Fetal Growth and Schizophrenia: A Nested Case-Control and Case-Sibling Study

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The association between low birth weight and schizophrenia has been suggested by many studies. Small for gestational age (SGA) is a measure used as a proxy for intrauterine growth restriction. We aim to examine if children who are born SGA are at increased risk of developing schizophrenia and whether an association may be explained by factors shared among siblings. We linked 3 population-based registers: the Danish National Medical Birth Register, the Danish Psychiatric Central Register, and the Danish Civil Registration register to identify all persons born between 1978 and 2000. A nested case-control study and a case-sibling study design were used. There were 4650 cases of schizophrenia. Incidence rate ratios (IRRs) were estimated using conditional logistic regression. SGA was defined as the lowest 10th birth weight percentile for a given sex and gestational age. SGA was associated with an IRR of 1.23 (95% CI: 1.11–1.37) for schizophrenia in the case-control study. An IRR of 1.28 (95% CI: 0.97–1.68) was found in the case-sibling study. There is a modest association between SGA and schizophrenia. Our results indicate that this association is due to an independent effect of factors associated with low birth weight for gestational age per se, rather than other factors shared by siblings.

Key words: register/Denmark/cohort study/epidemiology

Introduction

Intrauterine growth restriction (IUGR) is a term used to describe abnormally slow fetal growth.1 It is associated with short- and long-term health problems in fetuses, infants, and children. The cause of this condition is often difficult to establish, and both environmental and genetic factors may play a role; factors related to the mother, the placenta, and the fetus itself may be involved.2

Low birth weight3–7 and reduced length at birth5–7 have been associated with the risk of schizophrenia and both measures have been used as crude indicators of IUGR.5 Siblings have previously been studied in relation to different obstetric complications such as low birth weight.9–12 Small for gestational age (SGA), which is often used as a proxy for IUGR, can be defined by a number of criteria, of which the most commonly used is a birth weight <10th population decentile for gestational age.13 Studies of the association between SGA and schizophrenia have been inconclusive.3–7 SGA includes fetuses that are small but have reached their appropriate growth potential. The biological mechanisms and environmental factors underpinning a potential association between IUGR and schizophrenia are not yet fully established. The association might be explained by factors that are related to IUGR as well as schizophrenia. These potential risk factors could be environmental like smoking14 or diet.15 Fetal growth restriction may, in specific sensitive periods of fetal life, cause long-lasting changes in structure and functioning of the brain later in life, influencing the risk for psychiatric disease such as schizophrenia. IUGR may thus have a direct influence on the risk of schizophrenia.

One way of determining whether risk factors related to IUGR and schizophrenia play a role is to combine a case-control study with a case-sibling study. The approach of using siblings is advantageous in epidemiology because the nested case-control design used can take into account the relatedness of the cases and controls. Sibling designs are a unique tool to adjust associations for unmeasured confounding shared by siblings.16 Contrasting the unaffected members from the cases allows us to test whether IUGR is an independent risk factor or if it reflects other shared factors within the family. If associations seen in the case-control study remain in case-sibling analysis, then factors specific to each individual are involved in the association. Conversely, if the relationship disappears or substantially diminish in case-sibling analysis, then common factors to the siblings

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may be involved. It is important to disentangle whether the relationship between SGA and schizophrenia can be explained by familial or unique contributions in terms of preventive measures. In case, the association can be explained by individual factors then these families should be treated like other families. In case, the association is linked to unmeasured familial factors and not IUGR per se then an effort should be made in order to identify these factors.

We predict that SGA and schizophrenia are related. In order to examine this hypothesis, our aims were to (a) study the association between SGA and schizophrenia, (b) to evaluate whether the association was confounded by siblings' SGA, and (c) to compare healthy sibling controls to cases to investigate if the association was a direct association or attributable to shared familial factors.

Methods

The Danish Civil Registration System

The Danish Civil Registration System was established in 1968; since then, all Danish citizens have been registered by a unique personal identification number. The Civil Registration System holds information on gender, date of birth, vital status (continuously updated), and the personal identification numbers of parents. The personal identification number is used as a personal identifier in all national registers, enabling accurate linkage between registers.

Assessment of Schizophrenia and Other Mental Illness

The Danish Psychiatric Central Register contains data on all admissions to Danish psychiatric inpatient facilities. It presently includes data on approximately 680,000 persons and 2.9 million contacts. From 1969 to 1993, the diagnostic system used was the Danish modification of the International Classification of Diseases, 8th Revision (ICD-8); starting in 1994, the diagnostic system used was that of the International Classification of Diseases, 10th Revision (ICD-10). From 1995 onward, information on outpatient visits to Danish psychiatric facilities was included in the register.

Schizophrenia was defined as 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 that led to this diagnosis, irrespective of any other diagnosis they might have had.

Assessment of Gestational Age and Birth Weight

The Danish Medical Birth Register holds information on all live births in Denmark since 1973. Due to secular changes in recording regarding gestational age and birth weight, we restricted our analysis to children born between 1978 and 2000. Gestational age was recorded in completed weeks for this period, mainly based on the date of the last menstrual period but for the latest period ultrasound measurement was used when available. Birth weight was categorized in 100 g intervals.

We defined SGA by the lowest 10th percentile of birth weights for a given sex and gestational age.

Study Population

Case-Control Study. All singletons born in the period 1978–2000 and who had a diagnosis of schizophrenia in the period 1988–2010 were identified through the Civil Registration System, the Medical Birth Register, and the Psychiatric Central Register. Each case was matched to a random sample of all individuals of the same sex who were born on the same day and who were at risk of schizophrenia on the day when the case was diagnosed with schizophrenia using a nested case-control design.

Case-Sibling Study. All singletons born in the period 1978–2000 with at least 1 sibling were identified through the Danish Civil Registration System, by identification of the mother. Both maternal full and half siblings were included. Each person who was diagnosed with schizophrenia in the period 1988–2010 was matched with all siblings that were alive, had the same sex, and without a diagnosis of schizophrenia at the age when the case was first diagnosed.

Covariates

The firstborn child is on average smaller than the subsequently born children, and it has been suggested that the firstborn may have a higher risk for schizophrenia than subsequently born children. Mothers’ diagnoses 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. Children of schizophrenic mothers have a higher risk of developing schizophrenia and of IUGR.

Thus, the analyses were adjusted for the effect of birth order and maternal psychiatric illness.

In order to control for whether the individual effect of SGA was confounded by siblings SGA, we adjusted the individual effect of being SGA for family-averaged SGA. In the calculation of the family-averaged SGA, the index person was not included, in order to minimize the correlation between the individual effect of SGA and the family-averaged SGA. In our analysis, we included siblings to cases or controls born before 1978 (for the calculation of the family-averaged SGA). Due to changes in the Medical Birth Register, SGAs for all siblings born
before 1978 were calculated separately. Although children with no siblings (ie, only children) do not contribute with any extra information for the family-averaged SGA, they were included to show the effect for children born SGA with no siblings.

**Statistical Analysis**

The case-control and the case-sibling data were analyzed using conditional logistic regression with each case forming a separate stratum. Because all possible controls were selected within the appropriate risk sets, the estimated measures of relative risk are incidence rate ratios (IRRs). Although both data were analyzed using conditional logistic regression, the interpretation of data is different. In the case-control data based on the models described by Begg and Parides, we were able to adjust IRR of schizophrenia for the individual effect of SGA for the effect of family-averaged SGA. In the case-sibling analysis, we were able to further control for observed and unobserved factors, which are shared by siblings.

Data were analyzed using the PHREG procedure in SAS version 9.2 (SAS Institute).

**Results**

**Analyses of SGA in the Case-Control Study**

A total of 4650 persons born in Denmark between 1978 and 2000 had their first admission or outpatient contact for schizophrenia from 1988 to 2010. The cases were matched on sex and date of birth to a total of 325,727 population-based controls. The median was 21.23 years and the interquartile range was 4.99 years.

Table 1 shows the IRRs for schizophrenia. Having no siblings (only child) was associated with an IRR of 1.19 (95% CI: 1.08–1.32; table 1, column 3) compared with children having siblings. Children who are born SGA with siblings had an IRR of 1.30 (95% CI: 1.17–1.44; table 1, column 3), whereas children born SGA without siblings had an IRR of 1.51 (95% CI: 1.20–1.89). No significant difference between the 2 groups was found (P value .24).

Adjusting for family-averaged SGA resulted in a slight attenuation of the IRR for schizophrenia in children with siblings (1.28; 95% CI: 1.15–1.42; table 1, column 4), but did not alter the rate ratio of schizophrenia in those without siblings. In other words, adjusting for familial propensity for having children born SGA did not account for the association between IUGR and schizophrenia.

Further adjustment for maternal mental illness and birth order reduced the IRR for schizophrenia to 1.23 (95% CI: 1.11–1.37; table 1, column 5).

**Analyses of SGA in Case-Sibling Study**

For the case-sibling data, a total of 1420 persons born in Denmark between 1978 and 2000 had their first admission or outpatient contact for schizophrenia from 1988 to 2010. The cases were matched on sex and without a diagnosis of schizophrenia at the age when the case was first diagnosed to a total of 1593 sibling controls. The median was 20.48 years and the interquartile range was 4.33 years.

Table 2 shows the IRR for schizophrenia in the case-sibling design. Siblings born SGA had an IRR of 1.28 (95% CI: 0.97–1.68) compared with siblings not born SGA.

**Discussion**

The main finding of the present study was an association between SGA and the IRR for schizophrenia. We tested 2 alternative explanations for this association. First, that IUGR acts as an independent risk factor for schizophrenia; second, that IUGR is a marker for unknown factors shared among siblings. The first explanation is supported by our data because we found an association between SGA and schizophrenia in the case-control study as well as in the case-sibling study. However, we did not, in our data, find any support for our second explanation because the results in the case-sibling study, although not statistically significant, resembled those found in the case-control study.

<table>
<thead>
<tr>
<th>Cases/Controls</th>
<th>IRR</th>
<th>First Adjustment</th>
<th>Second Adjustment</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA, ≥1 sibling</td>
<td>412/23405</td>
<td>1.30 (1.17–1.44)</td>
<td>1.28 (1.15–1.42)</td>
</tr>
<tr>
<td>SGA, no sibling</td>
<td>96/3938</td>
<td>1.51 (1.20–1.89)</td>
<td>1.51 (1.20–1.89)</td>
</tr>
<tr>
<td>Only child</td>
<td>522/30073</td>
<td>1.19 (1.08–1.32)</td>
<td>1.20 (1.08–1.33)</td>
</tr>
</tbody>
</table>

*People with unknown SGA (410/28949, IRR 1.10 [0.99–1.24]), persons born SGA and with all siblings missing information on SGA (24/1638, IRR 1.09 [0.73–1.63]).

*Adjusted for family-averaged SGA.

*Further adjustment for maternal psychiatric illness and birth order.
### Table 2. Incidence Rate Ratios for Small for Gestational Age and Schizophrenia in Persons Born During 1978–2000 With a Sibling

<table>
<thead>
<tr>
<th>SGA Status</th>
<th>Cases/Sibling Controls</th>
<th>IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA</td>
<td>146/138</td>
<td>1.28 (0.97–1.68)</td>
</tr>
<tr>
<td>Not SGA</td>
<td>1174/1357</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

*People with unknown SGA 100/98, IRR 1.14 (0.84–1.55).*

### Strengths and Limitations

The use of population-based registries afforded the present study the ability to control for a history of maternal mental illness, which is an important confounder.

The use of a sibling design within the same cohort provided us with the opportunity to assess whether SGA was related to schizophrenia or due to some unmeasured shared familial factors. This design implies a smaller study population, which implies wider confidence intervals compared with the confidence interval in the case-control design, but the IRRs appear to be of the same magnitude. Although not statistically significant, the IRR for schizophrenia in the case-sibling study resembled that found in the case-control study. By use of this design, we were able to control for confounding by unmeasured and inherited shared risk factors. The combination of a large population cohort in combination with a case-sibling study within the same cohort is a major strength of this study. Thus, comparing results from our analyses allowed us to assess whether fixed factors or factors that change within the family explain the observed association between SGA and schizophrenia.

Whether a newborn is truly IUGR can be difficult to establish as SGA is a statistically defined population-based measure of low birth weight for a specific sex and gestational age. The main limitation is that SGA includes physiologically or constitutionally small babies for a gestational age as well as pathologically grown low-weight babies. A substantial proportion of fetal growth restricted infants may be missed because their weight is >10th percentile, and a fraction of perfectly normally grown babies may be categorized as growth restricted. The misclassification of constitutionally small children as SGA and growth restricted children as not SGA may have biased our results toward the null.

### Comparison With Other Studies

The relationship between growth restriction and schizophrenia has been explored in other studies. However, most investigators have not conducted specific analyses of growth restriction within families. A study from Finland used a Cox frailty model with family defining the random factor to investigate the influence of birth weight on schizophrenia. This study found an association between high birth weight and schizophrenia, but it did not find an association with low birth weight. However, neither of these studies has investigated the association between being born SGA and the rate of schizophrenia. To our knowledge, our study is the first study to investigate the association between SGA and schizophrenia in the population as well as in families.

### Possible Explanations

A novel contribution of this study is the demonstration that most of the association between SGA and schizophrenia may be attributed to characteristics that vary between siblings. It cannot be explained by factors that stay constant across pregnancies. Many environmental factors may change from one birth to another and exert differential effects on siblings. Pregnancy-specific effects that can vary between pregnancies in the same woman include gestational age, placentation function, maternal nutrition (diet and body weight), smoking in pregnancy, infections, and complications of pregnancy. These are all potential confounders or underlying causes that could account for the association between SGA and schizophrenia.

The fetal origin programming hypothesis suggests that IUGR may cause long-lasting changes in the function and structure of organs later in life and influence the risk of chronic diseases and behavioral problems.

Placental pathophysiology contributes to a variety of obstetric complications and impairments to fetal development, such as hypoxia, growth restriction, or immune dysregulation.

The placenta’s central role in regulating nutrient transport, endocrine function, and immune tolerance implicates its involvement in growth restriction, hypoxia, and related neurological complications. These challenges further elaborate detrimental effects on early brain development, increasing susceptibility to neurodevelopmental disorders.

Epigenetic changes in the expression of genes related to mental disorders could result from adverse environmental conditions during fetal life and may be reflected in both restricted fetal growth and later mental disorders.

Multivitamin use in pregnancy may be associated with increased birth weight and reduced SGA. A recent study found a curvilinear association for both low and high concentrations of neonatal vitamin D associated with schizophrenia risk. Also, folate and other dietary factors have been hypothesized to influence schizophrenia risk.

Various autoimmune diseases have been linked with schizophrenia. A meta-review of risk factors for SGA also reports that some autoimmune conditions could be linked to SGA, and it has been shown that the risk for IUGR is increased, eg, in untreated maternal celiac disease, but not if maternal celiac disease was treated.
Conclusion

The present results showed some evidence for the impact of IUGR on children's risk of developing schizophrenia. In addition, the results from the case-sibling study resembled those of the case-control study although not statistically significant. There are already many public health approaches to reduce IUGR. Improving the lifestyle and health of the mother may help reduce the occurrence of children born IUGR. It is conceivable that if such preventive measures were to be successful in reducing the occurrence of IUGR, then they may also contribute to a reduction in schizophrenia in the coming years.

Funding

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References