	1.93 (0.96–3.86)	1.82 (1.06–3.14)	1.60 (0.91–2.80)
Third-trimester bacterial infection	1.44 (0.62–3.31)	1.17 (0.50–2.78)	1.32 (0.69–2.53)	1.14 (0.59–2.22)
Any bacterial infection	2.21 (1.32–3.70)	—	1.80 (1.19–2.71)	—
Any exposure to analgesics	2.44 (1.05–5.65)	2.33 (1.00–5.44)	2.52 (1.35–4.72)	2.43 (1.30–4.57)
Parental social status				
High vs low	0.80 (0.46–1.39)	0.81 (0.49–1.41)	0.69 (0.46–1.05)	0.70 (0.46–1.06)
Missing vs low	1.41 (0.85–2.33)	1.46 (0.88–2.42)	1.10 (0.74–1.62)	1.13 (0.77–1.68)

Note: *ICD-8*, *International Classification of Diseases, Eighth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision.*
[a]Model including first-, second-, and third-trimester bacterial infection, any exposure to analgesics during pregnancy, and parental social status. (Including the interaction product term of first-trimester and second-trimester bacterial infection did not materially affect these risk estimates, and the interaction term was not statistically significant.) An analysis including parental social status as a semicontinuous variable yielded virtually the same results as those presented in the table.

for social status and any exposure to analgesics during pregnancy.

Results

A total of 85 cases according to *ICD-8* were identified at age 32–34 years (1.1%), and 153 cases with *ICD-8* and/or *ICD-10* schizophrenia were identified at age 45–47 years (1.9%).

Out of 7941 cohort members, 1087 (13.7%) were prenatally exposed to viral infection (by far, the most common viral infection was common cold). Of those with any viral infection, 447 individuals were exposed during the second trimester. The proportions of *ICD-8* schizophrenia and *ICD-8* and/or *ICD-10* schizophrenia among those with second-trimester viral infections were 0.7% and 2.0%, respectively.

Using either narrowly (*ICD-8*) or broadly defined schizophrenia (*ICD-8* and/or *ICD-10*) as outcome, unadjusted logistic regression analyses showed no significant associations with exposure to viral infection in the first, second, or third trimester or with a variable indicating any viral infection during pregnancy. For broadly defined schizophrenia, odds ratios were 0.52 (95% confidence interval [CI] 0.13–2.10), 1.02 (95% CI 0.52–2.00), and 1.29 (95% CI 0.71–2.34) for the 3 trimesters, respectively. In addition, preliminary analysis showed no interaction between any exposure to bacterial infection and any exposure to viral infection (data not shown). Consequently, maternal viral infections were not included as exposure variables in the subsequent analyses.

Table 1 shows the results of the univariate and multiple logistic regression using either narrowly (*ICD-8*) or broadly defined schizophrenia (*ICD-8* and/or *ICD-10*) as the outcome. The first column presents the unadjusted effects of the variables listed and the second column presents the adjusted effects with all the listed variables included in the regression model. The adjusted odds ratios of first-trimester bacterial infection were 2.53 (95% CI 1.07–5.96) and 2.14 (95% CI 1.06–4.31), while the adjusted odds ratios for second-trimester bacterial infection were 1.93 (95% CI 0.96–3.86) and 1.60 (95% CI 0.91–2.80) for the 2 outcomes. Thus, the effects were stronger for more narrowly defined schizophrenia with relatively early onset. The effect of parental social status was not significant, while a strong predictive effect of exposure to analgesics was observed.

Analyses of potential confounders showed significant relationships between any maternal intake of analgesics during pregnancy and first-, second-, or third-trimester bacterial infection and a marginally significant relationship between parental social status and second-trimester bacterial infection (but not first- or third-trimester infection). Based on previous research on the cohort, maternal schizophrenia, hypertension, third-trimester exposure to diuretics, single-mother status, and early weaning (breastfeeding for 2 weeks or less) were also considered potential confounders.[22,24,25] However, none of these variables were significantly associated with bacterial infection (see table 2), and consequently, they were not included as covariates in the analyses of the effects of bacterial infection.

A total of 206 cohort members were exposed to bacterial infection in the first trimester and 7735 were not. In all, 6 of 85 cases (7.1%) of *ICD-8 s*chizophrenia had been exposed to bacterial infection in the first trimester. Assuming a causal connection and using the method suggested in Altman et al,[26] we calculated the attributable

Table 2. Associations Between Potential Confounders and Any Bacterial Infection During Pregnancy

Variable	Bacterial Infection Status		*P* Value[a]
	Infection (n = 1065) Percent Exposed to Potential Confounder	No Infection (n = 6876) Percent Exposed to Potential Confounder	
Maternal schizophrenia	1.7	1.6	0.74
Second-trimester exposure to analgesics	2.7	1.6	0.02
Third-trimester exposure to diuretics	5.7	5.1	0.42
Hypertension during pregnancy	19.5	18.5	0.43
Offspring of single mother	39.5	37.9	0.32
Breastfed $\leq$2 weeks	23.5	24.0	0.77
Low parental social status	55.1	51.6	0.10

[a] *P* values refer to tests of differences between proportions.

risk for *ICD-8* schizophrenia of first-trimester exposure to bacterial infection to be 1.9% (95% CI 0.3–5.1). In total, 9 of 153 cases (5.9%) of *ICD-8*/*ICD-10* schizophrenia had been exposed during the first trimester yielding an attributable risk of 2.4% (95% CI 0.3–6.1).

Further analyses showed that 1065 subjects out of the sample of 7941 (13.4%) had been prenatally exposed to any bacterial infection. Out of all 153 cases with *ICD-8*/*ICD-10* schizophrenia, 32 (20.9%) had been exposed to any bacterial infection, whereas 13.3% of the remaining 7788 individuals had been exposed to any bacterial infection.

Table 3 shows the distribution of diagnoses among the 1065 mothers coded positive for any bacterial infection during the pregnancy. Urinary tract infections (bladder infection and ascending infection in the urinary tract) accounted for more than 62% of all bacterial infections. Approximately 20% of all bacterial infections were infections of the upper respiratory tract or "ear-nose-throat infections" (sinusitis, tonsillitis), about 1% had pneumonia, about 8% had venereal (gonococcal) infection, and the remaining 7% had unspecified bacterial infection.

Post hoc analyses of specific bacterial infections were conducted without taking the trimester of exposure into account. In all, 12 cases of broadly defined schizophrenia arose among the 216 cohort members who were exposed to upper respiratory tract or ear-nose-throat infections. Five cases of broadly defined schizophrenia arose among the 87 cohort members exposed to maternal gonococcal infection. Logistic regression analyses showed the odds ratio for broadly defined schizophrenia (*ICD-8* and/or *ICD-10*) to be 3.29 (95% CI 1.79–6.05) for any upper respiratory tract or ear-nose-throat infection and 3.41 (95% CI 1.36–8.57) for any gonococcal infection (using no bacterial infection as the reference category). Adjustment for parental social status did not substantially alter these estimates.

Discussion

We observed an increased risk of schizophrenia associated with prenatal exposure to bacterial infection in

Table 3. Distribution of Bacterial Infections (n = 1065) According to Clinical Diagnosis at Baseline and Percentage of Exposed Who Have Developed Schizophrenia (*ICD-8* or *ICD-10*) up to Age 45–47 y

Type of Infection	*N* and % of Total Sample	Number With Schizophrenia Among Exposed	% With Schizophrenia (95% Confidence Interval)[a]
Upper respiratory (except pneumonia) and ear-nose-throat	216 (2.7)	12	5.6 (2.9–9.5)
Pneumonia	13 (0.1)	0	0 (0.0–24.7)
Urinary tract infections (mainly cystitis)	657 (8.2)	13	2.0 (1.1–3.4)
Gonococcal infection	87 (1.1)	5	5.7 (1.9–12.9)
Any other bacterial infection	92 (1.2)	2	2.2 (0.3–7.6)
Not exposed to any bacterial infection	6876 (86.9)	121	1.8 (1.5–2.1)

Note: *ICD-8*, *International Classification of Diseases, Eighth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision.*
[a]Exact confidence intervals for proportions. The confidence intervals will contain the "true" percentage with schizophrenia in 95 of 100 samples (see Collet[27(p23–26)]).

the first trimester of pregnancy. Compared with unexposed individuals, the risk of *ICD-8* schizophrenia was 2.53-fold elevated in individuals who were exposed to bacterial infection in the first trimester, while the estimate for more broadly defined schizophrenia was 2.14. The association was independent of parental social status and prenatal exposure to analgesics. Confounding by unregistered factors is still a possibility, but maternal bacterial infection was not associated with potential confounders such as maternal schizophrenia, hypertension, and third-trimester exposure to diuretics.

From a methodological viewpoint, our prospective study is well suited to examine prenatal infections in relation to later schizophrenia. We cannot exclude the possibility that only the most severe infections were detected, but data on exposure to infection were recorded during pregnancy or shortly after delivery in a standardized fashion by one obstetrician. However, bacterial and viral diagnoses were, for the most part, clinical, and misclassification cannot be ruled out. Table 3 suggests that the overall effect of bacterial infection was primarily driven by upper respiratory tract and gonococcal infections. While we have no reason to question the validity of gonococcal infection, it is possible that some upper respiratory tract infections were erroneously classified as bacterial in origin instead of viral (eg, acute tonsillitis and sinusitis). When evaluating the possible bias introduced by such misclassification, it should be born in mind that no significant effects were associated with viral infection.

Almost all the identified cases of schizophrenia had been hospitalized. The *ICD-8* concept of schizophrenia in Denmark reflected diagnostic caution rather than over-inclusiveness. By including *ICD-10* diagnoses from 1994 until 2007, 68 new cases of schizophrenia were identified (including 3 outpatients who had never been hospitalized). The clinical reliability of *ICD-10* schizophrenia diagnoses against *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnoses has been shown to be relatively high,[28] but we observed a stronger association with *ICD-8* schizophrenia than with *ICD-8*/*ICD-10* schizophrenia. This difference in the strength of the association between bacterial infection and the disease is relatively small and should be interpreted with caution. However, it may reflect differences in diagnostic criteria (with the broad definition the cumulative incidence of the disease was 1.9%, which is relatively high[29]). It is, however, also possible that prenatal bacterial infections are primarily associated with early-onset schizophrenia.

In this study, we found no association between prenatal viral infection and risk of schizophrenia and no statistically significant interaction between exposure to viral and bacterial infection with respect to the risk of developing schizophrenia. These findings may reflect possible misclassifications of infections and limited statistical power (formal power calculations show that under most reasonable assumptions, our study had low power to detect small changes in the incidence of schizophrenia). However, previous research has found a relationship between maternal respiratory infections during pregnancy and offspring risk of schizophrenia,[17] and we interpret our findings in the light of these previous results. A few other studies have found associations with maternal nonviral infections during pregnancy and offspring risk of schizophrenia. These infections included pneumonia[17] and diphtheria,[30] but the statistical power of our study was insufficient to seek to replicate these findings.

Prenatal exposure to gonococcal infection was associated with increased offspring risk of schizophrenia. This finding could not be explained by social status differences and requires replication because, to our knowledge, it is the first study to suggest an association between maternal gonococcal infection during pregnancy and offspring risk of schizophrenia. Venereal disease has been linked with sociopsychiatric characteristics,[31] and residual confounding by unregistered correlates of gonococcal infection is a possibility. However, a birth cohort study has found exposure to genital and reproductive infections in the periconceptual period to be associated with a significantly increased risk of schizophrenia,[18] and increased IgG to herpes simplex type 2 has been linked with increased risk of psychotic disorder including schizophrenia.[32]

Much attention has previously been given to critical periods for infections during gestation in relation to risk of schizophrenia. We found that first-trimester bacterial infection had stronger effects on the risk of schizophrenia than second-trimester and third-trimester infections. Other studies suggest that infection during early pregnancy is associated with elevated schizophrenia risk. Thus, a 5-fold elevated risk of developing schizophrenia has previously been reported for individuals who were exposed to genital and reproductive infections during the period of conception.[18] Using archived maternal sera obtained during pregnancy and later analyzed for influenza antibodies, a 7-fold elevated risk of schizophrenia was associated with influenza exposure during the first trimester, while there was no increased risk associated with influenza exposure during the second or third trimester.[7] Thus, these studies to some extent corroborate our findings of stronger effects of infections during early pregnancy.

An association between risk of schizophrenia and prenatal exposure to bacterial infections might be mediated through transplacental passage of maternally produced cytokines in response to bacterial infections. Both viral and bacterial infections stimulate the production of maternal cytokines, and interleukin-8 (IL-8), for instance, crosses the placenta barrier and has been implicated in early brain development.[33] A recent study found elevated second-trimester levels of IL-8 in mothers of individuals who developed schizophrenia spectrum disorders.[34]

In conclusion, prenatal exposure to bacterial infections in the first trimester predicted schizophrenia independently

of other risk factors for the disorder, and our findings support previous studies that link respiratory infections during pregnancy with offspring risk of schizophrenia. We also found a significant relationship between prenatal exposure to gonococcal infection and offspring risk of schizophrenia that warrants further study and replication. Our findings add to the growing literature from cohort studies, suggesting an association between in utero exposure to infectious agents and risk of adult schizophrenia. It is of potential interest that a relationship was found with such infectious agents that can be treated with antibiotics. These infections may not, however, operate in isolation to increase vulnerability to schizophrenia. As has been suggested elsewhere,[35] future work is needed to identify susceptibility genes that may mediate the effect of infection on schizophrenia risk.

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