Association Between Prepartum Maternal Iron Deficiency and Offspring Risk of Schizophrenia: Population-Based Cohort Study With Linkage of Danish National Registers

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Recent findings suggest that maternal iron deficiency may increase the risk of schizophrenia-spectrum disorder in offspring. We initiated this study to determine whether maternal prepartum anemia influences offspring risk of schizophrenia. We conducted a population-based study with individual record linkage of the Danish Civil Registration System, the Danish Psychiatric Central Register, and the Danish National Hospital Register. In a cohort of 1 115 752 Danish singleton births from 1978 to 1998, cohort members were considered as having a maternal history of anemia if the mother had received a diagnosis of anemia at any time during the pregnancy. Cohort members were followed from their 10th birthday until onset of schizophrenia, death, or December 31, 2008, whichever came first. Adjusted for relevant confounders, cohort members whose mothers had received a diagnosis of anemia during pregnancy had a 1.60-fold (95% confidence interval 1.16–2.15) increased risk of schizophrenia. Although the underlying mechanisms are unknown and independent replication is needed, our findings suggest that maternal iron deficiency increases offspring risk of schizophrenia.

Key words: Schizophrenia/epidemiology/risk factor/Denmark/maternal iron deficiency/follow-up/cohort

Introduction

Converging evidence suggests that neurodevelopmental disruption plays a role in the vulnerability to schizophrenia and that prenatal nutritional factors may be involved in the etiology of the disorder.1 Maternal iron deficiency during pregnancy is an important nutritional factor that might cause adverse neurodevelopmental effects of potential relevance to the development of schizophrenia. Iron is essential for metabolic mechanisms associated with the development and maintenance of brain structures and functions relevant to schizophrenia,2 including myelination3,4 and dopaminergic neurotransmission.5 Iron deficiency leading to anemia impairs the oxygen-carrying capacity of the mother and can reduce oxygen delivery to the developing fetus6 and might disrupt neurodevelopment through its effect on birth outcomes.7 Researchers have begun to examine if failure to meet iron demands of the developing brain may have long-term psychiatric consequences. Insel et al8 recently studied a birth cohort born between 1959 and 1967 where maternal hemoglobin concentrations served as a marker for fetal iron deficiency. After adjustment for maternal education and ethnicity, the authors found a nearly 4-fold elevated risk for offspring schizophrenia-spectrum disorder (SSD) associated with low hemoglobin (a mean hemoglobin concentration of 10.0 g/dl or less) compared with a mean concentration of 12.0 g/dl (or higher). The risk estimate was based on 39 cases of SSD exposed to moderate (>10.0 but ≤12.0 g/dl) and 9 cases exposed to low hemoglobin levels (≤10.0 g/dl). This suggests that maternal iron deficiency may be a risk factor for SSD among offspring. However, further investigation in independent samples is warranted, and we initiated the current study to further examine whether a diagnosis of prepartum anemia during pregnancy influences the risk of schizophrenia in offspring. We aimed to investigate whether maternal anemia during pregnancy (prepartum anemia) is associated with offspring risk of schizophrenia when adjusting for potential confounders including parental psychiatric illness and urbanization. The potentially confounding effect of urbanization has not previously been addressed, and the effect of parental mental illness may also require additional research. Insel et al8 found similar or slightly lower rates of any mental condition in mothers with moderate hemoglobin levels.
(9.1%) or low hemoglobin levels (7.6%) when compared with the reference group (9.8%). However, it is also possible that women with severe mental illness, such as schizophrenia, display more suboptimal health behaviors involving nutritional intake. Moreover, paternal mental illness might indirectly influence the health behavior of the mother during her pregnancy. Hence, attempts to further examine if prepartum anemia is associated with offspring risk of schizophrenia should consider including paternal mental illness as well.

Methods

The Registers

The Danish Civil Registration System (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. The Danish National Hospital register (DNHR) was set up in 1977 and includes all hospital admissions in Denmark; in 1994, it was expanded to also include outpatient and emergency room contacts. The diagnoses were recorded according to International Classification of Diseases, Eighth Revision (ICD-8), until 1993 and according to International Classification of Diseases, Tenth Revision (ICD-10), from 1994 onward. The Danish Psychiatric Central Register was computerized in 1969 and contains data on all admissions to Danish psychiatric inpatient facilities. It presently includes data on approximately 710,000 persons and 3.2 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 ICD-8; starting in 1994, the diagnostic system used was that of the ICD-10.

Study Population

Using the Danish CRS, all singletons born in Denmark between 1 January 1978 and 31 December 1998, who were alive at the 10th birthday and whose mothers were born in Denmark constituted the study population (N = 115,752).

Assessment of Schizophrenia and Mental Illness

Cohort members and their mothers and fathers were linked with the Danish Psychiatric Central Register. Cohortees 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 that led to the diagnosis. Parents 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.

Assessment of Prepartum Anemia

The definition of a history of anemia was that the mother of the cohortee had been assigned a diagnosis of prepartum anemia (or anemia in graviditate) in the DNHR. Anemia is defined as hemoglobin of <110g/l during pregnancy (ICD-8 code 633 and ICD-10 code O990). We omitted all ICD-8 diagnoses that bore the modification code “suspected,” “not found.” Similar codes were omitted for the ICD-10. The omitted diagnoses constitute a minority of the total number of diagnoses with anemia (0.13%).

Assessment of Urbanization and Parental Age

Municipalities in Denmark were classified according to degree of urbanization, yielding the following categories: capital, capital suburb, provincial city, provincial town, and rural areas as previously described.

Maternal and paternal age at time of child’s birth was coded as previously described.

Short for Gestational Age

Maternal iron deficiency anemia may be associated with higher birth weight. We have previously calculated the sex-, birth-order-, and gestational age-specific z score of birth weight for babies and used the lowest 15th percentile of the z score to define “small for gestation” (SGA) for all babies. SGA has been linked with increased risk of schizophrenia in some studies, and with social factors. We included SGA as a potential confounder of a putative relationship between prepartum anemia and offspring risk of schizophrenia.

Study Design

We carried out a prospective cohort study following 1,115,752 persons from their 10th birthday until onset of schizophrenia, emigration from Denmark, death, or December 31, 2008, whichever came first.

Data Analysis

The relative risk (RR) of schizophrenia was estimated by a log linear Poisson regression model with the GENMOD procedure in SAS version 9.1.
No anemia as previously described. Due to missing data for this were based on likelihood ratio tests. During 1988–2008 Schizophrenia During the 11.3 Million Person-Years of Follow-up Born in Denmark 1978–1998 of Whom 3422 Developed Maternal Anemia in Graviditate Among the 1,115,752 People

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Cases</th>
<th>Number of Person-Years</th>
<th>Rate</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia in graviditate</td>
<td>41</td>
<td>94,759</td>
<td>4.33</td>
<td>1.95 (1.41–2.61)</td>
</tr>
<tr>
<td>No anemia diagnosis</td>
<td>3381</td>
<td>11,206,391</td>
<td>3.01</td>
<td>1 (reference)</td>
</tr>
</tbody>
</table>

*aThe estimate was adjusted for calendar year, age, and its interaction with gender.

age, and its interaction with sex. In subsequent analyses, we adjusted for history of schizophrenia, schizophrenia-like psychosis, or psychiatric admission in a parent and place of birth (capital, capital suburb, provincial city, provincial town, and rural areas) and parental age at time of child’s birth.

Age, calendar year, and history of mental illness in parents were treated as time-dependent variables, whereas all other variables were considered time independent. Age was categorized as 10–12 and in 1-year age levels thereafter. Calendar years were categorized as 1988–1995 and in 1-year periods thereafter. P values were based on likelihood ratio tests.

SGA was considered a potential confounder and coded as previously described. Due to missing data for this variable, we carried out restricted analyses with data available for SGA and all the above-mentioned variables.

We included calculations of the population-attributable risk (PAR) associated with prepartum anemia. PAR was estimated using the method described by Bruzzi et al.

### Results

In this population-based cohort of 1,115,752 individuals born in Denmark during 1978–1998, a total of 3422 developed schizophrenia during the 11.3 million person-years of follow-up from 1988 to 2008. Overall, 17,940 children were exposed to maternal prepartum anemia during pregnancy. This corresponds to a prevalence rate of 1.6% (17940/1115752). Among them, 41 developed schizophrenia later in life.

Table 1 presents the number of cases and incidence rates of schizophrenia according to a maternal diagnosis of prepartum anemia. Children born to mothers with a diagnosis of prepartum anemia had a 1.95-fold (95% CI = 1.41–2.61) increased risk of schizophrenia.

There was no evidence that a potential change in practice during the study period had any impact on the effect of anemia on the risk of schizophrenia (children born during 1978–1985: RR = 1.75 [CI = 1.17–2.59], children born during 1986-1998: RR = 2.27 [CI = 1.32–3.58], P = .464).

The potential confounding effect of a history of mental illness, urbanization of place of birth, and parental age at time of child’s birth is shown in Table 2. Adjustment for parental mental illness resulted in a slight attenuation of the RR (1.74 [CI = 1.26–2.33]). Adjustment for urbanization also resulted in a slight attenuation of the RR in the same order of magnitude as the effect of adjusting for parental mental illness. In the fully adjusted model (age, sex, calendar year, history of mental illness, maternal and paternal age, and urbanization), prepartum anemia was associated with a 1.60-fold significant increased risk of schizophrenia.

In the restricted cohort (N = 1,055,827), we adjusted for SGA (Table 3) and found that SGA did not confound the effect of prepartum anemia.

Further analyses yielded a PAR of 0.58% associated with prepartum anemia (the fraction of the total number of offspring cases with schizophrenia that would not have occurred if the effect of prepartum anemia had been eliminated).

### Discussion

The offspring of mothers with a diagnosis of prepartum anemia suffer a significantly increased risk of later developing schizophrenia. Adjusting for relevant confounders did not explain the increased risk associated with maternal prepartum anemia. The fully adjusted risk estimate
The strengths of this study are that it includes a large number of cases with schizophrenia and has the ability to control for relevant confounders, including a history of mental illness in both parents. Another methodological advantage is the large unselected general population–based sample with uniform follow-up through record linkage that minimizes selection bias. The data represent, to our knowledge, the largest cohort in which the relationship between prepartum anemia and offspring risk of schizophrenia has been examined.

Attributable risk is determined by the RR and the frequency of exposure in the population and is a measure of the impact that RR has on the population occurrence of the disease. The PAR was small in this study. However, the frequency of prepartum anemia may have been underestimated in this study, and we cannot exclude the possibility that this could have led to an underestimation of the population impact of prepartum anemia.

There are a number of possible interpretations of our findings, and some of them warrant further study. As mentioned previously, pregnancies registered in the DNHR with or without an anemia diagnosis could have been more complicated as pregnant women treated by their general practitioner for anemia are not registered in the Danish National Hospital. Further study is needed, preferably using data from both general practice and DNHR to examine this hypothesis further. Controlling for parental mental illness resulted in an attenuation of the risk estimate from the basic model of 1.95 to 1.74. This may be explained by women with schizophrenia being more likely to have suboptimal health behaviors, involving nutritional intake. Controlling for urban-rural differences also attenuated the effect of prepartum anemia. Possible hypotheses for this observed result include urban-rural differences in dietary pattern or in other correlates related to maternal anemia as well as to risk of schizophrenia. Urban-rural differences in the probability to be referred to, or seek hospital, for treatment of pregnancy-related conditions and complaints could also have contributed to attenuating the effect of prepartum anemia.

The first studies of the association between maternal anemia during pregnancy and offspring risk of schizophrenia did not find a significantly increased odds ratio, although their risk estimates were in the same directions as our findings. In the 1966 North Finland Birth Cohort Study, the adjusted offspring odds ratio of developing schizophrenia was 1.70 if mothers were diagnosed with anemia (<105 g/l) in the second trimester, but the confidence limits included unity (0.8–3.7). Insel et al. found that for every 1 g/dl decrease in the mean maternal hemoglobin concentration, a 27% increase in the risk of SSD was observed. Our finding based on a large general population–based study is consistent with these previous findings.

The biological plausibility and possible causal mechanisms that might underlie an association between maternal prepregnancy anemia/iron deficiency and offspring

Table 3. Adjusted Relative Risks of Schizophrenia According to Prepartum Anemia (Restricted Sample) Among 1 055 827 People Born in Denmark During 1978–1998, of Whom 3064 Developed Schizophrenia During 1988–2008

<table>
<thead>
<tr>
<th>Relative Risk (95% Confidence Interval)</th>
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<tbody>
<tr>
<td>Basic modela</td>
<td>2.03 (1.46–2.73)</td>
</tr>
<tr>
<td>Mental history of a parentb</td>
<td>1.82 (1.31–2.45)</td>
</tr>
<tr>
<td>Urbanicityc</td>
<td>1.84 (1.33–2.48)</td>
</tr>
<tr>
<td>Parents’ aged</td>
<td>1.94 (1.40–2.61)</td>
</tr>
<tr>
<td>Small for gestational agef</td>
<td>2.02 (1.45–2.71)</td>
</tr>
<tr>
<td>Fully adjusted modelg</td>
<td>1.67 (1.20–2.25)</td>
</tr>
</tbody>
</table>

The reference category was those with no anemia diagnosis. The estimate was adjusted for all variables in the basic model and urbanicity. The estimate was adjusted for all variables in the basic model and maternal and paternal age. The estimate was adjusted for all variables in the basic model and small for gestational age. The estimate was adjusted for all variables in the basic model, history of mental illness, maternal and paternal age, urbanization, and small for gestational age.

suggests a 60% increased risk of schizophrenia in offspring of mothers with a diagnosis of prepartum anemia.

Compared with other studies, the prevalence of prepartum anemia of 1.6% in this sample is quite low. This low prevalence may reflect that women treated by their general practitioner for anemia are not registered in the DNHR with an anemia diagnosis, unless also discharged from a hospital, an outpatient setting, or emergency room with that diagnosis. This raises the possibility that pregnancies registered with or without an anemia diagnosis could have been more complicated as pregnant women treated by their general practitioner for anemia are not registered in the Danish National Hospital. Further study is needed, preferably using data from both general practice and DNHR to examine this hypothesis further. Controlling for parental mental illness resulted in an attenuation of the risk estimate from the basic model of 1.95 to 1.74. This may be explained by women with schizophrenia being more likely to have suboptimal health behaviors, involving nutritional intake. Controlling for urban-rural differences also attenuated the effect of prepartum anemia. Possible hypotheses for this observed result include urban-rural differences in dietary pattern or in other correlates related to maternal anemia as well as to risk of schizophrenia. Urban-rural differences in the probability to be referred to, or seek hospital, for treatment of pregnancy-related conditions and complaints could also have contributed to attenuating the effect of prepartum anemia.

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The biological plausibility and possible causal mechanisms that might underlie an association between maternal prepregnancy anemia/iron deficiency and offspring
risk of schizophrenia have been addressed by Insel et al. Prepartum anemia could be a marker for an independent risk factor for schizophrenia or could be more directly involved in events associated with the pathogenesis of schizophrenia. Iron deficiency leading to anemia impairs the oxygen-carrying capacity of the mother and can reduce oxygen delivery to the developing fetus and might disrupt neurodevelopment through its effect on birth outcomes. Moreover, iron is involved in brain development. Iron is a coenzyme of dopamine synthesis, and its deficiency could alter dopamine receptor density and activity that have been implicated in the pathophysiological mechanisms of schizophrenia. Altered iron homeostasis in the brain might be associated with prepartum anemia or with alteration in iron regulation in the adult brain. Postmortem brain studies in patients with schizophrenia have demonstrated altered oligodendroglial function involving several signal transduction proteins, including transferrin and ferritin, which are iron transport proteins expressed in oligodendrocytes. In addition, there are clinical correlates of maternal iron deficiency anemia, which yet have to be examined in relation to offspring risk of schizophrenia. Maternal infections with Helicobacter pylori can cause iron deficiency anemia that is unresponsive to iron treatment. Somatic conditions associated with, for instance, prolonged intake of nonsteroid anti-inflammatory drugs (NSAIDs) may also be associated with maternal anemia. However, with the exception of older and obsolete analgesics, it is uncertain whether intake of NSAID and other analgesics during pregnancy is associated with offspring risk of schizophrenia. Other correlates of maternal prepartum anemia include inadequate weight gain and severe nausea/vomiting during pregnancy. However, in our study, inadequate weight gain would probably correlate with SGA status, and controlling for SGA status had no effect on the risk estimates of the study.

In conclusion, our population-based study demonstrates that offspring of mothers who had received a diagnosis of prepartum anemia suffer a significantly increased risk of later developing schizophrenia. The increased risk was not explained by age, sex, parental history of any mental illness, urbanization at place of birth, intrauterine growth restriction (SGA), or parental age at time of child's birth. Our findings suggest that maternal prepartum anemia (and iron deficiency) may increase the risk of schizophrenia among offspring. The finding is of interest because iron deficiency is treatable. Hence, more closely monitored pregnancies with special attention to iron status as well as to other causes of anemia might offer a potential for reducing the risk of schizophrenia.

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