Sibship Characteristics during Upbringing and Schizophrenia Risk

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The potential association between sibship characteristics and the risk of schizophrenia has been investigated previously. However, methods have differed and results have been conflicting. The authors explored the association between birth order, sibship size, and birth interval to siblings and schizophrenia while accounting for potential confounders. Using Danish Civil Registration System data, the authors established a cohort of 763,000 people. Schizophrenia was identified by linkage with the Danish Psychiatric Central Register. Overall, 2,536 people developed schizophrenia from 1986 to 2001. Children with no siblings and children with three or more siblings had significantly increased risks (relative risk = 1.22 and 1.27, respectively). This association was explained by change of residence and urbanization during upbringing. Children with half siblings had a significantly increased risk (relative risk = 1.20). The authors found a significantly increased risk associated with siblings 7–8 and 11–14 years younger (relative risk = 1.30 and 1.22, respectively) combined with a significantly decreased risk associated with siblings 2–10 and 12 or more years older (relative risk = 0.92 and 0.82, respectively). There was no consistent pattern between the birth interval to siblings and schizophrenia risk. Results of the association between sibship characteristics and schizophrenia from a single country may not be comparable with results from other countries, and sibship characteristics are minor determinants of schizophrenia risk.

birth intervals; birth order; confounding factors (epidemiology); only child; risk factors; schizophrenia; siblings; urbanization

Abbreviation: ICD-8, International Classification of Diseases, Eighth Revision; ICD-10, The ICD-10 Classification of Mental and Behavioural Disorders.

The potential association between sibship characteristics (e.g., birth order, sibship size, and birth interval to siblings) and the risk of schizophrenia has been investigated by several authors (1–6). However, methods have differed and results have been conflicting. Sham et al. (4) found a decreased risk in firstborn children and an increased risk in children with siblings who were 3–4 years older. Westergaard et al. (1) could not replicate these findings but found an increased risk associated with no siblings, three or more siblings, and a short birth interval between siblings.

It is very unlikely that sibship characteristics themselves would influence the risk of schizophrenia, suggesting that sibship characteristics are proxies for some unknown underlying cause(s) or exposure(s) responsible for the association between sibship characteristics and schizophrenia risk. Authors have used the birth order and birth interval to older siblings as proxy variables for prenatal exposure to infections (1, 3, 4), sibship size as a proxy variable for infections in childhood (1, 7), and a short birth interval to older siblings as a proxy variable for maternal folate depletion during pregnancy (6), while other authors studied the effect of sibship characteristics without reference to any specific hypothesis (2, 5).

Danish data suggest that sibship size increases with decreasing degree of urbanization but also that frequent change of residence, increasing degree of urbanization during upbringing (8), and increasing sibship size (1) increase schizophrenia risk. Therefore, one objective of this study is to explore the potential association between sibship characteristics and schizophrenia, while evaluating the potential confounding effect of change of residence and urbanization.
Sibship characteristics vary during upbringing for most children, meaning that, for example, an association between sibship size at the fifth birthday and schizophrenia may differ from that between sibship size at the 10th birthday and schizophrenia. Therefore, in addition to the associations explored in previous studies, we evaluate the potential association between sibship characteristics at various time points during upbringing and the risk of schizophrenia.

Detailed information on the timing of exposure in relation to sibship characteristics combined with appropriate adjustment for confounders may provide valuable information on the unknown underlying cause(s) or exposure(s) responsible for the association between sibship characteristics and schizophrenia.

MATERIALS AND METHODS

Study population

We used data from the Danish Civil Registration System (9) to obtain a large and representative set of data on Danish persons. The Danish Civil Registration System was established on April 1, 1968, when all people alive and living in Denmark were registered. Among many other variables, it includes information on the “CPR number” (personal identification number), gender, and date of birth, as well as continuously updated information on vital status and the CPR number of the parents. The CPR number is used as a personal identifier in all national registers, ensuring accurate linkage between registers. Our study population includes all persons born in Denmark from January 1, 1971, to December 31, 1983, who were alive at the 15th birthday and whose mothers were born in Denmark after April 1, 1935. The latter restriction ensures complete information on siblings through maternal identity (10).

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 (11), which has been computerized since April 1, 1968. The Danish Psychiatric Central Register contains data on all admissions to Danish psychiatric inpatient facilities and at present includes data on approximately 450,000 persons and 1.6 million admissions. From 1995 onward, information on outpatient visits to psychiatric departments was included in the register. From April 1969 to December 1993, the diagnostic system used was the Danish modification of the International Classification of Diseases, Eighth Revision (ICD-8) (12), and from January 1994 the diagnostic system used was The ICD-10 Classification of Mental and Behavioural Disorders (ICD-10) (13). Cohort members were classified with schizophrenia if they had been admitted to a psychiatric hospital or had been in outpatient care with a diagnosis of the disorder (ICD-8 code 295 or ICD-10 code F20). The date of onset was defined as the first day of the first contact (in- or outpatient) with a diagnosis of schizophrenia. Parents and siblings were categorized hierarchically with 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 in outpatient care with one of these diagnoses. The diagnostic categories used were identical to those used in previous studies (6, 8, 14).

Assessment of sibship size

We calculated the sibship size by age levels of the number of siblings who were alive at the child’s birth, fifth birthday, 10th birthday, and 15th birthday. Note that, except for twins, sibship size at birth is identical to birth order, as both indicate the number of older siblings. Sibship size was categorized as one, two, three, four, and greater than or equal to five.

Assessment of change of residence and of urbanization at birth and during upbringing

Municipalities in Denmark were classified according to the degree of urbanization (15): capital, capital suburb, provincial city with more than 100,000 inhabitants, provincial town with more than 10,000 inhabitants, or rural areas. For each person in the cohort, we compiled information on the degree of urbanization at the place of birth; the accumulated number of years each person had been living in each degree of urbanization from birth to the 15th birthday; and the number of changes of municipality at the following age levels: 0–3, 4–9, 10–12, and 13–14 years. These variables were identical to those used in a previous study on urbanicity during upbringing and schizophrenia risk (8).
Study design

A total of 763,000 persons in 496,000 sibships (defined by the identity of the mothers) were followed from their 15th birthday or January 1, 1986, whichever came later, until the date of onset of schizophrenia, the date of death, the date of emigration from Denmark, or December 31, 2001, whichever came first. Note that all information recorded on cohort members is independent of the disease status, and that all cohort members have complete information on all variables, except for the 0.6 percent of cohort members with a missing paternal link.

Statistical analyses

The relative risk of schizophrenia was estimated by log-linear Poisson regression (16) with the GENMOD procedure in SAS version 8.2 software (17). All relative risks were adjusted for age and its interaction with gender, calendar year, parental age, history of mental illness in a parent or sibling, and the degree of urbanization at the place of birth. This model includes 45 parameters. Age, calendar year, and history of mental illness in siblings were treated as time-dependent variables (18), whereas all other variables were treated as variables independent of time. To reduce the risk of residual confounding, age was categorized as 15, 16, 17, 18, 19, 20–21, 22–23, 24–25, 26–27, and 28–29 completed years; calendar year was categorized as 1986–1989, 1990–1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, and 2001 completed years; maternal age was categorized as 12–17, 18–19, 20–21, 22–24, 25–29, 30–34, 35–39, and ≥40 completed years; and paternal age was categorized as 12–17, 18–19, 20–21, 22–24, 25–29, 30–34, 35–39, 40–44, 45–49, and ≥50 completed years or unknown father. p values were based on likelihood ratio tests, and 95 percent confidence intervals were calculated by the Wald test (18). The adjusted-score test (19) suggested that the regression models were not subject to overdispersion.

Simplification of model

We used backward elimination (20) to reduce the number of parameters in the models describing the number of younger siblings at each of the 15 age levels (15 parameters) and the number of older siblings at each of the 15 age levels (15 parameters). At first, we fitted the full model with all variables (e.g., the number of siblings at 0 year, 1 year, 2 years, ..., 13 years, and 14 years younger than the individual) and used the Wald test (18) to evaluate the hypothesis that the parameter estimates associated with two successive age levels were equal (e.g., the risk associated with the number of siblings 1 year younger than the individual equals the risk associated with the number of siblings 2 years younger than the individual). The successive age levels whose parameter estimates were associated with the lowest significance level were collapsed into one variable (e.g., the number of siblings 1–2 years younger than the individual). This procedure was repeated until all successive parameters differed at a significance level of 0.05. This method is independent of prior assumptions about the association between sibship composi-

tion and schizophrenia. This simplification was performed separately for the number of younger siblings and the number of older siblings.

Population attributable risk

We calculated the population attributable risk as 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 or factors had been eliminated (21).

RESULTS

A total of 2,536 persons (1,657 males and 879 females) developed schizophrenia during the 7.5 million person-years of follow-up. Tables show the distribution of persons who developed schizophrenia, the crude incidence of schizophrenia per 10,000 person-years at risk, and the adjusted relative risks of schizophrenia according to sibship size and the sibship composition variables used. The term “person-years” means the total sum of the number of years that each individual in the study population had been under observation.

Overall, the crude incidence of schizophrenia in this cohort was 3.36 per 10,000 person-years at risk. For children who were only children (i.e., sibship size of one) at the 15th birthday, it was 4.57; for twins, 3.69; for children with half siblings at birth, 5.43; for children with a sibling 1 year younger, 3.68; and for children with a sibling 1 year older, it was 4.25 per 10,000 person-years at risk.

Sibship size

Sibship size at birth and at the fifth birthday had no significant effect on schizophrenia risk, while sibship size at the 10th and at the 15th birthdays had significant effects on schizophrenia risk (first adjustment) (table 1). Children with one sibling (i.e., sibship size of two) were chosen as the reference category. The effect of sibship size at the 10th and at the 15th birthdays was almost identical, with evidence of an elevated risk among only children and among children with a sibship size of four or more. When additional adjustment was made for change of residence and urbanization during upbringing (second adjustment) (table 1), the effect of sibship size at all ages was reduced; that is, the effect of sibship size is confounded by change of residence and urbanization during upbringing. Conversely, the effect of change of residence and urbanization during upbringing was not confounded by sibship size at any age (results not shown). With this adjustment, sibship size had no significant effect, but there was still some indication of an increased risk among only children and among children with a sibship size of four or more at the 10th and at the 15th birthdays.

Co-twinning

The relative risk for twins compared with that for singletons did not differ significantly (first adjustment) (table 2).
Half siblings

Children with half siblings had an increased risk of schizophrenia compared with children without (first adjustment) (table 2), and among those, there was a slightly greater risk associated with having half siblings from birth to the 15th birthday compared with having half siblings at birth (first adjustment) (table 2). However, these effects did not differ significantly.

Younger siblings

The relative risk of schizophrenia depends on the birth interval to younger siblings (first adjustment) (table 3). Using backward elimination, we simplified this model with 15 parameters to a model with four parameters: siblings who were 0–6, 7–8, 9–10, and 11–14 years younger (first adjustment, simplified model) (table 3). Siblings 0–6 and 9–10 years younger had no significant impact on schizophrenia.
Older siblings

The relative risk of schizophrenia depended on the birth interval to older siblings (first adjustment) (table 4). Using backward elimination, we simplified this model with 15 parameters to a model with four parameters: siblings who were 0–1, 2–10, 11, and 12 or more years older (first adjustment, simplified model) (table 4). Siblings 0–1 and 11 years older had no significant impact on schizophrenia risk, while siblings 2–10 and 12 or more years older significantly decreased the risk of schizophrenia compared with children who had no older siblings at these birth intervals.

Confounding by change of residence and urbanization during upbringing

When the sibship composition variables were further adjusted for change of residence and urbanization during upbringing, the elevated risk associated with a history of half siblings was reduced slightly, while the remaining sibship composition variables were not confounded by these variables (second adjustment) (tables 2, 3, and 4). Conversely, the effect of change of residence and urbanicity during upbringing was not confounded by the sibship composition (results not shown).

Population attributable risk

If the risk for children with half siblings could be reduced to the risk for children without, 3.6 percent of the cases of schizophrenia would not have occurred. If the risk for all children could be reduced to the risk for children with one

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**TABLE 2. Adjusted relative risks of schizophrenia in a population-based cohort of 763,000 people according to twins and half siblings, Denmark, 1986–2001**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of cases</th>
<th>Incidence*</th>
<th>First adjustment†</th>
<th>Second adjustment‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative risk</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Co-twinning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single birth</td>
<td>2,485</td>
<td>3.36</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Birth of twins</td>
<td>51</td>
<td>3.69</td>
<td>0.97</td>
<td>0.72, 1.30</td>
</tr>
<tr>
<td></td>
<td>p value§</td>
<td></td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Half siblings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History at birth</td>
<td>237</td>
<td>5.43</td>
<td>1.26</td>
<td>1.09, 1.46</td>
</tr>
<tr>
<td>History at 0–&lt;15 years</td>
<td>305</td>
<td>6.12</td>
<td>1.35</td>
<td>1.17, 1.56</td>
</tr>
<tr>
<td>No history before 15 years</td>
<td>1,994</td>
<td>3.02</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>p value§</td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

* Incidence of schizophrenia per 10,000 person-years at risk. The incidence measures the number of new cases per time period.
† Estimates of relative risk were adjusted for age and its interaction with gender, calendar year, degree of urbanization at birth, history of mental illness in a parent or sibling, and parental age at the time of the child’s birth and for all the sibship composition variables (i.e., variables included in tables 2, 3, and 4).
‡ Estimates of relative risk were adjusted for all the variables in the first adjustment and for change of residence and urbanization during upbringing.
§ p values were based on likelihood ratio tests.
¶ The risk associated with a history of half siblings before the 15th birthday was 1.20 (95% confidence interval: 1.04, 1.39) compared with that for children without such a history.
sibling with a birth interval of 2–6 years (older or younger sibling), 2.5 percent of the cases of schizophrenia would not have occurred.

**DISCUSSION**

**Sibship size**

The association between sibship size and schizophrenia risk depends on the age at which sibship size was measured, and this association was largely explained by change of residence and urbanization during upbringing. The effects of sibship size at the 10th and at the 15th birthdays were nearly identical. This finding was expected as, after the 10th birthday, changes in sibship size are less common in Denmark. After adjustment for change of residence and urbanization during upbringing, most of the effect of sibship size is due to an increased risk associated with only children and with children who had three or more siblings. We performed additional analyses and found that the increased risk in large sibships is largely explained by change of residence, while the increased risk in only children is largely explained by urbanization during upbringing. These findings indicate that the unknown causal factor responsible for the increased risk in large sibships is more closely related to change of residence than to sibship size, while the unknown causal factor responsible for the increased risk in only children is more closely related to urbanization during upbringing than to sibship size.

**TABLE 3. Adjusted relative risks of schizophrenia in a population-based cohort of 763,000 people according to interval to younger siblings, Denmark, 1986–2001**

<table>
<thead>
<tr>
<th>Sibship Characteristics and Schizophrenia Risk</th>
<th>2004;160:652–660</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISCUSSION</strong></td>
<td>***</td>
</tr>
<tr>
<td><strong>Sibship size</strong></td>
<td>***</td>
</tr>
<tr>
<td>The association between sibship size and schizophrenia risk depends on the age at which sibship size was measured, and this association was largely explained by change of residence and urbanization during upbringing. The effects of sibship size at the 10th and at the 15th birthdays were nearly identical. This finding was expected as, after the 10th birthday, changes in sibship size are less common in Denmark. After adjustment for change of residence and urbanization during upbringing, most of the effect of sibship size is due to an increased risk associated with only children and with children who had three or more siblings. We performed additional analyses and found that the increased risk in large sibships is largely explained by change of residence, while the increased risk in only children is largely explained by urbanization during upbringing. These findings indicate that the unknown causal factor responsible for the increased risk in large sibships is more closely related to change of residence than to sibship size, while the unknown causal factor responsible for the increased risk in only children is more closely related to urbanization during upbringing than to sibship size.</td>
<td>***</td>
</tr>
</tbody>
</table>
The birth intervals to younger and older siblings and having half siblings affect the risk of schizophrenia significantly, while having a co-twin had no significant impact on schizophrenia risk. Therefore, our study demonstrated that both current sibship size and past history of changes in sibship composition influence schizophrenia risk significantly. For example, based on table 1, people with identical sibship sizes at the 15th birthday have identical risks. However, people may have obtained their sibship size in many different ways. Among those with one sibling at the 15th birthday, some are only children from 0 to 7 years and get a younger sibling at age 8 years, while others at birth have an older sibling aged 8 years. According to our model, these children have risks of 1.30 (95 percent confidence interval: 1.14, 1.49) and 0.92 (95 percent confidence interval: 0.86, 0.98), respectively.

The relative risks associated with the birth interval to younger siblings differ from the risks associated with the birth interval to older siblings (compare tables 3 and 4). This finding indicates that these effects cannot be explained by common factors in mothers. If a common factor in mothers could explain these effects, tables 3 and 4 would show identical effects by birth interval. For example, for a mother having two children with an age difference of 8 years, the younger child has a risk of 0.92, while the older child has a risk of 1.30. However, common factors in mothers may explain the nearly identical effect of intervals to younger and older siblings from 2 to 6 years and again from 9 to 11 years (tables 3 and 4).

### Table 4. Adjusted relative risks of schizophrenia in a population-based cohort of 763,000 people according to interval to older siblings, Denmark, 1986–2001

<table>
<thead>
<tr>
<th>Interval to older siblings (no. of years older)†</th>
<th>No. of cases</th>
<th>Incidence‡</th>
<th>First adjustment§</th>
<th>First adjustment,§ simplified model</th>
<th>Second adjustment¶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative risk</td>
<td>95% confidence interval</td>
<td>Relative risk</td>
</tr>
<tr>
<td>0</td>
<td>8</td>
<td>3.04</td>
<td>0.70</td>
<td>0.35, 1.41</td>
<td>1.16</td>
</tr>
<tr>
<td>1</td>
<td>235</td>
<td>4.25</td>
<td>1.20</td>
<td>1.04, 1.37</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td></td>
<td></td>
<td>1.16</td>
<td>1.02, 1.33*</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>309</td>
<td>3.06</td>
<td>0.96</td>
<td>0.85, 1.08</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>294</td>
<td>3.13</td>
<td>0.98</td>
<td>0.86, 1.11</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>243</td>
<td>3.37</td>
<td>1.02</td>
<td>0.89, 1.17</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>179</td>
<td>3.02</td>
<td>0.91</td>
<td>0.78, 1.07</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>151</td>
<td>3.17</td>
<td>0.86</td>
<td>0.73, 1.02</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>122</td>
<td>3.15</td>
<td>0.83</td>
<td>0.69, 1.00</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>103</td>
<td>3.32</td>
<td>0.82</td>
<td>0.67, 1.01</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>98</td>
<td>3.92</td>
<td>0.98</td>
<td>0.80, 1.21</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>3.86</td>
<td>0.95</td>
<td>0.75, 1.21</td>
<td></td>
</tr>
<tr>
<td>2–10</td>
<td></td>
<td></td>
<td>0.93</td>
<td>0.87, 0.98*</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>77</td>
<td>5.09</td>
<td>1.24</td>
<td>0.98, 1.58</td>
<td>1.23</td>
</tr>
<tr>
<td>12</td>
<td>44</td>
<td>4.06</td>
<td>0.86</td>
<td>0.63, 1.17</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>34</td>
<td>4.28</td>
<td>0.85</td>
<td>0.60, 1.22</td>
<td></td>
</tr>
<tr>
<td>≥14</td>
<td>51</td>
<td>4.14</td>
<td>0.79</td>
<td>0.64, 0.99*</td>
<td></td>
</tr>
<tr>
<td>12–≥14</td>
<td></td>
<td></td>
<td>0.82</td>
<td>0.71, 0.96*</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05; ** p < 0.01 (p values were based on likelihood ratio tests).

† Categories are not mutually exclusive; for example, a person who has a sibling 4 years older and a sibling 8 years older belongs to both of these categories.

‡ Incidence of schizophrenia per 10,000 person-years at risk. The incidence measures the number of new cases per time period.

§ Estimates of relative risk were adjusted for age and its interaction with gender, calendar year, degree of urbanization at birth, history of mental illness in a parent or sibling, and parental age at the time of the child’s birth and for all sibship composition variables (i.e., variables included in tables 2, 3, and 4).

¶ Estimates of relative risk were adjusted for all the variables in the first adjustment and for change of residence and urbanization during upbringing.

## Sibship composition

The birth intervals to younger and older siblings and having half siblings affect the risk of schizophrenia significantly, while having a co-twin had no significant impact on schizophrenia risk. Therefore, our study demonstrated that both current sibship size and past history of changes in sibship composition influence schizophrenia risk significantly. For example, based on table 1, people with identical sibship sizes at the 15th birthday have identical risks. However, people may have obtained their sibship size in many different ways. Among those with one sibling at the 15th birthday, some are only children from 0 to 7 years and get a younger sibling at age 8 years, while others at birth have an older sibling aged 8 years. According to our model, these children have risks of 1.30 (95 percent confidence interval: 1.14, 1.49) and 0.92 (95 percent confidence interval: 0.86, 0.98), respectively.

The relative risks associated with the birth interval to younger siblings differ from the risks associated with the birth interval to older siblings (compare tables 3 and 4). This finding indicates that these effects cannot be explained by common factors in mothers. If a common factor in mothers could explain these effects, tables 3 and 4 would show identical effects by birth interval. For example, for a mother having two children with an age difference of 8 years, the younger child has a risk of 0.92, while the older child has a risk of 1.30. However, common factors in mothers may explain the nearly identical effect of intervals to younger and older siblings from 2 to 6 years and again from 9 to 11 years (tables 3 and 4).
Our results may support the hypotheses post factum that maternal folate depletion due to short birth interval to older siblings may increase schizophrenia risk, and that stress of getting younger siblings during puberty may increase schizophrenia risk. Furthermore, if divorces are more common in parents with a history of mental illness, the increased risk associated with a history of half siblings may be explained by undiagnosed mental illness in the parents of these children. However, other explanations may apply.

Comparison with previous studies

In previous studies on Danish data (1, 6), the authors found that sibship size and birth interval between siblings influence schizophrenia risk and that birth order had no influence on schizophrenia risk. In these studies, sibship size was measured as a time-varying variable that described the number of siblings from entry into the study (fifth birthday and 15th birthday, respectively) until censoring (end of study), estimating its effect using Poisson regression adjusting for age. As the incidence of schizophrenia for persons until the 15th birthday is very low and most siblings in Denmark are born with a birth interval of less than 15 years, this measure of sibship size corresponds approximately to measuring sibship size at the 15th birthday. We performed additional analyses in which we analyzed our data in exactly the same way as Westergaard et al. (1) and Smits et al. (6) had done. We found a similar association among schizophrenia risk, birth order, sibship size, and birth interval between siblings, except that a short birth interval to younger siblings had no effect in the current cohort, and we found a slightly lower effect of sibship size. The lack of association between a short birth interval to younger siblings and schizophrenia risk, which is also evident in table 3, and the lower impact of sibship size indicate that these associations may be more specific to late-onset cases of schizophrenia, as these studies include people with onset up to age 50 years, whereas our study includes only people with onset up to age 30 years.

Our study method on older siblings is almost equivalent to that used by Sham et al. (4), except that we used the birth interval to older siblings in fifteen 1-year age categories while Sham et al. (4) used the birth interval to older siblings in eight 1-year categories. Despite these similarities, Sham et al. (4) found an increased risk in children with siblings 3–4 years older, and we found a slightly protective, but significant effect of older siblings associated with these birth intervals.

Strengths and limitations

Our study demonstrated a significantly increased risk associated with siblings 7–8 and 11–14 years younger combined with a significantly decreased risk associated with siblings 2–10 and 12 or more years older. Although these effects appear significant, we found no consistent pattern between the birth intervals of younger and older siblings and the risk of schizophrenia.

The results of the study are based on patients with schizophrenia admitted to a psychiatric hospital or in outpatient care with a diagnosis of schizophrenia. Although not all cases of schizophrenia are admitted or in outpatient care during the first episode, many of these will eventually be admitted or receive outpatient care and thus subsequently become registered. Our results may apply only to early-onset schizophrenia, since we restricted our cohort members to a birth year of 1971 or later. This restriction was necessary to adjust for change of residence and urbanization during upbringing, as this information is accessible only for cohort members born in 1971 or later. Another potential weakness of our study is that we did not adjust for the potential impact of dependence between cohort members in families. Such adjustment is not feasible due to computational issues.

The strength of this study is the very large sample containing all children born in Denmark to Danish women. Furthermore, data were analyzed as a cohort study using the total population as the comparison group, which prevents bias from arising through inappropriate control groups.

Conflicting results between studies

Even if studies from different countries used identical measures of a proxy variable (e.g., sibship size) for the underlying risk factor and if the underlying risk factor had an identical effect, the association between the proxy measured and schizophrenia risk will differ between countries if the association between the proxy measured and the underlying risk factor differs. This may be the case if the sibship characteristics of these countries differ (e.g., if the underlying risk factor was maternal folate depletion during pregnancy and if we evaluate the effect of the proxy variable sibship size at the 15th birthday; if the average birth interval between siblings is smaller in Denmark than in the country for comparison, children from large sibships in Denmark would suffer more from maternal folate depletion compared with children in the other country. Results from Denmark would therefore find a greater effect of large sibship size compared with those from the other country). Conclusively, results on the association between sibship characteristics from a single country and schizophrenia may not be comparable with results from other countries. This observation may explain some of the conflicting results between studies, although differences in the methods used may also explain some differences.

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