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Association Between Parental Hospital-Treated Infection and the Risk of Schizophrenia in Adolescence and Early Adulthood

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It has been suggested that infection during perinatal life may lie at the etiological root of schizophrenia. It has thus been hypothesized that the origin of schizophrenia may lie either in direct fetal infection and/or in a generally increased familial susceptibility to infections, some of which may occur during pregnancy. We explored these 2 hypotheses by assessing maternal infection during pregnancy and maternal as well as paternal infection in general as predictors of schizophrenia in their offspring. We found a slightly increased risk to be associated with prenatal infection exposure. However, the effect of prenatal infection exposure was not statistically significantly different from the effect of infection exposure in general. Parental infection appeared to be associated with development of schizophrenia in adolescence and early adulthood. Our study does not exclude a specific effect of infection during fetal life; yet, it does suggest that schizophrenia is associated with an increased familial liability to develop severe infection.

Key words: register/Denmark/cohort study/epidemiology

Introduction

In a landmark study, Mednick et al[1] presented data that suggested that prenatal exposure to influenza infection during the second trimester was associated with schizophrenia illness later in life. Many studies have since tried to verify and expand this finding, though with mixed results. A recent meta-analysis by Selten et al[2] concludes that evidence to support the maternal influenza hypothesis remains insufficient.

Studies on the association between infection and schizophrenia may be grouped into ecological studies and studies of birth cohorts. A majority have used an ecological design and therefore lack information on individual exposure status as stated in a review by Brown et al.[3] Some birth cohort studies have investigated the possible association between maternal infection during pregnancy and schizophrenia. A study following offspring of women examined serologically for rubella has related rubella to schizophrenia and related disorders in the offspring.[4] Studies using stored sera from pregnant women have linked the presence of maternal antibodies to influenza A virus,[5] herpes simplex virus type 2 (HSV-2),[6] and the protozoan *Toxoplasma Gondii*[7] to the subsequent development of schizophrenia spectrum disorders. Mortensen et al[8] using neonatal blood spots found an association with maternal IgG against *T. Gondii* and HSV-2.[9] Although these studies measured maternal IgG antibodies against specific infections, they could not determine if the mother became infected during pregnancy. Despite numerous well-performed studies linking congenital or neonatal viral infections to schizophrenia, the viral hypothesis remains compelling but is as yet unproven. New data continue to emerge linking viral infections to the etiopathogenesis of schizophrenia and the use of biomarkers of prenatal infections in rigorous epidemiological designs of birth cohorts may provide new evidence to help confirm or refute findings from previous studies.

A variety of infections are associated with an increased risk of schizophrenia, and we may therefore hypothesize that pathogenic pathways relevant to many different infections are involved in the etiology of schizophrenia. For example, Gilmore et al[10] hypothesized that cytokines generated in response to maternal infection alter early brain development and increase the risk for schizophrenia. Their idea has found support in 2 studies, which reported a rise in the incidence of psychosis in offspring in response to fetal exposure to an increase in proinflammatory cytokines during pregnancy.[5,6]

The main focus in previous studies has been infection during the fetal period and the offspring's subsequent schizophrenia risk. The higher frequency/incidence of schizophrenia among the offspring may be rooted not only in the specific effects of in utero infection exposure

but also in the increased general maternal liability to develop infections of which some will inevitably occur during pregnancy. If this is the case, we would expect that the incidence of schizophrenia would be associated also with maternal infection that occurs outside the pregnancy period. If increased familial infection susceptibility contributes to the association between maternal infection and the risk of schizophrenia, we would expect an equally strong association with "paternal" infection. No studies have yet investigated the association between schizophrenia and maternal history of infection outside the pregnancy period or the history of paternal infection. We therefore conducted a population-based cohort study of the association between offspring schizophrenia and parental infection during and outside the fetal period of 1 115 752 Danes.

Methods

The Registers

The Danish Civil Registration System (CRS) was established in 1968, when all people living in Denmark were registered and since then a unique personal identification number has been assigned to all Danish citizens.[11] It includes information on CRS number, gender, date of birth, vital status (continuously updated), and the CRS numbers of the parents. The CRS number is used as a personal identifier in all national registers, enabling accurate linkage between registers. The Danish National Hospital Register[12] was set up in 1977. It includes data on all hospital admissions in Denmark; in 1994, it was expanded to also include outpatient and emergency room contacts. The Danish Psychiatric Central Research Register was computerized in 1969 and contains data on all admissions to Danish psychiatric inpatient facilities.[13] It presently includes data on approximately 720 000 persons and 3.2 million admissions. From 1995 onward, information on outpatient visits to Danish psychiatric facilities has been included in the register.

Diagnostic codes followed a Danish modified version of the International Classification of Diseases (ICD), eighth revision[14] from 1969 to 1993; since 1994, the ICD, tenth revision[15] has been used.

Study Population

We used the Danish CRS to identify all singletons born in Denmark between January 1, 1978 and December 31, 1998 who were alive at their 10th birthday and whose mothers were born in Denmark. This group formed the study population (N = 1 115 752).

Assessment of Schizophrenia and Mental Illness

Cohort members and their mothers and fathers were linked with the Danish Psychiatric Central Research Register.[13] Cohortees were classified as having schizophrenia if they had been admitted to a psychiatric hospital or had been under outpatient care with a diagnosis of this disorder (ICD-8 code 295 or ICD-10 code F20), irrespective of any other diagnosis they might have had. Parents were categorized hierarchically as having a history of schizophrenia, schizophrenia-like psychoses (ICD-8 codes 297, 298.39, and 301.83 or ICD-10 codes F21–F29), or other mental disorders (any ICD-8 or ICD-10 diagnosis).

Definition of Pregnancy Period

Conception was defined as 280 days before birth for all women.

Assessment of Infections

A history of infection was defined as the mother or father of the cohortee having been listed with a diagnosis of infection in the Danish National Hospital Register. We omitted all ICD-8 diagnoses that bore the modification code "suspected" and "not found." Similar codes were omitted for the ICD-10. Infections were grouped as general infections (ICD-8: 000–136, ICD-10: chapter I), skin infections (ICD-8: 680–686, ICD-10: L00–L08), respiratory infections (ICD-8: 460–486, ICD-10: J00–J18), infections related to the puerperium (ICD-8: 630, 635, 670; ICD-10: O23, O85, O86, O98, O264), genital infections (ICD-8: 612, 620, 622; ICD-10: N518B, N70, N71, N72, N76, N770D, N771B, N771L), other type of infections (ICD-8: 320, 321, 322, 323, 324, 540, 590, 59500, 59501, 710; ICD-10: G0, N300, K35, M00, P352, P352A, H031B).

Study Design

We performed a prospective cohort study where 1 115 752 persons were followed from their 10th birthday until onset of schizophrenia, emigration from Denmark, death or July 1, 2009, whichever came first. The follow-up period was from January 1, 1988 to July 1, 2009.

Data Analysis

The relative risk of schizophrenia was estimated by a log linear Poisson regression model using the GENMOD procedure in SAS version 9.2 (SAS institute, Cary, NC). This method approximates a Cox regression.[16] Main exposure variables were maternal infection and paternal infection. All relative risks were adjusted for calendar year, age, sex, and interaction between age and sex. In subsequent analyses, we adjusted for history of schizophrenia, schizophrenia-like psychosis, or psychiatric hospital contact in a parent. This factor was chosen for adjustment because it is a known risk factor for schizophrenia[17] and has also been found to be associated with infections.[18]

Age, calendar year, first infection after pregnancy, second infection after pregnancy, and history of parental mental illness were treated as time-dependent variables,[19]

whereas all other variables were considered time independent. Age was categorized as 10–12 years and as 1-year age levels thereafter. Calendar years were categorized as 1988–1995 and as 1-year periods thereafter.

Relative risks and CIs were calculated by log-likelihood estimation. *P* values and tests for differences were calculated using a likelihood ratio test.[19]

Power calculations were performed according to the method by Hsieh and Lavori,[17] which is implemented in the Stata procedure stpower cox.

Results

A total of 3722 developed schizophrenia during the 11.9 million person-years of follow-up from 1988 to 2009.

Table 1 presents the number of cases of schizophrenia according to maternal infection diagnosis during pregnancy. Children born to mothers with an infection diagnosis during pregnancy had a 1.39-fold (95% CI: 1.18–1.62) increased risk of schizophrenia. Table 1 also shows the estimates for paternal infection during pregnancy. This association was almost identical in magnitude to that of maternal infection. However, the association was only marginally statistically significant 1.46 (95% CI: 0.97–2.10).

Table 1 also features the potential confounding effect of a family history of mental illness. Adjustment for parental mental illness reduced the relative risk to 1.23 (95% CI: 1.04–1.94). The same attenuation in the relative risk was seen for paternal infection (1.31; 95% CI: 0.87–1.88).

Furthermore, we analyzed whether there was a possible trimester-specific effect (data not shown in table 1). We did find a relative risk of 1.55 (95% CI: 0.89–2.48) for the first trimester, 1.72 (95% CI: 1.15–2.46) for the second trimester, and 1.13 (95% CI: 0.93–1.35) for the third trimester after adjustment for a history of parental mental illness. However, although this could suggest a specific effect of second trimester exposure, the trimester effect could be reduced to the main effect of having an infection during pregnancy (relative risk 1.23; 95% CI: 1.04–1.44; test for difference $P = .11$). Thus, we cannot rule out random effect variation across trimesters.

Table 2 presents the relative risk and the number of schizophrenia cases according to maternal and paternal hospital contact with an infection diagnosis before, during, and/or after the pregnancy period. Children whose mothers had had an infection diagnosis had a 1.43-fold (95% CI 1.33–1.53) increased risk of schizophrenia. Children whose fathers had had a hospital contact with an infection had a 1.29-fold (95% CI: 1.19–1.39) increased risk. Adjustment for family history of psychosis attenuated the relative risk associated with maternal infections to 1.24 (95% CI: 1.16–1.33), whereas the effect of having a father who had had a hospital diagnosis of infection was reduced to 1.14 (95% CI: 1.05–1.23).

Table 3 shows the relative risk and the number of cases of schizophrenia according to the time of hospitalization for maternal infection.

We first compared the relative risk of having a schizophrenia diagnosis between offspring of mothers admitted to hospital with an infection and that of offspring of mothers who had not been registered as having had an infection. This relative risk was 1.09 (95% CI: 0.85–1.38).

The effect on the relative risk of the mother having had only one hospital contact with infection before or after pregnancy was a relative risk of 1.32 (95% CI: 1.21–1.44) compared with the mother having had no infection-related admission. Analysis of the difference between the 2 groups, ie, mothers hospitalized with an infection during pregnancy and mothers with one hospital contact before or after pregnancy, showed a *P* value of .13. Maternal infection during pregnancy was therefore not significantly different from a maternal hospital diagnosis of infection outside pregnancy in terms of the offspring's relative risk of acquiring a schizophrenia diagnosis.

We then compared the relative risk of having a schizophrenia diagnosis between offspring of mothers who had been admitted to hospital with an infection during pregnancy and had had at least one infection before and/or after pregnancy with that of offspring of mothers who had not been registered as having had an infection. This relative risk was 2.06 (95% CI: 1.44–2.84).

The effect on the relative risk of the mothers having had no infection during pregnancy and at least 2 infections before and/or after was 1.62 (95% CI: 1.47–1.78) relative to that of mothers without infections. We found no statistically significant ($P = .19$) difference between these 2 estimates, ie, mothers hospitalized with an infection during pregnancy and at least one infection outside pregnancy and mothers with at least 2 infections outside pregnancy.

Power calculations were done based on the estimates presented in table 3, under the assumption of a relative risk of 1.5. The power to find a true effect for the group with no infection during pregnancy and one infection before/after was 100%, whereas the power for the group with an infection during pregnancy and no infections before/after was 7.5%. The power for infection during pregnancy and at least one infection before/after was 3.4%, whereas the power for the group with no infection during pregnancy and at least 2 infections before/after was 91%.

Table 4 shows the relative risk and number of cases for the different types of maternal infection: general infections, skin infections, respiratory infections, infections related to the puerperium, genital infections, and other type of infections and the time at which the infection occurred. Having a genital infection during pregnancy was associated with a relative risk of offspring schizophrenia of 2.03 (95% CI: 1.02–3.56).

We also investigated if having more than one hospital contact with maternal infections was different from having only one hospital contact but found no significant

Table 1. Maternal and Paternal Infection During Pregnancy in a Cohort of 1 115 752 Persons Born Between 1978 and 1998 of Whom 3722 Developed Schizophrenia During 11.9 Million Person Years of Follow-Up

	Mother				Father			
			IRRs (95% CIs)				IRRs (95% CIs)	
Parental Infection During Pregnancy	Cases	Incidence Rate[a]	Basic Model[b]	Adjusted Model[c]	Cases[d]	Incidence Rate[a]	Basic Model[b]	Adjusted Model[c]
Infection	159	4.3	1.39 (1.18–1.62)	1.23 (1.04–1.44)	26	4.3	1.46 (0.97–2.10)	1.31 (0.87–1.88)
No infections	3563	3.1	1.00 (reference)	1.00 (reference)	3636	3.1	1.00 (reference)	1.00 (reference)

Note: IRR, incidence rate ratio.
[a]The incidence rate measures the number of new cases per 10 000 person years.
[b]Adjusted for calendar year, sex, and its interaction with age.
[c]Further adjustment for family history of psychosis.
[d]Because of father unknown ($N = 60$, IRR not shown but included in the model), the numbers do not add up to the total number of cases in the sample.

difference ($P = .20$). We performed the same test for the father and found a P value of .17.

We checked the possible interaction between maternal psychiatric illness and infection. The relative risk of being diagnosed with schizophrenia for children of a mother with schizophrenia/schizophrenic-like diagnosis and at least one infection was 6.22 (95% CI: 4.89–7.78). The relative risk for children of a mother with schizophrenia/schizophrenia-like diagnosis and no admissions with infection was 4.25 (95% CI: 3.33–5.33); and for offspring with a mother with a history only of at least one infection, the relative risk was 1.32 (95% CI: 1.22–1.42). This interaction did not reach the level of statistical significance in a multiplicative model ($P = .23$). Using the method described by Andersson et al[20] and in line with the analysis by Clarke et al,[21] we calculated the synergy index (S) for the possible synergistic action between schizophrenia or schizophrenia-like psychosis in the mothers and infections, $S = 1.46$ (95% CI: 0.99–2.15, $N = 74$). These estimates suggest that the risk of offspring exposed to maternal infections and whose mothers had a maternal history of schizophrenia-like psychosis is larger than what would be predicted under an additive model.

Discussion

Main Findings

In this national cohort study, we found an association between maternal infection leading to hospitalization and the later development of schizophrenia. The association was not confined to maternal infection during pregnancy. An equally strong association was found for infections before and after the pregnancy period. Our power calculations showed inadequate power for our findings during pregnancy (infection only during pregnancy, 7.4%; infection during pregnancy and before/after, 3.4%). A stronger effect during pregnancy may therefore

Table 2. Maternal and Paternal Hospital-Treated Infections Before, During, and After Pregnancy in a Cohort of 1 115 752 Persons Born Between 1978 and 1998, of Whom 3722 Developed Schizophrenia During 11.9 Million Person Years of Follow-Up

	Mother				Father			
			IRRs (95% CIs)				IRRs (95% CIs)	
Parental Infection	Cases	Incidence Rate[a]	Basic Model[b]	Adjusted Model[c]	Cases[d]	Incidence Rate[a]	Basic Model[b]	Adjusted Model[c]
≥1 infection	1234	4.1	1.43 (1.33–1.53)	1.24 (1.16–1.33)	794	4.1	1.29 (1.19–1.39)	1.14 (1.05–1.23)
No infections	2488	2.8	1.00 (reference)	1.00 (reference)	2868	2.9	1.00 (reference)	1.00 (reference)

Note: Abbreviation is explained in the first footnote to table 1.
[a]The incidence rate measures the number of new cases per 10 000 person years.
[b]Adjusted for calendar year, sex, and its interaction with age.
[c]Further adjustment for family history of psychosis.
[d]Because of father unknown ($N = 60$, IRR not shown but included in the model), numbers do not add up to the total number of cases in the sample.

Table 3. Maternal Infection Before, During, and After Pregnancy in a Cohort of 1 115 752 Persons Born Between 1978 and 1998 of Whom 3722 Developed Schizophrenia During 11.9 Million Person Years of Follow-Up

			IRRs (95% CIs)	
	Cases	Incidence Rate[a]	Basic Model[b]	Adjusted Model[c]
No infection during pregnancy, no infections before/after	2488	2.80	1.00 (Reference)	1.00 (Reference)
No infection during pregnancy, 1 infection before/after	625	3.77	1.32 (1.21–1.44)	1.21 (1.11–1.32)
Infection during pregnancy, no infections before/after	68	3.05	1.09 (0.85–1.38)	1.01 (0.79–1.28)
Infection during pregnancy, at least one infection before/after	34	6.36	2.06 (1.44–2.84)	1.72 (1.20–2.38)
No infection during pregnancy, at least 2 infections before/after	507	4.87	1.62 (1.47–1.78)	1.30 (1.18–1.44)

Note: Abbreviation is explained in the first footnote to table 1.
[a]The incidence rate measures the number of new cases per 10 000 person years.
[b]Adjusted for calendar year, sex, and its interaction with age.
[c]Further adjustment for family history of psychosis.

have been observed if the power for the pregnancy analysis had been adequate.

Furthermore, the risk of offspring schizophrenia was also associated with paternal infection. All of the different groups of infections studied were equally strongly associated with schizophrenia risk. The association with parental hospitalization for infection was attenuated but not eliminated by adjustment for parental mental illness.

Possible Mechanisms

A range of theories could plausibly explain our findings and they are not necessarily mutually exclusive.

Parental infection may reflect poor living conditions and social adversity rather than a particular genetic or biological susceptibility, and we had no possibility to adjust for this potential confounder. However, in their study of prenatal exposure to bacterial infection and schizophrenia, Sorensen et al[22] did not find parental social status to be significant. Furthermore, Byrne et al[23] found little evidence that socioeconomic status was consistently associated with an increased risk of schizophrenia, and no risk when the association was adjusted for parental mental illness like in the present study. We have therefore little reason to believe that poor socioeconomic status play an etiologic role in the Danish setting.

Genetic factors that are associated with an increased risk for schizophrenia may also be associated with an increased exposure and/or vulnerability to infectious diseases. A gene or gene cluster may separately contribute to infection susceptibility and to schizophrenia susceptibility, even if there is no causal effect of parental infection per se. Assuming this hypothesis, our data on parental hospital contact due to infection reflect a genetic infection susceptibility more than they indicate infection per se. Stefansson et al[24] found a significant association between an increased risk for schizophrenia and alleles at several loci on the major histocompatibility complex

Table 4. Type of Maternal Infection and Time of Occurrence in a Cohort of 1 115 752 Persons Born Between 1978 and 1988 of Whom 3722 Developed Schizophrenia During 11.9 Million Person Years of Follow-Up (Reference: people with no infections $N = 2488$)

	Adjusted Model[a] (95% CIs)					
	Cases	Before	Cases	During	Cases	After
General infections	55	1.15 (0.87–1.49)	20	1.02 (0.63–1.53)	210	1.18 (1.02–1.36)
Skin infections	12	0.77 (0.41–1.29)	[b]		109	1.16 (0.95–1.40)
Respiratory infections	38	1.41 (1.01–1.91)	[b]		92	1.29 (1.04–1.58)
Infections related to the puerperium	27	1.55 (1.03–2.22)	39	1.04 (0.74–1.40)	67	1.34 (1.04–1.69)
Genital infections	66	1.21 (0.93–1.53)	10	2.03 (1.02–3.56)	203	1.33 (1.15–1.53)
Other infections	44	1.03 (0.75–1.37)	12	1.44 (0.77–2.42)	225	1.38 (1.20–1.58)

[a]Adjusted for calendar year, age, and its interaction with sex and family history of psychosis.
[b]Less than 5 cases.

(MHC) region of chromosome 6. A number of autoimmune and infectious diseases have also been associated with this region. Yet, Stefansson et al[24] also point to the fact that many nonimmune-related genes are also found in the MHC region. Interestingly, MHC class I proteins have been shown to have much impact on neurodevelopment and synaptic plasticity irrespective of their role in the immune response.[25,26] Our data on parental hospitalization due to infection could reflect the combined effect of exposure to infection and a high genetic susceptibility to severe infection. Some indirect support for this can be found in the work by Asp et al.[27,28] In experiments where Tap1 knockout mice with reduced expression of MHC class I were exposed to neonatal Influenza A infection, Tap1−/− mice exhibited a stronger innate immune response and more long-term deficits in sensorimotor gating than in wild type mice. Equally, relevant are studies reporting an association between polymorphisms in MHC class I polypeptide-related sequence B and schizophrenia in interaction with Herpes virus infections.[29,30]

We did find a marginally significant synergy between maternal infection and psychiatric history; an observation that replicates the findings in a study by Clarke et al.[21] Some authors have suggested that a synergy index significantly above one may indicate a biological interaction between exposures.[31,32] However, several authors have advised against such a conclusion because it rests upon the somewhat unlikely assumption that there is no residual confounding from unmeasured or unknown risk factors.[33,34] Moreover, given the low ORs generally found in genetic association studies with schizophrenia, it is unlikely that a family history of treated mental illness is a strong measure of any single specific genetic variation of biological mechanistic importance to the reaction to infection. Although interesting, the finding of a possible synergy between parental psychosis and infection as a risk factor for schizophrenia in their offspring should therefore be interpreted cautiously, and the results should be further explored in followed-up studies of specific genetic mechanisms and infection markers.

We only had access to records of parental infection that involved hospital contact. As most infections do not require hospital contact, it is possible that rather than reflecting the presence or absence of infection, our data capture instances of clinically severe infection only. In other words, it is possible that our data are primarily indicators of host factors leading to high fever, sepsis, or other severe clinical manifestations. This should be borne in mind when interpreting our findings of an association that is not specific to maternal infection during pregnancy. We must assume that most women who have infections, whether during pregnancy or not, are not hospitalized. We must therefore expect a nondifferential misclassification of the exposure which, in turn, will bias our results toward no association. We therefore cannot rule out the possibility of a separate effect of an infection during pregnancy. Furthermore, our study does not address whether particular maternal infections that do not require hospitalization are associated with schizophrenia in their adult offspring. Furthermore, it is possible that the threshold for hospitalizing a pregnant mother with an infection may be lower than for a nonpregnant mother. We may therefore expect that women would be more prone to be hospitalized when pregnant than when nonpregnant and that the former would have less severe infections than the latter and that many of their infections would therefore not be risk factors for schizophrenia. This may have biased our findings in the direction of reducing the difference between infections during pregnancy and infections at other time points.

A number of studies[5,7–9] have previously associated the development of psychosis with exposure to infection during fetal life. Some of these studies have examined specific and better validated infections during pregnancy than those included in the present study. Maternal infection could permanently alter the peripheral immune system of the fetus. There is evidence to support that maternal infection during pregnancy has neurodevelopmental effects. We cannot exclude the possibility that these effects do exist, but we found no strong support for this in our study.

One explanation as to why we did not find any evidence for an increased risk for infection during pregnancy may be related to power. We may have had inadequate power to reliably estimate the effect of an infection during pregnancy, and we did however have adequate power to estimate the effect of maternal infection outside of pregnancy.

Our results may be rooted in an association between schizophrenia and a familial tendency to develop a serious inflammatory response that requires hospitalization. If so, it is possible that this response is mediated through cytokines, ie, the fetus could be exposed to high maternal cytokine levels, or the child could share the parental/mother's tendency to react to infection with high levels of cytokines later in life.

These explanations are not mutually exclusive. Several immune proteins including proinflammatory cytokines have been demonstrated to have alternative functions in neurodevelopment and synaptic plasticity.[25] These types of cytokines are the same as those that have been suggested to act through common pathways to alter fetal brain development and increase vulnerability to schizophrenia.[35–39] Furthermore, elevated proinflammatory cytokine levels have been observed in schizophrenic patients.[40]

Another explanation for the association between paternal infection and schizophrenia in offspring could be that the fathers have transmitted the infections to the mothers, and we cannot rule out this explanation in our data.

Strengths and Limitations

To our knowledge, this is the first study to be conducted on the possible association between schizophrenia and both maternal and paternal infection.

The strength of this study is that it is a nationwide cohort study with prospectively collected data. However, we only studied the risk associated with infections requiring hospital treatment. Diagnoses from the Danish Hospital Register were used and misclassification cannot be ruled out. Another potential problem is that the sensitivity of this measure of infection is low with the implication that our results may be biased toward no association, as described above.

Although it is possible that some of the diagnoses for infections requiring hospital treatment might have been given at a psychiatric hospital, we have reason to believe that this is very unlikely for 2 reasons. Firstly, the infections included in the present study are general infections requiring admission to a general hospital. Secondly, there is traditionally a clear separation between general hospitals and psychiatric hospitals in Denmark, and it has only been possible for a very short period of time to even record a diagnosis of infections in the register covering psychiatric hospitals. We also have reason to believe that this possibility is rarely.

Our estimates of parental infection could be biased because cohortees born early and late during the study period were not followed for equally long periods. Moreover, these estimates could also be biased because we had no information on parental infection prior to 1977. We performed an additional analysis with data on maternal or paternal infection occurring during the period of 5 years before and up until 5 years after birth. This analysis produced results almost identical to those of the entire study period.

We defined a pregnancy to start 280 days before the date of birth. This limits our knowledge as to the timing of the infection at the start of the pregnancy period.

It should be noted that the infection categories used are relatively crude and that each group could therefore harbor important distinct subgroups. It is difficult, however, to remedy this with the type of data available to us.

Conclusions

In conclusion, this study shows that paternal and maternal infections leading to hospitalization are associated with an increased risk of schizophrenia in their offspring. Our finding indicates that the association between schizophrenia and parental infection is not confined to maternal infection during pregnancy, and this could suggest that an increased familial liability to severe infection is an independent risk factor for schizophrenia. Our findings, however, cannot exclude a stronger effect of infection exposure during pregnancy because our study had limited power to detect effects in this period.

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