

## EFFECTS OF FAMILY HISTORY AND PLACE AND SEASON OF BIRTH ON THE RISK OF SCHIZOPHRENIA

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## ABSTRACT

**Background** Although a family history of schizophrenia is the best-established risk factor for schizophrenia, environmental factors such as the place and season of birth may also be important.

**Methods** Using data from the Civil Registration System in Denmark, we established a population-based cohort of 1.75 million persons whose mothers were Danish women born between 1935 and 1978. We linked this cohort to the Danish Psychiatric Central Register and identified 2669 cases of schizophrenia among cohort members and additional cases among their parents.

**Results** The respective relative risks of schizophrenia for persons with a mother, father, or sibling who had schizophrenia were 9.31 (95 percent confidence interval, 7.24 to 11.96), 7.20 (95 percent confidence interval, 5.10 to 10.16), and 6.99 (95 percent confidence interval, 5.38 to 9.09), as compared with persons with no affected parents or siblings. The risk of schizophrenia was associated with the degree of urbanization of the place of birth (relative risk for the capital vs. rural areas, 2.40; 95 percent confidence interval, 2.13 to 2.70). The risk was also significantly associated with the season of birth; it was highest for births in February and March and lowest for births in August and September. The population attributable risk was 5.5 percent for a history of schizophrenia in a parent or sibling, 34.6 percent for urban place of birth, and 10.5 percent for the season of birth.

**Conclusions** Although a history of schizophrenia in a parent or sibling is associated with the highest relative risk of having the disease, the place and season of birth account for many more cases on a population basis. (N Engl J Med 1999;340:603-8.)

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**T**WIN and adoption studies strongly suggest that genetic transmission accounts for most of the familial aggregation of schizophrenia.<sup>1,2</sup> However, little is known about the contribution of familial aggregation to the occurrence of schizophrenia in the general population and the mode of inheritance of the disease. Environmental risk factors have also been suggested, including maternal obstetrical complications,<sup>3,4</sup> influenza infection during the mother's pregnancy,<sup>5</sup> season of

birth,<sup>6</sup> urban place of birth or upbringing,<sup>7</sup> and low social class.<sup>8</sup>

Questions about the relative importance of genetic and environmental risk factors for mental disorders, as well as their possible interaction, remain to be answered.<sup>9</sup> Such questions would ideally be addressed by large studies of incident cases of schizophrenia in representative samples of the general population. Population-based studies of family history as a risk factor for schizophrenia<sup>10</sup> have been based on prevalence rather than incidence and have not evaluated or quantified the relative contributions of, or interactions between, genetic and environmental risk factors for schizophrenia.

We used Danish population-based registries to study the effects of family history, nonfamilial risk factors, and their interactions on the risk of schizophrenia.

## METHODS

The study was approved by the Danish Scientific Ethics Committees. All live-born children and new residents in Denmark are assigned a unique personal identification number, and information about them is recorded in the Civil Registration System.<sup>11</sup> Individual information is kept under the personal identification number in all national registers, thus ensuring accurate linkage of information between registers without the necessity to reveal a person's identity. We used data from the Danish Civil Registration System to obtain a large and representative set of data on children born to Danish women. As described in detail elsewhere,<sup>12</sup> we identified all women born in Denmark between April 1, 1935, and March 31, 1978, and all their offspring (2,043,492 people) who were alive on April 1, 1968, or who were born between that date and December 31, 1993. The identity of the father was available for 1,996,726 (97.7 percent) of the offspring. The offspring constituted the study population. A person could be included both as an offspring and as a mother or a father.

The study population (mothers, fathers, and offspring) were then linked with the Danish Psychiatric Central Register. The Danish Psychiatric Central Register has been computerized since April 1, 1969.<sup>13</sup> It contains data on all admissions to Danish psychiatric inpatient facilities and at present includes data on approximately 340,000 persons and 1.4 million admissions. There are no private facilities for inpatient psychiatric treatment in Denmark.

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The diagnostic system used during the study period was the *International Classification of Diseases, 8th Revision* (ICD-8),<sup>14</sup> and the diagnosis of interest was schizophrenia (ICD-8 code 295). In ICD-8 schizophrenia is defined by prototypic descriptions of symptoms, such as bizarre delusions, delusions of control, abnormal affect, autism, hallucinations, and disorganized thinking,<sup>15</sup> whereas in the third edition, revised, and fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R and DSM-IV, respectively) and the *International Classification of Diseases, 10th Revision* (ICD-10), most of the same symptoms have been transformed into explicit criteria. However, in a Danish register sample of 53 patients with schizophrenia as defined by ICD-8, 48 patients (91 percent) also met the criteria for schizophrenia as defined by DSM-III-R,<sup>16</sup> suggesting that the vast majority of persons whom we identified as having schizophrenia would meet the DSM-III-R criteria for the disorder.

Overall, 1.75 million offspring were followed from their fifth birthdays or April 1, 1970, whichever came later, until the date of onset of schizophrenia, the date of death, the date of emigration, or December 31, 1993, whichever came first. Offspring were recorded as having schizophrenia if they had been admitted to a psychiatric hospital with a diagnosis of the disorder. The date of onset was defined as the first day of the first admission leading to a diagnosis of schizophrenia. Parents were recorded as having schizophrenia if they had ever been admitted with this diagnosis. The register was assumed to be almost 100 percent complete during the study period.<sup>13</sup>

The relative risk of schizophrenia among the offspring was estimated by log-linear Poisson regression<sup>17</sup> with the SAS GENMOD procedure.<sup>18</sup> All relative risks were adjusted for age, sex, interactions between age and sex, calendar period when schizophrenia was diagnosed (1970 to 1974, 1975 to 1979, 1980 to 1984, 1985 to 1989, or 1990 to 1993), and age of the mother and father at the time of the child's birth. Age, calendar period of diagnosis, and schizophrenia in a sibling were treated as time-dependent variables, whereas schizophrenia in a parent was treated as a variable that was independent of time. The place of birth was classified according to the degree of urbanization: capital, suburb of the capital, provincial city with more than 100,000 inhabitants, provincial town with more than 10,000 inhabitants, or rural area.

The effect of the month of birth was modeled as a sine function with a period of 12 months and with both the amplitude and the time of the peak risk estimated. The variance of the time of the peak risk and that of the amplitude were calculated by the delta method.<sup>19</sup> The adjusted-score test<sup>20</sup> suggested that the final regression model was not subject to overdispersion. P values were based on two-tailed likelihood-ratio tests, and 95 percent confidence limits were calculated by Wald's test.<sup>21</sup>

The population attributable risk is an estimate of the fraction of the total number of cases of schizophrenia in the population that would not have occurred if the effect of a specific risk factor had been eliminated — that is, if the risk could have been reduced to that of the exposure category with the lowest risk. The estimation was carried out as described by Bruzzi et al.,<sup>22</sup> on the basis of adjusted relative risks and the distribution of exposure in the cases. The population attributable risk for season of birth, a continuous variable, was estimated by using a categorical approach in which the fitted sine function was used to estimate relative risks for the 15th day of each month.

## RESULTS

Table 1 shows the distribution of persons in whom schizophrenia developed and the person-years of exposure to risk in the study population, according to risk factors. Schizophrenia was diagnosed in a total of 1857 sons and 812 daughters during the nearly 25 million person-years of follow-up. Among these patients, 79 had a mother with schizophrenia, 33 had a father with schizophrenia, and 4 had two parents

**TABLE 1.** DISTRIBUTION OF 2669 CASES OF SCHIZOPHRENIA AND 24.9 MILLION PERSON-YEARS AT RISK IN A POPULATION-BASED COHORT OF 1.75 MILLION PEOPLE.

VARIABLE	NO. OF CASES	PERSON-YEARS
Age (yr)		
5–14	35	13,594,827
15–19	635	5,234,270
20–24	1152	3,539,876
25–29	659	1,894,835
30–34	170	602,770
≥35	18	66,536
Sex		
Male	1857	12,831,518
Female	812	12,101,597
Place of birth		
Capital	860	4,256,525
Suburb of capital	233	2,251,541
Provincial city (>100,000 population)	350	3,284,950
Provincial town (>10,000 population)	737	9,047,311
Rural area	400	5,665,501
Greenland	11	47,586
Other countries	74	342,050
Unknown	4	37,651
Family history of schizophrenia		
Parent		
Father affected, mother affected	4	1,067
Father affected, mother not affected	33	44,251
Father not affected, mother affected	64	55,683
Father not affected, mother not affected	2317	24,144,738
Father unknown, mother affected	15	5,494
Father unknown, mother not affected	236	681,881
Sibling		
One or more affected siblings	59	25,534
No affected siblings	2610	24,907,580

with schizophrenia. Fifty-nine patients had at least one sibling with schizophrenia at the time that they received their own diagnosis of the disorder. Overall, there were 52 sibships with 2 affected siblings, 2 sibships with 3 affected siblings, and 1 sibship with 4 affected siblings.

The relative risks associated with the risk factors identified in our study are shown in Table 2. Schizophrenia in a parent or sibling, here referred to as a family history of schizophrenia, was associated with the highest relative risk of having the disease. There was a slight reduction in the estimated risk associated with any specific category of family history after adjustment for a family history of schizophrenia (Table 2, second adjustment). Further adjustment for place and season of birth (the full model) resulted in only a slight additional reduction in the association between family history and schizophrenia (Table 2). In the following discussion, we will refer only to the results of the full model.

The risk of schizophrenia was increased by a history of schizophrenia in the mother (relative risk, 9.31; 95 percent confidence interval, 7.24 to 11.96), the father (relative risk, 7.20; 95 percent confidence

**TABLE 2.** ADJUSTED RELATIVE RISK OF SCHIZOPHRENIA ACCORDING TO FAMILY HISTORY, PLACE OF BIRTH, AND SEASON OF BIRTH.

VARIABLE	RELATIVE RISK (95% CI)*		
	FIRST ADJUSTMENT	SECOND ADJUSTMENT	THIRD ADJUSTMENT (FULL MODEL)
Family history			
Parent			
Father affected, mother affected	65.49 (24.55–174.73)	59.74 (22.39–159.45)	46.90 (17.56–125.26)
Father affected, mother not affected	8.34 (5.91–11.76)	7.97 (5.65–11.24)	7.20 (5.10–10.16)
Father not affected, mother affected	11.33 (8.84–14.53)	10.19 (7.93–13.09)	9.31 (7.24–11.96)
Father not affected, mother not affected†	1.00	1.00	1.00
Father unknown, mother affected	20.99 (12.59–35.00)	17.12 (10.24–28.64)	14.18 (8.48–23.70)
Father unknown, mother not affected	2.48 (2.14–2.88)	2.45 (2.11–2.84)	2.00 (1.72–2.32)
Sibling			
One or more affected siblings	9.04 (6.97–11.72)	7.33 (5.63–9.53)	6.99 (5.38–9.09)
No affected siblings†	1.00	1.00	1.00
Other factors			
Place of birth			
Capital	2.49 (2.21–2.80)	2.49 (2.20–2.80)	2.40 (2.13–2.70)
Suburb of capital	1.64 (1.40–1.93)	1.64 (1.40–1.93)	1.62 (1.37–1.90)
Provincial city (>100,000 population)	1.57 (1.36–1.81)	1.57 (1.36–1.81)	1.57 (1.36–1.81)
Provincial town (>10,000 population)	1.24 (1.10–1.41)	1.24 (1.10–1.41)	1.24 (1.10–1.41)
Rural area†	1.00	1.00	1.00
Greenland	3.71 (2.03–6.75)	3.71 (2.04–6.76)	3.71 (2.04–6.76)
Other countries	3.52 (2.74–4.52)	3.52 (2.73–4.52)	3.45 (2.69–4.44)
Unknown	1.28 (0.48–3.42)	1.26 (0.47–3.39)	1.22 (0.46–3.27)
Season of birth (amplitude of sine function)‡	1.12 (1.06–1.18)	1.11 (1.06–1.18)	1.11 (1.06–1.18)

\*The relative risk was adjusted initially for age–sex interaction, calendar year of diagnosis, and ages of the father and mother (first adjustment) and then for family history or, alternatively, other factors as well (second adjustment). The third adjustment (full model) was for all the variables listed. CI denotes confidence interval.

†This was the reference category.

‡For all three adjustments, the estimated peak of the sine function was at March 6 (95 percent confidence interval, February 6 to April 5).

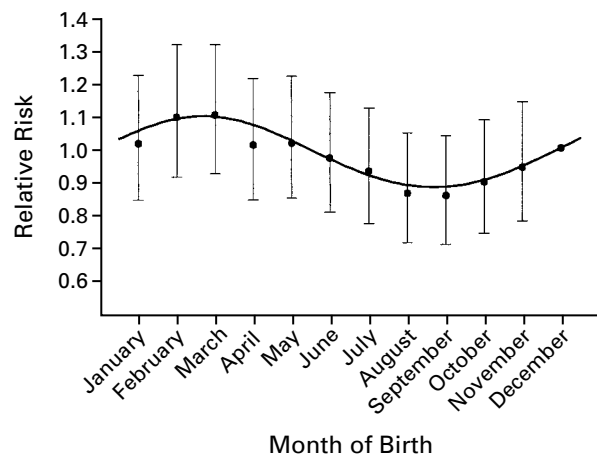
interval, 5.10 to 10.16), or a sibling (relative risk, 6.99; 95 percent confidence interval, 5.38 to 9.09). The risk associated with having a sibling with schizophrenia was not affected by the sex of the sibling, and the risk associated with having a parent with schizophrenia was not significantly affected by which parent had the disease. The relative risk was 46.90 (95 percent confidence interval, 17.56 to 125.26) if both the father and the mother had been hospitalized with schizophrenia, and there was no statistical interaction between the father's status and the mother's status with respect to the disorder. The risk of schizophrenia for persons with unknown fathers and no maternal history of schizophrenia was twice the risk for persons with no parental history of the disorder (the reference group).

Among the other risk factors for schizophrenia, the strongest was an urban place of birth. As compared with persons born in rural areas, those born in the capital (Copenhagen) had a relative risk of 2.40 (95 percent confidence interval, 2.13 to 2.70), those born in provincial cities with more than 100,000 inhabitants or in suburbs of the capital had relative risks of approximately 1.6, and those born in towns with more than 10,000 inhabitants had a rel-

ative risk of 1.24 (95 percent confidence interval, 1.10 to 1.41). The risk of schizophrenia was also increased for children born to Danish mothers in countries other than Denmark (relative risk, 3.45; 95 percent confidence interval, 2.69 to 4.44) or in Greenland (relative risk, 3.71; 95 percent confidence interval, 2.04 to 6.76).

Figure 1 shows the effect of the month of birth on the risk of schizophrenia. The amplitude of the sine function was estimated to be 1.11 (Table 2), which means that the maximal and minimal relative risks associated with the month of birth were 1.11 and 1/1.11, respectively. The time of the peak risk was estimated to be March 6, which means that children born in early March had a risk that was 1.1 times (95 percent confidence interval, 1.06 to 1.18) the risk for those born in early June or early December.

There was no interaction between season of birth and the other variables in the model. There was a weak interaction ( $P=0.03$ ) between the variables for the presence or absence of a family history of schizophrenia and those for place of birth. However, if an urban place of birth is seen as involving exposure to an unknown urban factor, there is no clear trend in the interaction. Thus, it appears that family history



**Figure 1.** Relative Risk of Schizophrenia According to Month of Birth.

The data points and vertical bars show the relative risks and 95 percent confidence intervals, respectively, with the month of birth analyzed as a categorical variable, and the curve shows the relative risk as a fitted sine function of the month of birth. The reference category is December.

**TABLE 3.** POPULATION ATTRIBUTABLE RISK ACCORDING TO FAMILY HISTORY, PLACE OF BIRTH, AND SEASON OF BIRTH.

VARIABLE	POPULATION ATTRIBUTABLE RISK (%)
Schizophrenia in one or both parents	3.8
Schizophrenia in one or more siblings	1.9
Schizophrenia in parent or sibling	5.5
Place of birth	34.6
Season of birth	10.5
Place and season of birth	41.4
All variables listed above	46.6

was more important in association with birth in a suburb of the capital or in a provincial town and less so in association with birth in the capital, a provincial city, or a rural area.

There were no interactions between sex or age and the variables shown in Table 2. Exclusion of the youngest age group (5 to 14 years), in which the risk of schizophrenia was very low, resulted in no changes in the risk estimates or only minor changes (data not shown).

The population attributable risks associated with the risk factors in the full model are shown in Table 3. A family history of schizophrenia accounted for 5.5 percent of the cases of schizophrenia, the season of birth accounted for 10.5 percent, and an urban

place of birth accounted for 34.6 percent. The risk factors in Table 3 are not mutually exclusive, and the estimates of attributable risk are not additive.

## DISCUSSION

Schizophrenia in a parent or sibling was associated with the highest risk of schizophrenia in this study. The estimate of the risk associated with a family history of schizophrenia could have been artificially increased if clinicians were more likely to diagnose the disorder in a person with one or more family members who had the same disorder than in a person with no affected family members. However, our risk estimates were very similar to those in studies that used standardized diagnostic procedures and case-finding methods that were independent of psychiatric treatment.<sup>1,10</sup> Therefore, we do not believe that this potential bias had any substantial effect on our results.

Some studies have reported higher rates of schizophrenia among the relatives of female patients with schizophrenia than among the relatives of male patients with schizophrenia.<sup>23</sup> However, in line with a population-based study reported in 1995,<sup>24</sup> we found no support for such differences. Our finding of an excess number of men with schizophrenia is consistent with the results of other register-based studies.<sup>25</sup> The effects of the risk factors included in our study were identical for men and women.

We found a twofold increase in the risk of schizophrenia among persons with unknown fathers as compared with persons with known fathers without schizophrenia. This difference might be explained by the lower socioeconomic status of the mothers of these offspring or by difficulties in growing up in a family without a father. If the difference was due to a higher proportion of cases of schizophrenia among unknown fathers, at least 16 percent of the fathers of the 46,766 offspring with unknown fathers must have had schizophrenia. Such a large proportion of unknown fathers with schizophrenia is highly unlikely, since it is of the same order of magnitude as the total number of men hospitalized during the study period for schizophrenia in Denmark. We must conclude that there is no strong empirical evidence to support any of these hypotheses, although the finding itself seems to be robust.

The prevalence of schizophrenia is higher in urban areas than in rural areas.<sup>7,26,27</sup> The difference has been ascribed to selective migration from rural to urban areas before the onset of schizophrenia, but this hypothesis does not explain our finding of a higher risk among people born in urban areas. Other possible explanations include increased exposure to infections during pregnancy and childhood because of more crowded living conditions or more perinatal complications in urban areas. Alternatively, one could hypothesize that persons with an unex-

pressed genetic predisposition for schizophrenia are more likely to migrate to urban areas, but a family history of schizophrenia does not explain or affect the urban–rural differences we observed. Furthermore, we estimated that if the risk of schizophrenia for persons born in the capital or its suburbs as compared with the risk for those born elsewhere in Denmark (relative risk, 1.74) could be explained by the presence of undiagnosed schizophrenia in parents, 9.5 percent of the 435,124 children who were born in the capital or its suburbs must have had a parent who transmitted a genetic risk equal to that transmitted by a parent with diagnosed schizophrenia. This proportion seems unrealistically high. Finally, differences in the availability of psychiatric services might explain urban–rural differences. This seems unlikely, however, because distances are small in Denmark, services are free, and place of birth, not place of residence, was the variable studied.

An interesting finding was the highly increased risk of schizophrenia in persons born to Danish women outside Denmark. This increase is probably not due to a tendency for mentally ill parents to leave the country temporarily, since the mothers and fathers of these persons did not have an increased likelihood of having schizophrenia. A possible explanation is the theory proposed by Wessely et al.<sup>28</sup> These authors reported an increased risk of schizophrenia in second-generation black Caribbean immigrants living in London and suggested that it could be explained by maternal exposure to infective agents uncommon in their country of origin.

The effect of season of birth on the risk of schizophrenia was of the expected magnitude and had the expected periods of maximal risk (February and March) and minimal risk (August and September).<sup>6</sup> We replicated a previous finding that there was no interaction between season of birth and family history of schizophrenia.<sup>29</sup> However, we did not replicate a previous finding that the association between winter birth and schizophrenia occurred only among persons born in urban areas.<sup>30</sup> Lewis<sup>31</sup> suggested that an association between the season of birth and schizophrenia is a methodologic artifact due to the so-called age–incidence effect — that is, persons born in January are older than those born later in the year within the same age category and thus have spent more time at risk for schizophrenia. This concern was not relevant to our cohort study, however, since all age-specific person–years were calculated exactly for each person.

There is strong evidence that the most important risk factors in families with more than one affected member are genetic.<sup>32,33</sup> However, the absence of consistent interactions between the family-history variables and the variables that are less likely to be genetically determined means that our results do not support the notion that birth in February or March

and an urban place of birth are less important risk factors in cases in which there is a family history of schizophrenia.

Although a family history of schizophrenia was the strongest risk factor in terms of relative risk, by far the most important factors in terms of attributable risk were the place of birth and the season of birth. Obviously, neither of these factors is relevant as a direct basis for intervention, nor are they plausible in terms of biologically meaningful exposure affecting the human brain. Instead, place and season of birth must be seen as proxy variables for factors that contribute more directly to the risk of schizophrenia. Our estimates of attributable risk do not exclude the possibility that genetic factors are necessary causes of schizophrenia in most or all cases. They do, however, suggest that such factors are not sufficient and that environmental factors are major determinants of schizophrenia.

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