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Hospital Contacts With Infection and Risk of Schizophrenia: A Population-Based Cohort Study With Linkage of Danish National Registers

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Infections and immune responses have been suggested to play an important role in the etiology of schizophrenia. Several studies have reported associations between maternal infections during pregnancy and the child's risk of schizophrenia; however, infection during childhood and adolescence unrelated to maternal infection during pregnancy has not been studied to nearly the same extent and the results are far from conclusive. Data were drawn from 2 population-based registers, the Danish Psychiatric Central Register and the Danish National Hospital Register. We used a historical population-based cohort design and selected all individuals born in Denmark between 1981 and 1996 (n = 843 390). We identified all individuals with a first-time hospital contact with schizophrenia from 1991 through 2010. Out of the 3409 individuals diagnosed with schizophrenia, a total of 1549 individuals had had a hospital contact with infection before their schizophrenia diagnosis (45%). Our results indicate that individuals who have had a hospital contact with infection are more likely to develop schizophrenia (relative risk [RR] = 1.41; 95% CI: 1.32–1.51) than individuals who had not had such a hospital contact. Bacterial infection was the type of infection that was associated with the highest risk of schizophrenia (RR = 1.63; 95% CI: 1.47–1.82). Our study does not exclude that a certain type of infection may have a specific effect; yet, it does suggest that schizophrenia is associated with a wide range of infections. This association may be due to inflammatory responses affecting the brain or genetic and environmental risk factors aggregating in families.

Key words: register/Denmark/cohort study/epidemiology

Introduction

Recent years have seen accumulating evidence that the immune system in general and infections in particular may play an important role in the etiology and pathophysiology of schizophrenia. The timing of infection has been linked with schizophrenia from fetal life through childhood to adulthood. Thus, several studies have linked the exposure to a wide range of prenatal maternal infections to an increased risk of schizophrenia in the offspring.[1,2] However, the role of infections during childhood and adolescence unrelated to maternal infection during pregnancy has not been studied to nearly the same extent as prenatal maternal infections.[3] The few published studies on infection during childhood[4–7] have primarily focused on infections related to the central nervous system (CNS), and a recent meta-analysis[3] demonstrated their significant association with schizophrenia. The authors of this meta-analysis concluded that in general studies on infections during childhood were lacking.[3] A broad range of infections in the individual have previously been associated with an increased risk of schizophrenia spectrum disorder; however, that study did not focus specifically on schizophrenia or on possible sensitive exposure periods to infection during childhood.[8] Nor did the study focus on a possible difference between viral and bacterial infections.[8]

The mechanisms by which infections raise the risk of schizophrenia are not well understood and they may be numerous. There is growing evidence that infection not necessarily directly involved with the CNS is just as important as infections that does affect the CNS.[9] Inflammation and infections can give rise to a wide range of CNS-related symptoms, and there is a growing recognition that these CNS-related symptoms persist beyond

the acute illness phase.[9] Nonetheless, the effects of exposure to infections not directly affecting the CNS on the risk of schizophrenia are still unclear.

The present lack of population-based studies and the absence of detailed knowledge of the effect of non-CNS infections accordingly need to be addressed. We therefore conducted a population-based cohort study exploring all types of infections before onset of schizophrenia and the extent to which the risk of schizophrenia differed according to the site of these infections. Firstly, we tested the hypothesis that an increased risk of schizophrenia depends on the type of infection. Secondly, we examined whether this risk differed according to the site of these infections. Finally, we determined if there was any association between the risk of schizophrenia and age of first hospital contact with infection or the number of such hospital contacts. A model adjusting for family history of infection was applied to examine if our findings in the offspring had been confounded by parental exposure to infection.

Material and Methods

Study Design

We performed a register-based prospective cohort study in which 843 390 persons born in the period 1981–1996 and whose mothers were born in Denmark were followed from their 10th birthday until the onset of schizophrenia, emigration from Denmark, death, or January 1, 2011, whichever came first. The follow-up period spanned from January 1, 1991 to December 31, 2010.

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.[10] The CRS includes information on the CRS number, gender, date of birth, vital status (continuously updated), and the CRS numbers of the subject's parents. The CRS number is used as a personal identifier in all national registers, which enables accurate linkage of data between registers. The Danish National Hospital Register[11] was set up in 1977. It includes data on all hospital admissions in Denmark; in 1995, it was expanded to include also 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.[12] 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.

The diagnostic codes used in these registers conformed to a Danish modified version of the International Classification of Diseases, Eighth Revision (ICD-8)[13] from 1969 to 1993; since 1994, the International Classification of Diseases, Tenth Revision (ICD-10)[14] has been used.

Assessment of Schizophrenia and Other Mental Illness

Data on cohort members and their mothers and fathers were linked with the Danish Psychiatric Central Research Register.[12] Cohort members were classified as having schizophrenia if they had been admitted to a psychiatric hospital or had received outpatient care with a diagnosis of this disorder (ICD-8 code: 295; 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; ICD-10 codes: F21–F29), or other mental disorders (ICD-8 codes: 290–315; ICD-10 codes: F00–F99).

Assessment of Infections

A history of infection was defined as the person having been recorded 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. First, all infection codes were grouped according to type of infection: bacterial, viral, and other (for diagnostic codes, see supplementary table S1). Each type of infection was also grouped according to the site of infection. Infections were grouped as sepsis (ICD-8: 038; ICD-10: A40, A41), hepatitis (ICD-8: 070; ICD-10: B15–B19), intestinal infections (ICD-8: 000–009, 540; ICD-10: A00–A09, K35), skin infections (ICD-8: 680–686, 050–057, 110, 111, 035; ICD-10: L00–L08, B00–B09, A46), respiratory infections (ICD-8: 460–486; ICD-10: J00–J18), urinary tract infections (ICD-8: 580, 590, 59500, 59501; ICD-10: N00, N10, N300, N390), genital infections (ICD-8: 612, 620, 622; ICD-10: N518B, N70, N71, N72, N76, N770D, N771B, N771L), CNS infections (ICD-8: 04000–04399, 013, 320, 322, 392, 474, 04509–04699, 32300, 07199, 07202, 07501, 07929, 09049, 05201, 05302, 05403, 05501, 05601, 03609, 02701, 06209–06599, 09490–09499; ICD-10: I02, G00–G07, A17, A80–89, B003, B004, B010, B011, B020, B021, B050, B051, B060, B261, B262, B375, B451, B582, B602, A022C, A548A, A548D, A521A, A521B, A229C, A321, A504, A390, E236A), ottis media (ICD-8: 381–382; ICD-10: H65–67), and other types of infections. The same codes were used to identify a history of infection in the mother and father.

Data Analysis

The relative risk (RR) of schizophrenia was estimated by a log linear Poisson regression model using the GENMOD procedure in SAS version 9.2 (SAS Institute). This method approximates a Cox regression.[15] All RRs

were adjusted for calendar year, age, sex, and interaction between age and sex. Subsequent analyses were performed where we adjusted for parental history of mental illness. This factor was chosen for adjustment because it is a known risk factor for schizophrenia[16] and because it has been found to be associated with infections.[17]

Age, calendar year, first infection, first maternal infection, first paternal infection, and history of parental mental illness were treated as time-dependent variables,[18] whereas all other variables were considered time independent. Age was categorized as 10–13 and as 1-year age levels thereafter. Calendar years were categorized as 1991–1995 and as 1-year periods thereafter. RRs and CIs were calculated by log-likelihood estimation. *P* values and tests for differences were calculated using a likelihood ratio test.[18]

Results

This study population counted 843 390 persons born in Denmark between 1981 and 1996. In this cohort, a total of 3409 individuals developed schizophrenia during the 9.7 million person years of follow-up from 1991 to 2010. A total of 1549 individuals had had a hospital contact with infection before being diagnosed with schizophrenia (45%). In the basic model, all estimates are adjusted for age, sex, calendar year, and interaction between sex and age; in the fully adjusted model, additional adjustment was made for family history of mental illness.

Table 1 presents the overall effect of exposure to infection and the number of cases of schizophrenia according to the type of infection. Persons with an infection had a 1.52-fold (95% CI: 1.42–1.62) increased risk of schizophrenia compared with persons with no infections, and additional adjustment for parental history of mental illness reduced the RR to 1.41 (95% CI: 1.32–1.51). Bacterial infection was associated with the most elevated risk; hence, it increased the risk of schizophrenia 1.73-fold (95% CI: 1.55–1.92) compared with persons without a hospital contact with infections. Additional adjustment for parental mental illness reduced the RR to 1.63 (95% CI: 1.42–1.82).

Table 2 shows the RR and the number of cases of schizophrenia according to sites of infection. The increased risk of schizophrenia risk was infection site specific. Having a genital infection carried a RR of 3.47 (95% CI: 2.33–4.96) in the fully adjusted model. The group genital infection comprised only young adults and adults. There was no evidence of an increased risk of schizophrenia following CNS infection (RR = 0.98; 95% CI: 0.58–1.52) in this sample; however, the results were only based on 17 cases when only the first infection was considered. When the analyses were expanded to investigate the first CNS infection regardless of other types of infections, only 4 more cases were included and the results were similar (results not shown).

Table 3 provides the RR and the number of schizophrenia cases according to age upon exposure to the first infection. As can be seen, the age group 25–29 had a 2.07-fold (95% CI: 1.19–3.32) increased risk; after adjustment for parental mental illness, the risk was 2.02 (95% CI: 1.16–3.24).

We evaluated the dose–response relationship by estimating the RR according to increasing number of infections compared with no infection. The RR of schizophrenia and the number of cases related to the number of infections are given in table 4. The group with 1 infection had a 1.30-fold (95% CI: 1.20–1.42) increased risk, whereas the group with 5 or more infections had a 2.14-fold (95% CI: 1.84–2.48) increased risk after adjustment.

Table 1. Risk of Schizophrenia Associated With Type of First Infection in a Cohort of 843 390 Persons Born Between 1981 and 1996 of Whom 3409 Developed Schizophrenia During 9.7 Million Person Years of Follow-up

		Incidence Rate Ratios (95% CI)	
Hospital Infection	Cases	Basic model[a]	Fully adjusted model[b]
Infection	1549	1.52 (1.42–1.62)	1.41 (1.32–1.51)
No infections	1860	1.00 (reference)	1.00 (reference)
Type of infection			
Bacterial	415	1.73 (1.55–1.92)	1.63 (1.47–1.82)
Viral	382	1.40 (1.25–1.56)	1.30 (1.16–1.45)
Other type	752	1.48 (1.36–1.61)	1.37 (1.25–1.49)
No infections	1860	1.00 (reference)	1.00 (reference)

Note: [a]Adjusted for calendar year, sex, and its interaction with age. [b]Further adjustment for parental history of mental illness.

Table 2. Risk of Schizophrenia Associated With Site of First Infection in a Cohort of 843 390 Persons Born Between 1981 and 1996 of Whom 3409 Developed Schizophrenia During 9.7 Million Person Years of Follow-up

		Incidence Rate Ratios (95% CI)	
Site of Infection	Cases	Basic model[a]	Fully adjusted model[b]
Sepsis	26	2.26 (1.49–3.25)	2.08 (1.38–3.00)
Hepatitis	5	4.05 (1.45–8.71)	3.43 (1.23–7.39)
Intestinal	195	1.44 (1.24–1.67)	1.34 (1.15–1.55)
Skin	141	1.47 (1.23–1.73)	1.38 (1.16–1.63)
Respiratory	502	1.52 (1.38–1.68)	1.41 (1.27–1.55)
Urologic	79	2.26 (1.79–2.81)	2.08 (1.65–2.59)
Genital	28	3.88 (2.60–5.54)	3.47 (2.33–4.96)
Central nervous system	17	1.01 (0.60–1.57)	0.98 (0.58–1.52)
Ottis media	165	1.34 (1.14–1.57)	1.23 (1.05–1.44)
Other types	391	1.48 (1.32–1.64)	1.39 (1.25–1.55)
No infections	1860	1.00 (reference)	1.00 (reference)

Note: [a]Adjusted for calendar year, sex, and its interaction with age. [b]Further adjustment for parental history of mental illness.

Table 3. Risk of Schizophrenia Associated With Age at First Infection in a Cohort of 843 390 Persons Born Between 1981 and 1996 of Whom 3409 Developed Schizophrenia During 9.7 Million Person Years of Follow-up

		Incidence Rate Ratios (95% CI)	
Age	Cases	Basic model[a]	Fully adjusted model[b]
Birth to 12 mo	370	1.57 (1.41–1.76)	1.40 (1.25–1.57)
1	245	1.50 (1.31–1.71)	1.37 (1.20–1.56)
2	114	1.51 (1.25–1.82)	1.39 (1.15–1.68)
3	67	1.21 (0.94–1.53)	1.13 (0.88–1.43)
4	71	1.60 (1.25–2.01)	1.52 (1.19–1.92)
5–9	190	1.38 (1.18–1.59)	1.32 (1.13–1.53)
10–14	147	1.46 (1.23–1.72)	1.40 (1.18–1.65)
15–19	229	1.61 (1.40–1.84)	1.54 (1.33–1.76)
20–24	101	1.73 (1.41–2.11)	1.66 (1.35–2.01)
25–29	15	2.07 (1.19–3.32)	2.02 (1.16–3.24)
No infection	1860	1.00 (reference)	1.00 (reference)

Note: [a]Adjusted for calendar year, sex, and its interaction with age.
[b]Further adjustment for parental history of mental illness.

Table 4. Risk of Schizophrenia and Association With Number of Infections in a Cohort of 843 390 Persons Born Between 1981 and 1996 of Whom 3409 Developed Schizophrenia During 9.7 Million Person Years of Follow-up

		Incidence Rate Ratios (95% CI)	
Number of Infections	Cases	Basic model[a]	Fully adjusted model[b]
1	717	1.36 (1.25–1.49)	1.30 (1.20–1.42)
2	362	1.46 (1.31–1.64)	1.36 (1.22–1.53)
3	189	1.65 (1.42–1.91)	1.50 (1.29–1.74)
4	87	1.54 (1.24–1.90)	1.36 (1.09–1.68)
≥5	194	2.53 (2.17–2.92)	2.14 (1.84–2.48)
No infection	1860	1.00 (reference)	1.00 (reference)

Note: [a]Adjusted for calendar year, sex, and its interaction with age.
[b]Further adjustment for parental history of mental illness.

Table 5 displays the RR that the child would develop schizophrenia with additional adjustment for the effect of family members having been exposed to infection. The offspring had an increased risk of 1.37 (95% CI: 1.28–1.47) for schizophrenia in the fully adjusted model, whereas the effect of maternal exposure to infection was 1.21 (95% CI: 1.13–1.29) in the fully adjusted model. No significant sex difference was found on the risk of developing schizophrenia between males and females exposed to infections ($P = .12$).

Sensitivity Analysis

When the analyses were restricted to include only inpatients, the results were similar (results not shown).

Table 5. Risk of Schizophrenia in Offspring Adjusted for Infection in Family Members in a Cohort of 843 390 Persons Born Between 1981 and 1996 of Whom 3409 Cases Developed Schizophrenia During 9.7 Million Person Years of Follow-up

		Incidence Rate Ratios (95% CI)	
Hospital Diagnosed Infection	Cases	Basic model[a]	Fully adjusted model[b]
Child			
Infection	1549	1.45 (1.35–1.55)	1.37 (1.28–1.47)
No infection	1860	1.00 (reference)	1.00 (reference)
Father[c]			
Infection	1076	1.33 (1.23–1.43)	1.21 (1.13–1.31)
No infection	2273	1.00 (reference)	1.00 (reference)
Mother			
Infection	1477	1.34 (1.25–1.43)	1.21 (1.13–1.29)
No infection	1932	1.00 (reference)	1.00 (reference)

Note: [a]Adjusted for calendar year, sex, and its interaction with age.
[b]Further adjustment for parental history of mental illness.
[c]Unknown father, $N = 60$, incidence rate ratio: 2.58 (1.98–3.31).

Discussion

To the best of our knowledge, this is the first study that offers a detailed examination of the association between the first hospital contact for infection and the risk of schizophrenia. In this national cohort study, we found an association between a first-time hospital contact with infection and an elevated risk of subsequent development of schizophrenia. Each number of infections in the offspring increased the risk of schizophrenia. Bacterial infection was found to increase the risk of schizophrenia more than viral and other types of infections. In general, we only found small differences in risk related to the site of infection, except for hepatitis and genital infections. This is consistent with the findings by Benros et al[8] for schizophrenia spectrum diagnosis. It should, however, be noted that the number of cases obtained in the present study is small, and our results concerning hepatitis should therefore be interpreted with caution. It has been hypothesized that infections acquired earlier in life may have more serious consequences,[5] but no studies have confirmed this association.[5] In this large-scale cohort study, the association between age at first hospital infection and schizophrenia did not differ significantly between age groups.

To our knowledge, no attempt has yet been made to determine the individual effect on the immune response of being exposed to either viral or bacterial infection and how this affects the subsequent risk of schizophrenia. It is uncertain whether the type of infectious agent (virus or bacterium) affects the immune response in a specific manner and if it has a bearing on the ensuing risk of developing schizophrenia. We found that exposure to a bacterial infection carried a higher risk than exposure to

viral infection. The reason for this could be that bacterial infection generally trigger a more severe immune response than viral infection. This, in turn, probably increases the likelihood of immune components (such as cytokines, chemokines, and antibodies) affecting the brain possibly due to increased permeability of the blood brain barrier caused by inflammation. A faulty or overtaxed immune system may promote inflammation and hence give rise to a neuroendocrine or neurotransmitter dysfunction that may tilt the brain toward schizophrenia. However, treatment is also different depending on whether the infectious agent is of viral or bacterial origin. Bacterial infections are most often treated with antibiotics, whereas viruses do not respond to antibiotics. Thus, the difference in risk between bacterial and viral infections could be attributed to the type of treatment with antibiotics affecting the gut microbioma for instance and some antibiotics may also affect neurotransmitters.[19] Furthermore, differences in patterns of use of antipyretics and pain relievers (non-steroidal anti-inflammatory drug or paracetamol) could also contribute to specific bacterial vs viral effects.

We used a history of parental infections as a marker of hereditary propensity to infection and found that parents who had been exposed to infection was, indeed, a risk factor for the offspring to develop schizophrenia, which is consistent with previous finding.[20] The estimate for the child was not affected by parental exposure, which indicates that the results were not confounded by parental exposure to infection. The association between an increased risk of schizophrenia in individuals with parents who had been diagnosed with infection could stem from parental infections having been passed on to the child or to maternal infection during pregnancy; however, a previous study by Nielsen et al[20] found that the elevated risk of schizophrenia was unrelated to the time of parental infection, ie, whether infection occurred before, during, or after pregnancy. This finding could also be explained by parental transfer of genetic risk markers. Genome-wide association studies have reported a significant association between schizophrenia and markers close to the major histocompatibility complex region on chromosome 6.[21,22] This region includes several immunity-related genes and a histone gene cluster relevant to gene expression. It also contains genes involved in brain development, memory, and cognition.[22]

Over the years, associations between CNS infection and psychiatric disorders have been reported, yet it has been difficult to characterize how infections impact psychiatric disorders. Studies concerning childhood exposure to infections in the CNS of bacterial or viral origin are few.[4,5,23] Our data do not replicate the findings of a meta-analysis that showed an increased risk of schizophrenia following CNS infections.[3] When investigating hospitalization for first CNS infection in our cohort, regardless of other types of infections, a similar effect to the one shown in table 2 was found (only 4 more cases were included, results not shown). CNS infections are relatively rare, and we therefore only have a few cases in the present material, which may explain why no association was found. Furthermore, only very severe CNS infections are classified because only neurological symptoms of classic encephalitis would lead to a positive cerebrospinal fluid analysis. Encephalitis is known to cause severe psychiatric symptoms but is also a very rare disease and difficult to classify. A limitation of the present study is therefore that we were unable to distinguish between viral and bacterial CNS infections due to the small number of cases with a CNS infection.

The association shown with a broad range of infections raising the risk of schizophrenia suggests that a common mechanism, possibly one that involves an inflammatory response and the immune system, may be important for the pathogenesis of schizophrenia. Meyer et al[24] suggest that prenatal infection primes the organism for an altered inflammatory response to later inflammatory activators, the latter acting as a second hit. This second hit may take the form of genetic mutation, eg, in interleukin 18, or the form of stress or more direct immune activators, such as infection.[25] Alternatively, the infection could be triggered by or work in synergy with some unknown environmental stimuli that occur before the onset of schizophrenia and are unrelated to prenatal exposure to infection.

It is likely that unmeasured family-level confounders of the relationship between parental infection and schizophrenia in offspring largely overlap with the confounders that affect the relationship between infection and schizophrenia. Adding a history of parental mental illness to the analysis had no substantial influence on our results, which suggests that this established risk factor is not mediated by infection. Validation of the diagnoses in the Psychiatric Central Register indicated that schizophrenia is diagnosed with reasonable accuracy. A study assessing 300 randomly drawn patient case records in the Psychiatric Central Register found that 97.5% of the patients diagnosed with schizophrenia in 2009 fulfilled the diagnostic criteria of the ICD-10.[26]

The major strength of this study is that it is a nationwide cohort study with prospectively collected data and that all individuals were followed from birth until onset of a possible schizophrenia diagnosis. However, this was also a limitation because we only had complete information on those who were born after 1980, and the oldest individuals in our study would hence be 29 years of age. This might have caused the possible effect of hospital contacts with infection to have been underestimated. In support of this possibility speaks that the risk of schizophrenia spectrum disorders after hospital contact for infection was higher in a larger cohort studied by Benros et al[8] than the risk reported in the present study, possibly due to a longer follow-up period.

The categorization of the site of infection was broad and each group could therefore contain important

subgroups that went unnoticed in the present study. The infections studied were based on diagnoses from the hospital register and misclassification cannot be ruled out. Benfield et al[27] reviewed the medical records from 142 admissions for various infectious diseases registered in the Danish National Hospital Register. They found that among cases discharged with an infectious disease, 99% had an infection according to medical charts.

We only had access to records of infection that involved hospital contact. However, most infections do not require hospital contact, and it is therefore entirely possible that rather than reflecting the presence or absence of infection, our data capture instances of clinically severe infection only. In other words, our results might not be generalizable to the type of infection that go untreated or are treated by a general practitioner, which would be milder forms of infections in most cases. This probably also explains why we find a higher risk of developing schizophrenia for bacterial than for viral infections because the former often run a more severe course and are more prone to require hospitalization.

A procedural change in the hospitals took place during the study period: outpatients were also included in the National Hospital Register as from 1995 and onward. This inclusion of outpatients could have caused an under ascertainment bias for the period before 1995. We do not believe that this is the case as an analysis including only inpatients yielded estimates practically identical to the ones presented here. We observed that 38% of all persons in our study had been admitted to a hospital for at least 1 infectious disease during the study period. We cannot exclude the possibility that noninfectious diseases could influence and confound the relationship between infections and schizophrenia.

Conclusion

An increased risk of schizophrenia was detected after a hospital contact with infection, especially in relation to hepatitis and genital infections, but all sites of infections increased the risk for schizophrenia. Bacterial infection was found to be the type of infection associated with the highest risk of schizophrenia. Future studies that can establish more explicit links between specific infectious agents and schizophrenia may provide pathways toward prevention.

Supplementary Material

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

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