

# Exposure to Prenatal and Childhood Infections and the Risk of Schizophrenia

## Suggestions From a Study of Sibship Characteristics and Influenza Prevalence

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**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 ( $n = 2669$ ) 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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**M**ANY 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.<sup>1-7</sup> 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,<sup>8</sup> 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,<sup>9-17</sup> 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.<sup>18-21</sup>

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.<sup>22</sup> 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.<sup>41</sup> 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 women 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.<sup>42</sup>

### 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.<sup>43</sup> 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.

### DATA ANALYSIS

Overall, the study cohort consisted of 1 746 366 persons who were followed up for a diagnosis of schizophrenia from their fifth birthday or April 1, 1970, whichever came last, until the first day of the first admission for which the discharge diagnosis was schizophrenia (the onset date), the date of death, the date of emigration, or December 31, 1993, whichever came first. Poisson regression models were used to estimate the possible effect on schizophrenia risk of birth order, sibship size, interval to the nearest older and younger siblings, and influenza prevalence during fetal life.<sup>44</sup> The analyses were performed using the SAS GENMOD procedure.<sup>45</sup> Ratios of incidence rates were used as a measure of the relative risk (RR). The *P* values were based on 2-tailed likelihood ratio tests, and 95% confidence intervals (CIs) were calculated using the Wald test.

All RRs were adjusted for age and the interaction with sex, calendar period, month of birth, degree of urbanization of place of birth, maternal and paternal age at birth of the child, and schizophrenia in the mother and/or father. Selection of these adjustments was based on a previous study<sup>42</sup> and was made to account for a possible confounding effect of these factors. Month of birth (seasonality) was described using a sine function that estimated both the amplitude and the time peak.<sup>42</sup> Parents were registered as being affected with schizophrenia if they had ever been admitted with this diagnosis. For categorical variables, the category with the largest number of cases was chosen as the reference.

The possible association between schizophrenia and number of reported influenza cases per population during the month of birth and for each of the 9 months preceding the month of birth was investigated using 2 different models for the exposure. First, risk of exposure to influenza during a month was arbitrarily categorized as low, intermediate, or high, respectively, if the number of influenza notifications was less than 5, 5 to less than 10, or 10 or more per 1000 persons in the population. Second, the number of notifications of influenza per 100 population for a given month was treated as a continuous variable, using a log-linear association between the risk of schizophrenia and the prevalence of influenza. We focused on the prevalence of influenza 3 to 5 months prior to birth, since most studies reporting positive associations found associations between influenza exposure during these months and schizophrenia risk. For both models of exposure to influenza, all 9 months prior to birth and the month of birth were initially included in the model. We then tested whether months 0 through 2 and 6 through 9 prior to birth could be omitted from the model; they could be, leaving months 3, 4, and 5 prior to birth in the model. For each of these months, we then tested whether the 2 other months could be omitted from the model; they could be. Finally, we separately included each of the other 9 months prior to birth and the month of birth in the model.

Population-attributable risks were estimated as described by Bruzzi et al,<sup>46</sup> based on adjusted RRs and the distribution of the exposure among cases.

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,<sup>22-30</sup> others, including 2 studies that obtained individual information on maternal influenza

infection during fetal life,<sup>31,32</sup> found no support for such an association.<sup>33-38</sup>

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.<sup>39,40</sup> Coming from a large sibship<sup>1-7</sup> and

**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\***

	Cases, No.	Person-years	RR <sub>1</sub> † (95% CI)	P	RR <sub>2</sub> ‡ (95% CI)	P
<b>Birth order</b>						
1	1513	12 640 153	1	.34	1	.21
2	847	8 630 609	1.08 (0.99-1.18)		1.06 (0.97-1.17)	
3	243	2 814 978	1.09 (0.94-1.26)		0.98 (0.84-1.15)	
4+	66	847 374	1.09 (0.84-1.41)		0.83 (0.63-1.11)	
<b>Sibship size</b>						
1	244	2 179 111	1.10 (0.96-1.27)	<.001	1.13 (0.98-1.31)	<.001
2	1045	11 670 223	1		1	
3	845	7 562 496	1.06 (0.97-1.17)		1.07 (0.97-1.18)	
4	362	2 528 991	1.23 (1.09-1.39)		1.26 (1.11-1.44)	
5+	173	992 294	1.39 (1.18-1.64)		1.46 (1.22-1.75)	
<b>Interval to nearest older sibling, y</b>						
No older siblings	1513	12 640 153	0.80 (0.72-0.90)	.006§	...	.03§
<2	412	2 881 698	1		1	
2 to <3	315	3 235 907	0.84 (0.73-0.98)		0.86 (0.74-1.00)	
3 to <4	182	2 420 072	0.73 (0.61-0.87)		0.75 (0.63-0.90)	
4 to <5	116	1 462 823	0.83 (0.67-1.03)		0.87 (0.70-1.07)	
5 to <6	58	862 954	0.76 (0.58-1.01)		0.80 (0.60-1.06)	
≥6	73	1 429 507	0.72 (0.55-0.94)		0.75 (0.58-0.98)	
<b>Interval to nearest younger sibling, y</b>						
No younger siblings	839	10 071 352	0.85 (0.75-0.96)	<.001	...	.005
<2	477	3 060 079	1		1	
2 to <3	437	3 677 571	0.88 (0.77-1.00)		0.91 (0.80-1.04)	
3 to <4	290	2 940 681	0.76 (0.66-0.88)		0.80 (0.69-0.93)	
4 to <5	185	1 904 430	0.76 (0.64-0.90)		0.80 (0.67-0.95)	
5 to <6	114	1 183 860	0.74 (0.60-0.90)		0.77 (0.63-0.95)	
≥6	327	2 095 143	0.93 (0.81-1.08)		0.98 (0.84-1.13)	

\*CI indicates confidence interval.

†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.

‡Adjusted for the same covariates as RR<sub>1</sub> as well as birth order and sibship size.

§Test for heterogeneity including only persons with older siblings.

||Test for heterogeneity including only persons with younger siblings.

having a short interval to siblings<sup>7</sup> 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.

## SIBSHIP 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

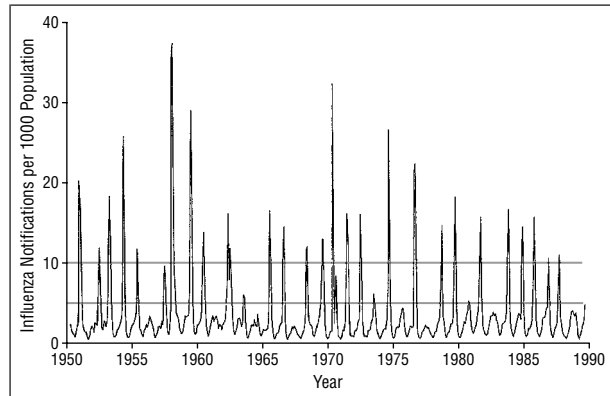
**Table 2. Relative Risk of Schizophrenia According to Combinations of Birth Order and Sibship Size\***

Birth Order‡	Sibship Size, Relative Risk (95% CI)†				
	1	2	3	4	5+
1	1.12 (0.96-1.30)	1	1.03 (0.91-1.16)	1.27 (1.06-1.52)	1.58 (1.22-2.06)
2		1.04 (0.91-1.19)	1.18 (1.03-1.35)	1.26 (1.02-1.55)	1.48 (1.09-2.00)
3			1.03 (0.85-1.25)	1.20 (0.93-1.54)	1.54 (1.10-2.16)
4+				1.25 (0.89-1.76)	0.99 (0.68-1.45)

\*CI indicates confidence interval.

†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.

‡Test for interaction between birth order and sibship size:  $P = .58$ .



The monthly influenza prevalence in Denmark from 1950 to 1988.

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 a sibship size of 2. The population-attributable risks for short intervals (<2 years) to the nearest older and younger siblings were 2.8% and 2.3%, respectively. Overall, these sibship characteristics accounted for 10.3% of the cases of schizophrenia in the population.

## INFLUENZA

The monthly prevalence of influenza in the population from 1950 to 1988 is shown in the **Figure**. There was no association between schizophrenia risk and the prevalence of influenza 3, 4, or 5 months prior to the month of birth; during any other month prior to birth; or during the month of birth. The results for influenza exposure 3, 4, and 5 months prior to birth analyzed as a categorical variable are shown in **Table 3**. The results when analyzed as a continuous variable were as follows: the relative increases in schizophrenia risk per percentage of

the population notified with influenza 3, 4, and 5 months prior to the month of birth were 0.96 (95% CI, 0.88-1.04), 1.00 (95% CI, 0.92-1.09), and 1.01 (95% CI, 0.93-1.10), respectively. Including all 3 months in the model at the same time instead of each month separately had a negligible effect on the results.

There was no interaction between sex and influenza exposure or between birth order and influenza exposure in either model. Adjustment for seasonality of birth in 12 categories instead of by a sine function or omission of adjustment for seasonality did not affect the result. Adjusting for sibship size or omission of adjustment for degree of urbanization of the place of birth also had no effect on the risk estimates.

## COMMENT

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.

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 suggestion made by Sham et al<sup>8</sup> of increased risk associated with having siblings 3 to 4 years older. These analyses did not support such an association.

Our finding of an increased risk of schizophrenia associated with having many siblings, independent of birth order and short interval to the nearest older or younger sibling, is suggestive of environmental factors being involved in the etiology.<sup>47,48</sup> The association between sibship size and schizophrenia risk could be indicative of a possible association between schizophrenia and exposure to infections in childhood.<sup>39,40</sup> In addition, the increased risk of schizophrenia associated with short in-

**Table 3. Relative Risk (RR) of Schizophrenia According to the Prevalence of Influenza 3, 4, and 5 Months Prior to the Month of Birth\***

No. of Months Prior to Birth†	Influenza Prevalence‡	Cases, No.	Person-years	RR (95% CI)§	P
3	Low	2198	20 586 580	1	.36
	Intermediate	225	1 954 900	0.95 (0.82-1.10)	
	High	246	2 391 635	0.91 (0.79-1.04)	
4	Low	2198	20 626 653	1	.92
	Intermediate	214	1 923 135	0.98 (0.84-1.14)	
	High	257	2 383 326	1.01 (0.88-1.17)	
5	Low	2208	20 662 056	1	.91
	Intermediate	217	1 925 463	1.03 (0.89-1.20)	
	High	244	2 345 595	1.01 (0.88-1.17)	

\*CI indicates confidence interval.

†Each month was included in the model separately.

‡The prevalence of influenza during the month was categorized as low, intermediate, or high for influenza notifications of less than 5, 5 to less than 10, and 10 or more per 1000 population, respectively.

§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.

tervals to the nearest older and younger siblings supports 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.<sup>49</sup> 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,<sup>50</sup> 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.<sup>49</sup> 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<sup>51</sup>; furthermore, this neurodevelopmental disorder has been associated with short interval to the previous pregnancy.<sup>52</sup> In addition, prenatal famine has been associated with both neural tube defects and schizophrenia.<sup>53</sup> 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.<sup>24,26,30</sup> Barr et al<sup>24</sup> 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 al<sup>26</sup> that included the birth cohorts studied by Barr et al<sup>24</sup> (birth cohorts 1911-1965) and used more suitable models found no consistent association between fetal exposure to influenza and schizophrenia risk.

Takei et al<sup>30</sup> studied births in Denmark from 1915 to 1970, but in contrast to Barr et al<sup>24</sup> and Adams et al,<sup>26</sup> 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-

phrenia. Thus, our study does not support an association between schizophrenia risk and prenatal exposure to the influenza virus or other common infections. The finding of an association between schizophrenia risk, large sibship size, and short interval to the nearest older sibling as well as the nearest younger sibling is compatible with the hypothesis that environmental exposure, perhaps to common infections in childhood, may be a risk factor for schizophrenia, although other explanations may also be possible.

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