Exposure to Prenatal and Childhood Infections and the Risk of Schizophrenia

Suggestions From a Study of Sibship Characteristics and Influenza Prevalence

Tine Westergaard, MD; Preben B. Mortensen, MD, PhD; Carsten B. Pedersen, MSc; Jan Wohlfahrt, MSc; Mads Melbye, MD, DMSc

Background: It has been proposed that infections, perhaps prenatal exposure to the influenza virus, might increase the risk of schizophrenia. To address this hypothesis, we studied the possible influence on schizophrenia risk of sibship characteristics and ecological influenza prevalence data. Birth order and influenza prevalence were used as proxy measures for exposure to prenatal infection, and sibship size and interval to siblings were used as proxy measures for exposure to common childhood infections.

Methods: We established a population-based cohort of 1,746,366 persons whose mothers were Danish-born women born since 1935 by using data from the Civil Registration System. Schizophrenia in cohort members (n = 2,669) and their parents was identified by linkage with the Danish Psychiatric Case Register. Birth order, sibship size, and interval to siblings were calculated for each cohort member based on person-identifiable information on all siblings. The number of notifications of influenza per month in Denmark was obtained from the National Board of Health and Statens Serum Institut.

Results: There was no association between birth order and schizophrenia risk or between schizophrenia risk and influenza prevalence during any month of prenatal life. Coming from a large sibship was associated with an increased schizophrenia risk. The relative risks were 1.26 (95% confidence interval [CI], 1.11-1.44) and 1.46 (95% CI, 1.22-1.75) for sibships of 4 and 5 or more, respectively, vs a sibship of 2. Short interval (<2 years) to the nearest older sibling and nearest younger sibling was associated with a risk of 1.22 (95% CI, 1.05-1.38) and 1.15 (95% CI, 1.03-1.28), respectively, compared with longer intervals.

Conclusions: Our findings do not support the hypothesis that schizophrenia is associated with prenatal exposure to common infections or influenza. However, they are compatible with the hypothesis that environmental exposure, perhaps to common infections in childhood, may be a risk factor, although other explanations are also possible.

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Many have hypothesized that prenatal exposure to infectious agents may increase the risk of schizophrenia. If such an association exists, the risk of schizophrenia might increase with the number of older siblings a child has (ie, birth order). This rationale is based on findings from several studies that the risk of a large variety of common infections is likely to increase with the number of children in the family. Thus, the more siblings a person has while in utero, the more likely that a sibling would introduce common infections into the family and thereby increase the risk of maternal infection. An association between birth order and the risk of schizophrenia was reported in a study by Sham et al, who in particular found that the risk was increased in subjects with siblings who were 3 to 4 years older. However, results from studies on family structure have been inconsistent, which may be explained in part by the methods used. Lack of appropriate reference groups has been a major concern in many of these studies, particularly in studies that lacked an actual control group but instead generated an internal comparison group based on the sibship constellations of cases only. Such a procedure may introduce serious bias because of changes in birth rate and family size over time.

The influenza virus is an infectious agent that has received much attention as a possible risk factor for schizophrenia. In particular, an association between in utero exposure to influenza during the second trimester and subsequent risk of schizophrenia has been suggested. However, although many studies have reported on this possible association, the methods used...
MATERIALS AND METHODS

COHORT

Data from the Civil Registration System were used to generate a complete sibship database for persons born to Danish-born women. All liveborn children and new residents of Denmark are recorded in the Civil Registration System and assigned a unique personal identification number.\(^4\) Individual information is kept under this identification number in all national registers, enabling secure linkage of information between registers. The registration system also includes person-identifiable information on parents and offspring of individuals as well as information on date of birth, sex, place of birth, and continuously updated information on vital status. We established a population-based sibship database by extracting data on all woman born in Denmark on April 1, 1935, or later and all their offspring who were alive on April 1, 1968, or born between that date and December 31, 1988. The offspring constituted the study cohort, which was similar to that of a previous study.\(^2\)

IDENTIFICATION OF CASES AND PARENTS WITH SCHIZOPHRENIA

Members of the study cohort and their parents were linked with the Danish Psychiatric Case Register. The Danish Psychiatric Case Register is a national register that has been computerized since April 1, 1969. It contains data on all admissions to Danish psychiatric inpatient facilities.\(^4\) No private facilities exist, and there is no fee for psychiatric inpatient treatment in Denmark. The diagnostic system used during the study period was the International Classification of Diseases, Eighth Revision; persons with schizophrenia were identified under International Classification of Diseases, Eighth Revision, code 295.

SIBSHIP CHARACTERISTICS

Using the complete person-identifiable information on all cohort members, we calculated their birth order, sibship size, and interval to nearest older and younger siblings. Birth order was calculated as 1 plus the number of children born to the same mother who were alive at the child’s birth. Sibship size was defined as birth order plus the number of liveborn children who had been born to the mother after the child’s birth and was calculated as a time-dependent variable.

INFLUENZA REGISTRATIONS

Monthly registrations of the number of mandatorily reported cases of influenza in Denmark were obtained from the National Board of Health for the period from 1950 through 1979 and from Statens Serum Institut from 1980 through 1988. The size of the Danish population per year was obtained from Statistics Denmark, Copenhagen.

have varied considerably and the results have been inconsistent. Thus, while several ecological studies have reported an association between influenza epidemics in the population during fetal life and the risk of schizophrenia,\(^2\)\(^3\)\(^\text{0}\) others, including 2 studies that obtained individual information on maternal influenza infection during fetal life,\(^\text{31}\)\(^\text{32}\) found no support for such an association.\(^\text{33}\)\(^\text{38}\)

While most attention has focused on prenatal exposure to infection as a risk factor for schizophrenia, some authors have also suggested that infection in childhood may be important.\(^\text{39}\)\(^\text{40}\) Coming from a large sibship\(^\text{42}\) and
having a short interval to siblings\textsuperscript{2} is likely to increase the risk of common infections in childhood and could potentially be associated with an increased schizophrenia risk. Because birth order, sibship size, and age interval between siblings are highly correlated, we studied these factors together to estimate their possible independent effects and to attempt to distinguish between the hypotheses of a possible influence of prenatal and childhood exposure on schizophrenia risk.

In the present study, we used a large, population-based cohort design to address these hypotheses. Specifically, we studied the possible influence on schizophrenia risk of birth order, sibship size, interval between siblings, and influenza prevalence in the population during fetal life.

**RESULTS**

Overall, 2669 cohort members (1857 males and 812 females) developed schizophrenia during the 24,933,115 person-years of follow-up. Thirty-five cases (1.3%) were aged 5 to 14 years at diagnosis, 635 (24%) were 15 to 19 years, 1152 (43%) were 20 to 24 years, 659 (25%) were 25 to 29 years, 170 (6%) were 30 to 34 years, and 18 (<1%) were 35 years or older. Overall, 27 cases (1%) were born from 1950 to 1954, 378 (14%) from 1955 to 1959, 938 (35%) from 1960 to 1964, 916 (34%) from 1965 to 1969, 379 (14%) from 1970 to 1974, and 31 (1%) from 1975 to 1984. Fifty-nine patients had at least 1 sibling with schizophrenia at the time of their diagnosis.

<table>
<thead>
<tr>
<th>SIBSHIIP CHARACTERISTICS</th>
</tr>
</thead>
</table>

Table 1. Relative Risk (RR) of Developing Schizophrenia According to Sibship Characteristics in a Population-Based Cohort of 1.7 Million Persons Where 2669 Developed Schizophrenia\textsuperscript{*}

<table>
<thead>
<tr>
<th>Cases, No.</th>
<th>Person-years</th>
<th>RR\textsuperscript{†} (95% CI)</th>
<th>P</th>
<th>RR\textsuperscript{‡} (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth order</td>
<td>1513</td>
<td>12,640,153</td>
<td>1</td>
<td>1</td>
<td>1.26 (0.95-1.67)</td>
</tr>
<tr>
<td>2</td>
<td>244</td>
<td>2,179,111</td>
<td>1.09 (0.98-1.21)</td>
<td>.34</td>
<td>1.06 (0.97-1.17)</td>
</tr>
<tr>
<td>3</td>
<td>1045</td>
<td>11,670,223</td>
<td>1.08 (0.98-1.19)</td>
<td>.34</td>
<td>1.06 (0.97-1.17)</td>
</tr>
<tr>
<td>4+</td>
<td>992,294</td>
<td>1.39 (1.18-1.64)</td>
<td>.001</td>
<td>1.26 (1.11-1.44)</td>
<td>.001</td>
</tr>
<tr>
<td>Sibship size</td>
<td>1</td>
<td>315</td>
<td>2,325,907</td>
<td>1.08 (0.96-1.22)</td>
<td>.001</td>
</tr>
<tr>
<td>2</td>
<td>182</td>
<td>2,420,572</td>
<td>0.87 (0.71-1.07)</td>
<td>.001</td>
<td>1.07 (0.98-1.17)</td>
</tr>
<tr>
<td>3</td>
<td>116</td>
<td>1,426,823</td>
<td>0.83 (0.66-1.04)</td>
<td>.001</td>
<td>0.80 (0.69-1.06)</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>826,954</td>
<td>0.76 (0.57-1.01)</td>
<td>.001</td>
<td>0.75 (0.64-0.90)</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>1,429,507</td>
<td>0.72 (0.55-0.94)</td>
<td>.001</td>
<td>0.75 (0.58-0.98)</td>
</tr>
<tr>
<td>Interval to nearest older sibling, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No older siblings</td>
<td>1513</td>
<td>12,640,153</td>
<td>1</td>
<td>1</td>
<td>1.26 (0.95-1.67)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>412</td>
<td>2,881,698</td>
<td>1.08 (0.98-1.19)</td>
<td>.34</td>
<td>1.06 (0.97-1.17)</td>
</tr>
<tr>
<td>2 to &lt;3</td>
<td>315</td>
<td>2,325,907</td>
<td>1.08 (0.96-1.22)</td>
<td>.34</td>
<td>1.06 (0.97-1.17)</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td>182</td>
<td>2,420,572</td>
<td>0.87 (0.71-1.07)</td>
<td>.001</td>
<td>1.07 (0.98-1.17)</td>
</tr>
<tr>
<td>4 to &lt;5</td>
<td>116</td>
<td>1,426,823</td>
<td>0.83 (0.66-1.04)</td>
<td>.001</td>
<td>0.80 (0.69-1.06)</td>
</tr>
<tr>
<td>5 to &lt;6</td>
<td>58</td>
<td>826,954</td>
<td>0.76 (0.57-1.01)</td>
<td>.001</td>
<td>0.75 (0.58-0.98)</td>
</tr>
<tr>
<td>6+</td>
<td>73</td>
<td>1,429,507</td>
<td>0.72 (0.55-0.94)</td>
<td>.001</td>
<td>0.75 (0.58-0.98)</td>
</tr>
<tr>
<td>Interval to nearest younger sibling, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No younger siblings</td>
<td>839</td>
<td>10,071,352</td>
<td>1</td>
<td>1</td>
<td>1.26 (0.95-1.67)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>477</td>
<td>3,060,079</td>
<td>1</td>
<td>1</td>
<td>1.26 (0.95-1.67)</td>
</tr>
<tr>
<td>2 to &lt;3</td>
<td>437</td>
<td>3,677,571</td>
<td>0.88 (0.77-1.00)</td>
<td>.001</td>
<td>0.91 (0.80-1.04)</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td>290</td>
<td>2,940,681</td>
<td>0.76 (0.66-0.88)</td>
<td>.001</td>
<td>0.89 (0.78-1.02)</td>
</tr>
<tr>
<td>4 to &lt;5</td>
<td>185</td>
<td>1,904,630</td>
<td>0.76 (0.64-0.90)</td>
<td>.001</td>
<td>0.80 (0.67-0.95)</td>
</tr>
<tr>
<td>5 to &lt;6</td>
<td>114</td>
<td>1,183,860</td>
<td>0.74 (0.60-0.90)</td>
<td>.001</td>
<td>0.77 (0.63-0.95)</td>
</tr>
<tr>
<td>6+</td>
<td>327</td>
<td>2,095,143</td>
<td>0.93 (0.81-1.08)</td>
<td>.001</td>
<td>0.98 (0.84-1.13)</td>
</tr>
</tbody>
</table>

\textsuperscript{*} CI indicates confidence interval.

\textsuperscript{†} Adjusted for age and the interaction with sex, calendar period, seasonality of birth, urbanization of place of birth, schizophrenia in parents, and age of mother and father at birth of the child.

\textsuperscript{‡} Adjusted for the same covariates as RR\textsuperscript{1} as well as birth order and sibship size.

\textsuperscript{§} Test for heterogeneity including only persons with older siblings.

\textsuperscript{\|} Test for heterogeneity including only persons with younger siblings.

**SIBSHIIP CHARACTERISTICS**

There was no association between birth order and schizophrenia risk (Table 1), while there was a significant association between sibship size and schizophrenia risk (P < .001). Coming from a sibship size of 4 or 5 or more increased the risk compared with a sibship size of 2 (RR, 1.26 [95% CI, 1.11-1.44] and RR, 1.46 [95% CI, 1.22-1.75], respectively). The risk of schizophrenia for combinations of birth order and sibship size is illustrated in Table 2. The table shows that, for a given birth order, the risk of schizophrenia generally increased with increasing sibship size, while for a given sibship size the birth order estimates remained fairly stable. There was no interaction between birth order and sex or between sibship size and sex. Adjustment for schizophrenia in siblings or omission of adjustment for seasonality had negligible effects on the estimates in Tables 1 and 2.

A short interval to the nearest older sibling and a short interval to the nearest younger sibling were also associated with an increased risk of schizophrenia after adjustment for birth order and sibship size (Table 1). The RRs for schizophrenia were 1.22 (95% CI, 1.07-1.38) for
an interval of less than 2 years vs 2 years or more to the nearest older sibling and 1.15 (95% CI, 1.03-1.28) for an interval of less than 2 years vs 2 years or more to the nearest younger sibling. Adjustment for interval to nearest older sibling and/or nearest younger sibling had only a minor effect on the risk estimates associated with birth order and sibship size for persons with siblings.

The impact of large sibship size and short intervals between siblings on the population level was evaluated by population-attributable risks. It was estimated that the fraction of persons with schizophrenia in the population would be reduced by 5.8% if the risk for persons with large sibship size (3, 4, or 5+) could be reduced to the risk of persons with siblings 3 to 4 years older. These analyses did not support such an association. Overall, we found no association between birth order and risk of schizophrenia or between influenza prevalence during fetal life and schizophrenia risk. Thus, our study does not support the hypothesis that in utero exposure to influenza or other common infections may increase the risk of developing schizophrenia. Separate analyses were performed that particularly addressed the possible association between birth order, interval to siblings, sibship size, and the risk of schizophrenia. This design clearly reduces the risk of selection bias and avoids problems with inappropriate reference groups, which have been of concern in previous studies on family structure. Furthermore, we were able to adjust the analyses for schizophrenia in parents and siblings and other potential confounders, such as maternal age, degree of urbanization, and seasonality of birth.

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To our knowledge, the present study is the first to use a population-based cohort design to address the possible association between birth order, interval to siblings, sibship size, and the risk of schizophrenia. This design clearly reduces the risk of selection bias and avoids problems with inappropriate reference groups, which have been of concern in previous studies on family structure. Furthermore, we were able to adjust the analyses for schizophrenia in parents and siblings and other potential confounders, such as maternal age, degree of urbanization, and seasonality of birth.

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This hypothesis, assuming that the risk of transmission of common infections between children is likely to increase the closer they are in age.

However, although childhood infection may explain our findings, sibship characteristics are only proxy measures for exposure to infections. Other physical factors or particular psychological or psychosocial factors that may be associated with such sibship constellations could also in theory explain our findings. Large sibship sizes have in some cultures been associated with low socioeconomic status. However, a large population-based study from Denmark found that what seemed to be an association between low socioeconomic status and large sibships in large part could be explained by the degree of urbanization. A factor that we were able to adjust for in our analyses. Religious beliefs and ethnicity are other factors that have been associated with sibship size. However, all cohort members had mothers born in Denmark, a country composed mainly of Protestants or nonreligious residents and with relatively few immigrants.

The finding of an increased risk of schizophrenia associated with a short interval (<2 years) to the nearest older sibling could also suggest that nutritional deficiency during fetal brain development is involved in the etiology of schizophrenia in some cases. Folate deficiency has been associated with neural tube defects; furthermore, this neurodevelopmental disorder has been associated with short interval to the previous pregnancy. In addition, prenatal famine has been associated with both neural tube defects and schizophrenia. If a link between short pregnancy interval, nutritional deficiency, and schizophrenia exists, the association would most likely be strongest for very short intervals. However, the RRs of schizophrenia for persons with an interval of less than 1 year to their nearest older sibling (RR, 0.87 [95% CI, 0.58-1.30]) did not differ significantly from the RR associated with an interval of 1 to less than 2 years (reference group), but the estimate was only based on 25 cases. As opposed to other ecological studies on influenza prevalence in the population during fetal life and the possible association with schizophrenia risk, we were able to take into account the actual person-years at risk in the population developing schizophrenia and to adjust for several potential confounders, and we are confident that we included only incident cases of schizophrenia in the study. There have been 3 previous ecological studies from Denmark on the same topic. Barr et al24,26,30 studied births from 1911 through 1950 in Denmark and reported an association between schizophrenia risk and relatively high levels of influenza exposure for the season during the sixth month of gestation. However, a larger study by Adams et al26 that included the birth cohorts studied by Barr et al26 (birth cohorts 1911-1965) and used more suitable models found no consistent association between fetal exposure to influenza and schizophrenia risk.

Takei et al30 studied births in Denmark from 1915 to 1970, but in contrast to Barr et al24 and Adams et al,26 they entered the influenza notifications during a month as a continuous variable into their model. They found that the risk of schizophrenia increased, with an RR of 1.10 (95% CI, 1.00-1.21) per 100 000 notifications of influenza 4 months prior of birth. We performed an additional analysis in which we analyzed our data in exactly the same way as Takei et al had done (data not shown), but we again found no association (RR, 1.00). Theoretically, the differences between our findings could be caused by an effect of fetal exposure to influenza in the older birth cohorts that is not present in more recent times, or the association may be restricted to those in whom schizophrenia develops at an older age, since our study only included young adults. Alternatively, the association found by Takei et al could be the result of multiple testing or the presence of outliers in the older data. A model in which the exposure is entered as a continuous variable is particularly vulnerable to outliers. However, irrespective of which of the above explanations accounts for the differing findings, our data do not support a general effect of influenza prevalence during fetal life on schizophrenia risk.

CONCLUSIONS

We found no association between birth order or influenza prevalence during fetal life and the risk of schizo-
REFERENCES


8. Sham PC, MacLean CJ, Kendell RE.Msp. 1969:1;659-678.


