Are the Cause(s) Responsible for Urban-Rural Differences in Schizophrenia Risk Rooted in Families or in Individuals?

Carsten B. Pedersen and Preben Bo Mortensen

From the National Centre for Register-based Research, University of Aarhus, Aarhus, Denmark.

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Many studies have identified urban-rural differences in schizophrenia risk. Hypothetical underlying cause(s) may include toxic exposures, diet, infections, and selective migration. The authors investigated whether the underlying cause(s) responsible for the urban-rural differences were rooted in families or in individuals. Linking data from the Danish Civil Registration System and the Danish Psychiatric Central Register, a population-based cohort of 711,897 people aged 15 years or more was established. Overall, 2,720 persons developed schizophrenia during the period 1970–2001. The authors evaluated whether the nearest older sibling’s place of birth had an independent effect on schizophrenia risk. If the cause(s) responsible for the urban-rural differences are rooted in individuals only, the nearest older sibling’s place of birth should have no independent effect. In this analysis, the nearest older sibling’s place of birth had an independent effect; among persons who lived in a rural area during their first 15 years of life, the relative risk was 1.59 (95% confidence interval: 1.10, 2.30) if their nearest older sibling had been born in the capital area as compared with a rural area. Some of the cause(s) responsible for the urban-rural differences in schizophrenia risk are rooted in families, but some might also be rooted in individuals.

cities; environment; family characteristics; genes; risk factors; schizophrenia; siblings; urbanization

Abbreviations: CI, confidence interval; CRS, Civil Registration System; ICD, International Classification of Diseases.

Editor’s note: An invited commentary on this article appears on page 979.
to distinguish whether urban-rural differences in schizophrenia risk were rooted in families or in individuals. We evaluated the potential association between the individual’s place of birth (and fetal life and upbringing) and the nearest older sibling’s place of birth. The following results were possible: First, the nearest older sibling’s place of birth could have had no independent effect when results were controlled for individual’s place of birth (and fetal life and upbringing). This result would have suggested that the urban-rural differences were linked to the individual’s own urban residence. Second, the nearest older sibling’s place of birth could have had an independent effect when results were controlled for individual’s place of birth (and place of fetal life and upbringing). This result would have suggested that some of the urban-rural differences were linked to the family’s urban residence prior to the individual’s conception (i.e., rooted in the family). Note that individuals’ urban residence covered the period from birth (or conception) onwards, while families’ urban residence also covered the period before the birth (or conception) of the individual.

Factors linked to individuals’ urban residence consisted of environmental factors that operated within families during the individual’s upbringing—that is, individual-specific environmental factors, such as traffic-related exposures. Factors linked to families’ urban residence would consist of genetic and/or environmental factors shared by family members that exerted an influence on families before the individual’s birth and during the individual’s upbringing. The latter might include infections resulting from keeping pets (17, 18), diet, tendency to engage in outdoor activities (19), misuse of cannabis and alcohol (20), maternal lead level during pregnancy (21), or other family-level factors.

MATERIALS AND METHODS

Study population

We used data from the Danish Civil Registration System (CRS) (22) to obtain a large and representative set of data on residents of Denmark aged 15 years or more. The CRS was established in 1968, when all people living in Denmark were registered. Among many other variables, it includes information on CRS number, gender, date of birth, vital status (continuously updated), and the CRS numbers of the parents. The CRS number is used as a personal identifier in all national registers, enabling accurate linkage between registers.

Our study population included all persons born in Denmark during the period 1956–1986 who were alive on their 15th birthday, whose fathers had been born in Denmark, and whose mothers had been born in Denmark after April 1, 1935 (1.51 million people). The latter restriction ensured complete information on all siblings through parental identity (23). Furthermore, to obtain information on older sibling’s place of birth and to avoid bias due to instability in siblings with different parents, which might increase the risk of schizophrenia (24) and might affect place of birth, we restricted our study population to people with at least one older full sibling (711,897 people). Full siblings (hereafter called siblings) were defined as those who had the same mother and father as the index subject.

Assessment of schizophrenia and mental illness in a parent or sibling

The study population and their mothers, fathers, and siblings were linked with the Danish Psychiatric Central Register (25), which was computerized in 1969. The Danish Psychiatric Central Register contains data on all admissions to Danish psychiatric inpatient facilities. It presently includes data on approximately 450,000 persons and 1.6 million admissions. From 1995 onward, information on outpatient visits to Danish psychiatric facilities was included in the register. From 1969 to 1993, the diagnostic system used was the Danish modification of the International Classification of Diseases, Eighth Revision (ICD-8) (26); starting in 1994, the diagnostic system used was that of the International Classification of Diseases, Tenth Revision (ICD-10) (27). Cohort members were classified as having schizophrenia if they had been admitted to a psychiatric hospital or had been under outpatient care with a diagnosis of the disorder (ICD-8 code 295 or ICD-10 code F20). Date of onset was defined as the first day of the first (inpatient or outpatient) contact with the health-care system associated with a diagnosis of schizophrenia. Parents and siblings were categorized hierarchically as having a history of schizophrenia, schizophrenia-like psychoses (ICD-8 codes 297, 298.39, and 301.83 or ICD-10 codes F21–F29), or other mental disorders (any ICD-8 or ICD-10 diagnosis), respectively, if they had been admitted to a psychiatric hospital or had been under outpatient care with one of these diagnoses. The diagnostic categories used were identical to those used in previous studies (1–3, 24). This study was approved by the Danish Data Protection Agency.

Assessment of change of residence and urbanization

Municipalities in Denmark were classified according to degree of urbanization by Statistics Denmark (28), yielding the following categories: the capital area (Copenhagen and its suburbs), provincial areas, and rural areas. For each cohort member, we compiled information on degree of urbanization at the place of birth. For people born in 1971 or later, we also compiled information on the accumulated number of years of residence in each type of urbanization area from birth to the 15th birthday and the number of changes in municipality at various ages (0–3, 4–9, 10–12, and 13–14 years). These variables were identical to those used in previous studies (1, 24), except that in order to simplify the presentation of our findings, we grouped the previous five-level urbanization variable (1, 2, 4) into a three-level variable (3).

Assessment of family’s urban residence prior to individual’s birth

We used the nearest older sibling’s degree of urbanization at the place of birth as a proxy for urbanization of the family’s residence prior to the individual’s birth. We used this
proxy variable because we had information on place of birth for all people born in Denmark but only had information on place of residence from 1971 onwards.

**Study design**

A total of 711,897 people with older full siblings were followed from their 15th birthday or April 1, 1970, whichever came last, to the date of onset of schizophrenia, the date of death, the date of emigration from Denmark, or December 31, 2001, whichever came first.

**Statistical analyses**

The relative risk of schizophrenia was estimated by Poisson regression (29, 30). All relative risks were adjusted for age and its interaction with gender, calendar year, parental age, and history of mental illness in a parent or sibling. Age, calendar year, and history of mental illness in siblings were treated as time-dependent variables (31), whereas all other variables were treated as independent of time. All p values were two-sided and based on likelihood ratio tests, and 95 percent confidence limits were calculated by Wald’s test (31). The adjusted-score test (32) suggested that the regression models were not subject to overdispersion. Because Cox regression is very computer-intensive for large studies, we used Poisson regression as an approximation (33).

Place of upbringing was modeled statistically as the accumulated number of years of residence in the capital area and a provincial area. This means that people who had lived entirely in a rural area during upbringing were chosen as the reference category and that the effect of these two variables measured the effect of exchanging upbringing in a rural area with upbringing in an area with the corresponding degree of urbanization. This method was identical to that used previously (1, 24). We used trends to summarize the risk associated with degree of urbanization; it was entered into the model as a continuous variable, scored as follows: 0, rural area; 0.50, provincial area; 1.00, capital area. Using this scoring, the estimated relative risk measured the effect of birth or residence in the capital area as compared with a rural area.

In principle, the effect of a person’s urban residence could be estimated using a nested case-control study matching the data individually on siblings, thereby controlling for shared genetic and environmental factors among siblings (34). However, for these data, such a study would have had several limitations: First, only siblings with different degrees of urbanization of place of birth would have contributed to the estimation of the effect of the individual’s place of birth (34); this means that the oldest sibling would have had to have changed municipality for the sibling pair to contribute information, and the greater the birth interval the greater the chance that the sibling pair would contribute information. Second, the birth interval between siblings would have affected schizophrenia risk (24). Third, the higher the age at a change of municipality, the greater the risk of schizophrenia would have been (1). Although it might be possible to adjust for the latter two items (24), such a study would almost certainly contain bias due to the first item: only 15.9 percent of the subjects (those who were not born under the same degree of urbanization as the nearest older sibling) would contribute information. Such persons would probably not be representative of the total population of siblings. Thus, the current strategy was more suitable for distinguishing whether urban-rural differences in schizophrenia risk were rooted in families or in individuals.

**RESULTS**

Our study cohort included 711,897 persons born in Denmark in 1956–1986 who had an older full sibling. These people were followed for development of schizophrenia during the period 1970–2001, contributing 9.5 million person-years at risk. A total of 2,720 persons developed schizophrenia. This corresponded to a crude incidence rate of 2.86 per 10,000 person-years at risk.

In this cohort, 83.5 percent of the subjects had been born in a place with the same degree of urbanization as their nearest older sibling; 10.6 percent had been born at a lower degree of urbanization than the nearest older sibling; 5.3 percent had been born at a higher degree of urbanization than the nearest older sibling; and for the remaining 0.6 percent, the nearest older sibling had been born abroad. The mean birth interval between the study subject and the nearest older sibling was 3.6 years (standard deviation, 2.1).

Table 1 shows the number of people who developed schizophrenia and the crude incidence of schizophrenia per 10,000 person-years at risk according to the individual’s place of birth and the nearest older sibling’s place of birth. For example, among the 2,720 people who developed schizophrenia, 888 had been born in the capital area; and among those, 60 had a nearest older sibling who had been born in a provincial area. For people born in the capital area whose nearest older sibling had been born in a provincial area, the crude incidence of schizophrenia was 4.93 per 10,000 person-years at risk.

**Individual’s and nearest older sibling’s place of birth**

The relative risk of schizophrenia according to the individual’s and the nearest older sibling’s place of birth (i.e., interaction or effect modification) is shown in table 2. Among persons born in a rural area, the risk of schizophrenia was 1.73 (95 percent confidence interval (CI): 1.26, 2.37) if the nearest older sibling had been born in the capital area and 1.21 (95 percent CI: 1.01, 1.45) if the nearest older sibling had been born in a provincial area, as compared with individuals whose nearest older sibling had been born in a rural area (reference category). Therefore, among individuals born in a rural area, the greater the degree of urbanization of the nearest older sibling’s place of birth, the greater the risk of schizophrenia. Summarizing this dose-response association as a trend, we found that the risk of schizophrenia was 1.61 (95 percent CI: 1.25, 2.08) if the nearest older sibling had been born in the capital area as compared with a rural area (see trend in table 2).
Among individuals whose nearest older sibling had been born in the capital area, there was no evidence of a dose-response association between schizophrenia risk and degree of urbanization of the individual’s birthplace. Summarizing this association as a trend, we found that the risk of schizophrenia was 1.00 (95 percent CI: 0.78, 1.29) if the individual had been born in the capital area as compared with a rural area (see trend in table 2).

The following results were restricted to people born in 1971 or later. This restriction was necessary to obtain information on place of upbringing. The restricted cohort included 434,407 people followed during 3.8 million person-years at risk; 1,128 of these persons developed schizophrenia during the period 1986–2001. The relative risk of schizophrenia was compared between individuals born in the capital area, provincial area, rural area, and abroad. The crude incidence rate measured the number of new cases occurring per 10,000 person-years at risk (without adjustments).

### Place of upbringing and nearest older sibling’s place of birth

The following results were restricted to people born in 1971 or later. This restriction was necessary to obtain information on place of upbringing. The restricted cohort included 434,407 people followed during 3.8 million person-years at risk; 1,128 of these persons developed schizophrenia during the period 1986–2001. The relative risk of schizophrenia was compared between individuals born in the capital area, provincial area, rural area, and abroad. The crude incidence rate measured the number of new cases occurring per 10,000 person-years at risk (without adjustments).

### Table 1: Distribution of 2,720 incident cases of schizophrenia diagnosed during 1970–2001 among persons aged 15 years or more and crude incidence of schizophrenia according to place of birth and nearest older sibling’s place of birth, Denmark*

<table>
<thead>
<tr>
<th>Nearest older sibling’s place of birth</th>
<th>Individual’s place of birth</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capital area</td>
<td>Provincial area</td>
</tr>
<tr>
<td>Capital area</td>
<td>803</td>
<td>4.14</td>
</tr>
<tr>
<td>Provincial area</td>
<td>60</td>
<td>4.93</td>
</tr>
<tr>
<td>Rural area</td>
<td>20</td>
<td>4.61</td>
</tr>
<tr>
<td>Abroad</td>
<td>5</td>
<td>3.54</td>
</tr>
<tr>
<td>Total</td>
<td>888</td>
<td>4.19</td>
</tr>
</tbody>
</table>

* Analyses were carried out in a population-based cohort of 711,897 people born in Denmark in 1956–1986 who had an older full sibling.
† Crude incidence rate of schizophrenia per 10,000 person-years at risk. The crude incidence rate measured the number of new cases occurring per 10,000 person-years at risk (without adjustments).

### Table 2: Adjusted relative risk of schizophrenia among persons aged 15 years or more according to place of birth and nearest older sibling’s place of birth, Denmark, 1970–2001*

<table>
<thead>
<tr>
<th>Nearest older sibling’s place of birth</th>
<th>Individual’s place of birth</th>
<th>Trend† ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capital area</td>
<td>Provincial area</td>
</tr>
<tr>
<td>Capital area</td>
<td>1.91</td>
<td>1.70, 2.15</td>
</tr>
<tr>
<td>Provincial area</td>
<td>2.37</td>
<td>1.81, 3.10</td>
</tr>
<tr>
<td>Rural area</td>
<td>2.17</td>
<td>1.38, 3.39</td>
</tr>
<tr>
<td>Trend† ‡</td>
<td>0.79</td>
<td>0.56, 1.10</td>
</tr>
</tbody>
</table>

* Analyses were carried out in a population-based cohort of 711,897 people born in Denmark in 1956–1986 who had an older full sibling, where 2,720 developed schizophrenia during the period 1970–2001.
† Trends were used to summarize the risk associated with degree of urbanization, scoring a rural area as 0, a provincial area as 0.5, and the capital area as 1. Using this scoring, the estimated relative risk measured the effect of birth in the capital area compared with a rural area.
‡ For each nearest older sibling’s place of birth, the trend summarizes the risk of schizophrenia associated with the degree of urbanization of the individual’s place of birth, measured as the effect of birth in the capital area compared with a rural area.
§ RR, relative risk; CI, confidence interval.
¶ Persons born in a rural area whose nearest older sibling had also been born in a rural area were chosen as the reference category (except for trend analyses). The test for interaction between individual’s place of birth and nearest older sibling’s place of birth produced a p value of 0.001. Individuals (born in Denmark) whose nearest older sibling had been born abroad had a relative risk of 2.00 (95 percent confidence interval: 1.28, 3.13). Estimates of relative risk were adjusted for age and its interaction with gender, calendar year, and history of mental illness in a parent or sibling.
# For each individual’s place of birth, the trend summarizes the risk of schizophrenia associated with the degree of urbanization of the nearest older sibling’s place of birth, measured as the effect of the nearest older sibling’s having been born in the capital area compared with a rural area.
schizophrenia according to place of upbringing (as described by the statistical model used) and the nearest older sibling’s place of birth (i.e., interaction or effect modification) is shown in table 3. Persons who had lived in a rural area during the first 15 years of life and whose nearest older sibling had also been born in a rural area were chosen as the reference category (except for trend analyses). Place of upbringing was modeled as the accumulated number of years of living in the capital area and a provincial area (see Materials and Methods). Estimates measured the combined effect of living the first 15 years of life under each degree of urbanization and the nearest older sibling’s place of birth. The test for interaction between the individual’s place of upbringing and the nearest older sibling’s place of birth produced a p value of 0.001. Estimates of relative risk were adjusted for age and its interaction with gender, calendar year, history of mental illness in a parent or sibling, and change of residence during upbringing.

Interchangeability of individual’s and nearest older sibling’s place of birth

The findings in table 2 were consistent. First, among individuals whose nearest older sibling had been born in the capital area, the individual’s place of birth had no effect. Second, among individuals born in the capital area, the nearest older sibling’s place of birth had no effect. Third, among individuals whose nearest older sibling had been born in a rural area, the greater the degree of urbanization of the individual’s birthplace the greater was the risk of schizophrenia. Fourth, among individuals who had been born in a rural area, the greater the degree of urbanization of the nearest older sibling’s birthplace the greater was the risk of schizophrenia. Fifth, among individuals who had been born in a provincial area or whose nearest older sibling had been born in a provincial area, the effects were somewhat intermediate. Sixth, almost the same tendency was observed when place of residence during upbringing was compared with the nearest older sibling’s place of birth (table 3), except that 1) among individuals whose nearest older sibling had been born in the capital, place of residence during upbringing may also have contributed to the risk of schizophrenia and 2) the nearest older sibling’s place of birth had no significant effect among individuals who had lived in a provincial area during their first 15 years. In summary, these results suggest that individual’s place of birth (and upbringing) and nearest older sibling’s place of birth were virtually interchangeable in terms of schizophrenia risk—that is, both variables contributed to the risk of schizophrenia.

Additional analyses

Our findings might be explained by the fact that the nearest older sibling’s place of birth could be a proxy for factors operating during fetal life. We performed additional analyses in which place of upbringing was extended to include maternal residence 1 year prior to the individual’s birth (i.e., from 1 year before the individual’s birth to the individual’s 15th birthday) and found results similar to those presented (table 3).

Excluding people with any history of psychiatric admission or outpatient care in a parent or sibling (excluding 1.6 million person-years in which 1,127 people developed schizophrenia according to place of upbringing (as described by the statistical model used) and the nearest older sibling’s place of birth (i.e., interaction or effect modification) is shown in table 3. Persons who had lived in a rural area during the first 15 years of life and whose nearest older sibling had also been born in a rural area were chosen as the reference category (except for trend analyses). Place of upbringing was modeled as the accumulated number of years of living in the capital area and a provincial area (see Materials and Methods). Estimates measured the combined effect of living the first 15 years of life under each degree of urbanization and the nearest older sibling’s place of birth. The test for interaction between the individual’s place of upbringing and the nearest older sibling’s place of birth produced a p value of 0.001. Estimates of relative risk were adjusted for age and its interaction with gender, calendar year, history of mental illness in a parent or sibling, and change of residence during upbringing.

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schizophrenia) had only a minor impact on the results presented. The effect of the nearest older sibling’s place of birth was not modified by the birth interval between the subject and the nearest older sibling ($p = 0.85$). Using the previous five-level categorization of degree of urbanization (1, 2, 4) instead of the three-level categorization (3) had no impact on our findings. Including second-born individuals only (excluding 2.9 million person-years in which 852 people developed schizophrenia) had only a minor impact on the results presented.

**DISCUSSION**

Many studies have demonstrated than an urban birth or upbringing increases the risk of schizophrenia (1–8). In a previous study (1), we found that 1) there was evidence of a dose-response relation between urbanicity during upbringing and schizophrenia risk; 2) the period of exposure associated with the urban-rural differences ranged from birth to at least the 15th birthday; 3) no age periods during upbringing were associated with particular vulnerability to residence in urban areas; 4) among individuals moving to a higher degree of urbanization during upbringing, the risk of schizophrenia increased, while among individuals moving to a lower degree of urbanization, the risk decreased; and 5) urbanicity at birth was explained by urbanicity during upbringing. On the basis of those previous findings, we concluded that continuous or repeated exposures incurred during upbringing that occur more frequently in urbanized areas may be responsible for the association between urbanization and schizophrenia risk and that candidate risk factors would include infections, diet, and exposure to pollution (1).

In this study, however, the nearest older sibling’s place of birth was independently associated with risk of schizophrenia, even after we controlled for urban birth or urbanicity during upbringing and fetal life. Therefore, the urban-rural differences in schizophrenia risk were related to the family’s urban residence prior to the individual’s conception—that is, some of the cause(s) responsible for the urban-rural differences were rooted in families. The conclusion in our previous study, which was based on almost identical data (1), cannot in itself explain this finding. Therefore, we need to consider additional potential causes of the urban-rural differences in schizophrenia risk (1).

The first potential explanation is that some risk exposures are accumulated during families’ residence in urban areas (e.g., maternal lead concentration (21), maternal toxoplasma infection (17), infections in siblings (35, 36)) and are transmitted to their children during fetal life or upbringing, increasing the children’s risk of schizophrenia. Below we outline two additional potential explanations for the urban-rural differences in schizophrenia risk. However, before proceeding, we must discuss the concept of selective migration.

**Selective migration**

Selective migration was reviewed as “social drift” and “social residue” by Freeman (10). “Social drift” is the migration of persons affected by psychiatric morbidity to urban areas, while “social residue” refers to the migration of mentally healthy persons away from urban areas. For incidence studies, selective migration as reviewed by Freeman (10) applied only to migration of the individual prior to disease onset/registration. If urban exposure was measured prior to the prodromal phase (e.g., urbanicity at birth), selective migration of the individual could not artificially generate the effect of urbanicity at birth on schizophrenia risk, which was demonstrated in this study and in other studies based on incidence rates (1–5, 37, 38). However, selective migration towards urban areas of families with some unknown trait might explain the urban-rural differences in schizophrenia risk, if the unknown trait was linked to the risk of schizophrenia in their children. It is important to distinguish between selective migration of the individual and selective migration of the family. All previous papers on selective migration in relation to schizophrenia risk implicitly defined selective migration as selective migration of the individual.

The second potential explanation for the urban-rural differences is that some families have a genetic liability that is related to both the family’s migration towards the city and the risk that their children will develop schizophrenia. A recent Australian study showed that monozygotic (i.e., identical) twins were more likely to live under the same degree of urbanization during adulthood than dizygotic twins (39). If this finding could be generalized to the total Danish population, there might be a genetic component involved in the choice of where people live when they have children. Whether this potential genetic component is also linked to the risk of schizophrenia is unknown.

The third potential explanation is that some families may have a familial trait linked to the environment that is related to both the family’s migration towards the city and the likelihood that they will be exposed to some risk unknown risk factor(s) for schizophrenia and/or are more vulnerable to such factor(s). For example, one could hypothesize that families who are more likely to live at least parts of their lives in cities also differ from other families with respect to exposure to pet-related infections (17), diet, tendency to engage in outdoor activities (19), misuse of cannabis and alcohol (20), and mental health problems (2, 4), regardless of whether they currently live in a city.

None of the three potential explanations are mutually exclusive.

**Strengths and limitations**

Our results might apply only to people with older siblings, but since the effects of place of birth and place of upbringing were almost identical in people with older siblings and people without them (results not shown), we believe that our results can be generalized at least to the Danish population. The strength of this study was the large sample containing all nonfirstborn children born in Denmark to Danish women. Restricting the analyses to the second-born child in each family, thereby controlling for the potential impact of statistical dependence between cohort members, had only a minor effect on the results presented.
For individuals aged 5–15 years, the higher the age the greater the schizophrenia risk associated with a change of residence during upbringing (1). Since the results in table 3 were adjusted for change of residence, and change of residence had no effect for individuals under age 5 years, change of residence during upbringing could not explain our findings.

On the basis of our findings, we cannot exclude the possibility that some of the urban-rural differences in schizophrenia risk were related to the individual’s urban residence as well. Among persons whose nearest older sibling had been born in the capital area, place of birth had no effect on the risk of schizophrenia (table 2), while place of residence during upbringing had a weak nonsignificant impact on the risk of schizophrenia (table 3).

Concluding remarks

Although higher parental education might be one of the schizophrenia risk factors rooted in families, the risk associated with a higher education in parents was too small (1.1- to 1.4-fold) to be the sole explanation for our findings (40). It is unlikely that our results were influenced by urban-rural differences in sibling size, insofar as a previous study showed that sibling size was reducible to place of upbringing (24).

We conclude that some of the cause(s) responsible for the urban-rural differences in schizophrenia risk are rooted in families, but some might also be rooted in individuals. To advance the understanding of urban-rural differences in schizophrenia risk, we need direct measurements of genes and/or environmental factors associated with schizophrenia risk.

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