Association of Schizophrenia With Low Maternal Body Mass Index, Small Size at Birth, and Thinness During Childhood

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Background: Nutritional factors in early life may contribute to the neurodevelopmental deficit in schizophrenia. This study explores the influence of maternal body size, size at birth, and childhood growth on future risk for schizophrenia.

Subjects and Methods: This population-based cohort study comprised births at Helsinki University Central Hospital in Helsinki, Finland, from 1924 to 1933. Prospective data from birth and school health records of 7086 individuals were collected and linked to the Finnish Hospital Discharge Register.

Results: Schizophrenia or schizoaffective disorder had been diagnosed in 114 individuals. A lower late-pregnancy maternal body mass index (BMI) increased the risk (odds ratio [OR], 1.09 per kilogram/meter²; 95% confidence interval [CI], 1.02-1.17) for schizophrenia among the offspring. The risk of schizophrenia increased with low birth weight (OR, 1.48 per kilogram; 95% CI, 1.03-2.13), shortness at birth (OR, 1.12 per centimeter; 95% CI, 1.03-1.22), and low placental weight (OR, 1.22 per 100 g; 95% CI, 1.04-1.43). Schizophrenia cases were thinner than comparison subjects from 7 to 15 years of age. In a joint model comprising late-pregnancy maternal BMI, body size at birth, and childhood BMI, childhood BMI was an independent predictor of schizophrenia, whereas other factors exhibited attenuated effects.

Conclusion: Indicators of intrauterine and childhood undernutrition are associated with an increased lifetime risk of schizophrenia.

Arch Gen Psychiatry. 2001;58:48-52

Schizophrenia is a severe syndrome with a prevalence of approximately 1.3% in the Finnish adult population. Although the etiopathogenesis of schizophrenia is inconclusive, the evidence supports genetic predisposition and disturbed early neurodevelopmental processes as important underlying factors. Published data indicate that an array of adverse pregnancy and perinatal factors are related to subsequent schizophrenia, including infections during the second trimester of pregnancy, starvation in utero, and obstetric complications. Preeclampsia, which is associated with a reduced nutritional supply to the fetus, is the obstetric complication most strongly associated with schizophrenia. Delayed motor development and lower childhood educational achievements in people who later develop the syndrome indicate that schizophrenia originates long before the onset of evident illness.

An association between low birth weight (<2500 g) and schizophrenia has been reported in a retrospective case-control study and replicated in a recent population-based prospective study from northern Finland, which found that low birth weight and the combination of low birth weight and short gestation (<37 weeks) were more common among schizophrenic subjects. However, that study did not find a connection between schizophrenia and low weight for gestational age. In a Swedish population-based cohort, small birth size for gestational age and a low ponderal index (birth weight/length³) were associated with increased risk of schizophrenia, but only among men. However, both cohort studies were restricted to prenatal and perinatal risk factors and had a follow-up only until subjects were in their 20s, which excluded later cases of schizophrenia from the analyses. In the British 1946 birth cohort with 30 schizophrenia cases, no evidence of differences between cases and controls in birth weight or in height and weight at ages 7 and 11 years was found.

We assembled a cohort of 7086 men and women who were born at Helsinki University Central Hospital in Helsinki, Finland, between 1924 and 1933. The aim of the study was to clarify the effects of fetal and childhood nutrition, as reflected in late-pregnancy maternal body mass index (BMI), size at birth, and growth dur-
SUBJECTS AND METHODS

SAMPLE

The risk set originated from 27,068 men and women born at the public Helsinki University Central Hospital between 1924 and 1933. The hospital served both people living within Helsinki (population 221,524 in 1933) and people living outside the city in southern Finland. This study included children who went to primary schools in the city of Helsinki. Both birth and school health records were available for 8,580 subjects. School health records of subjects born at the Helsinki hospital but who lived outside the city and went to rural primary schools were not included.

We used birth and school health records to trace 7,086 subjects who still lived in Finland in 1971. At that time, a unique personal identification number was assigned to all residents by the Finnish Population Register.

RISK FACTORS

Data on mothers’ height, weight in late pregnancy, age, parity, and the date of the last menstrual period were extracted from birth records together with data on the newborns’ length, weight, head circumference, and placental weight. Using the father’s occupation, the subjects were grouped according to a social classification used by the Central Statistical Office of Finland. Overall, 78% of the fathers were laborers, and 10% were lower middle class. Together these constitute the lower social class as opposed to the upper social class, which is subdivided into upper middle class (2%) and self-employed (2%). The social status of 8% could not be classified.

For each subject, height and weight were measured during school medical examinations twice a year from ages 6 to 16 years. The number of household inhabitants and the number of rooms in the home had been recorded when the child first began school.

IDENTIFICATION OF CASES

Using the unique personal identification number, the individuals were linked with the Finnish Hospital Discharge Register (HDR). The HDR was founded in 1967 and covers all psychiatric and general hospitals. It contains data on primary diagnosis and up to 3 subsidiary diagnoses on both discharges and deaths of inpatients, regardless of length of hospitalization. The HDR is a valid and reliable tool for epidemiological research. Accuracy of primary diagnoses in the HDR is acceptable; a 96% agreement between HDR data and case notes has been reported in a schizophrenia sample. The predictive power of an HDR diagnosis in a broad schizophrenia spectrum is 0.95 when compared with a “gold standard” consensus diagnosis made against clinical records by 2 senior research psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) criteria.

Diagnoses have been entered in the HDR according to the International Classification of Diseases, Eighth Revision (ICD-8) until 1986, according to ICD-9 using the DSM-III-R criteria between 1987 and 1995, and according to ICD-10 criteria from 1996 onward. The first 3 digits from the cause of admission were used to identify the occurrence of schizophrenia, schizophreniform disorder, or schizoaffective disorder: 295 in ICD-8 and ICD-9 and F20 and F25 in ICD-10.

STATISTICAL ANALYSES

In this study, any individual found in the HDR with a primary or subsidiary diagnosis as defined previously until December 1996 was assigned to the schizophrenia group. This group of broad schizophrenia was compared with the remainder of the risk set. We used multiple logistic regression analysis to calculate odds ratios (ORs) for schizophrenia, adjusting for sex. Odds ratios are reported with 95% confidence intervals (CIs). The independent variables we included were maternal, neonatal, and childhood growth measurements. We assessed the joint effect of variables in this sequence by including them simultaneously in a multiple regression analysis. Childhood heights, weights, and BMIs were all converted to age- and sex-specific z scores using the method of Royston. We interpolated between successive z scores with a piecewise linear function and obtained a z score at each birthday from age 7 years to age 15 years. We then converted back these z scores to obtain the corresponding height, weight, and BMI at each age.

RESULTS

In the cohort, 114 cases with a hospital diagnosis of broad schizophrenia were identified, which indicates a cumulative incidence of 1.6% (1.3% in men and 1.9% in women). A primary diagnosis of schizoaffective disorder was found in 16 cases, and the remainder were diagnosed with schizophrenia. None had a diagnosis of schizophreniform disorder. The occurrence of schizophrenia was not related to year of birth.

The mean±SD age of mothers in the cohort was 27.6±5.7 years, and the mean±SD parity was 2.3±1.8. Mothers’ late-pregnancy BMI was significantly related to the occurrence of schizophrenia in their offspring. Table 1 presents ORs for schizophrenia associated with a unit decrease in late-pregnancy body size. Mothers’ late-pregnancy BMI was significantly related to the occurrence of schizophrenia in their offspring. Table 2 indicates that this finding depended mainly on an increased risk with late-pregnancy BMIs of 30 or less. Mothers’ heights were not related to schizophrenia in offspring.

BIRTH SIZE

Table 1 presents ORs for schizophrenia associated with a unit decrease in late-pregnancy body size. Mothers’ late-pregnancy BMI was significantly related to the occurrence of schizophrenia in their offspring. Table 2 indicates that this finding depended mainly on an increased risk with late-pregnancy BMIs of 30 or less. Mothers’ heights were not related to schizophrenia in offspring.
CHILDHOOD SOCIOECONOMIC CIRCUMSTANCES

The average number of inhabitants in the homes where the boys and girls grew up was 5 (range, 1-27). The average number of rooms in the house was 2 (range, 1-14), and 47% lived in homes with only 1 room. As in previous studies,12,13 we used the ratio of the number of inhabitants to the number of rooms as an index of crowding. Families living in less crowded conditions were of higher social class, and the children were taller and weighed more between ages 7 and 15 years.12,13 However, the level of crowding in the household during childhood was not related to the risk of broad schizophrenia (OR, 0.93; 95% CI, 0.38-1.47), nor was risk related to social class at birth, defined by the father’s occupation (OR, 1.38; 95% CI, 0.91-2.09).

COMMENT

Schizophrenia is a disorder with a multifactorial pathogenesis. The importance of pregnancy and delivery factors has been highlighted in previous studies. The present study is unique in combining maternal, birth, and childhood growth characteristics. Our results indicate that in a semiurban setting, small infants who are born to lean mothers and become thin in childhood are at increased risk for schizophrenia.

Table 1. Odds Ratios for Schizophrenia Associated With a Unit Decrease in Body Size in 7086 Men and Women in Helsinki, Finland

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Subjects</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers’ late-pregnancy body size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>15.5</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>14.5</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Placental weight, 100 g</td>
<td>12.5</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Neonatal body size</td>
<td>11.5</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>11.0</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Length at birth, cm</td>
<td>10.9</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Ponderal index, kg/m²</td>
<td>10.8</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>10.7</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Childhood body size</td>
<td>10.6</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Weight at age 7 y, kg</td>
<td>10.5</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Height at age 7 y, cm</td>
<td>10.4</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>BMI at age 7 y, kg/m²</td>
<td>10.3</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Weight at age 15 y, kg</td>
<td>10.2</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>Height at age 15 y, cm</td>
<td>10.1</td>
<td>2.60 (1.54-4.40)</td>
</tr>
<tr>
<td>BMI at age 15 y, kg/m²</td>
<td>10.0</td>
<td>2.60 (1.54-4.40)</td>
</tr>
</tbody>
</table>

P for trend = .009

*OR indicates odds ratio; CI, confidence interval; and BMI, body mass index.
†Data on 577 mothers missing.
‡Data on 27 newborns missing.
schizophrenia. Leanness during childhood seems to be an independent, additive risk factor to small size at birth. Thus, our results support the role of early life and childhood influence in the pathogenesis of schizophrenia.

Our study was restricted to men and women born at Helsinki University Central Hospital. About 60% of Helsinki births occurred at this hospital. The fathers of 78% of the cohort subjects were classified as laborers. The subjects may be unrepresentative of all people living in Helsinki, although we know that in 1930, around 60% of the city’s men were laborers. This would introduce a bias only if the associations between maternal, neonatal, and childhood body size and schizophrenia differed between people born in the hospital and those born in other places.

Subjects who died before 1971 and subjects who never went to primary school, such as severely mentally retarded children, are excluded from our cohort. Some subjects were lost because of early mortality; infant mortality was 6.5% during the period between 1924 and 1933. Therefore, the associations in our study are representative of a population that has reached middle age. One can assume that adverse maternal, pregnancy, and childhood factors exert their maximum effect early in life, and thus the possible bias arising from selective loss of people who died before middle age is more likely to lead to an underestimation of the associations between early risk factors and schizophrenia than to an overestimation.

We were able to trace 92% of the people originally identified through birth and school records. Our findings gain strength from the prospectively collected growth data and the occurrence and coverage of the HDR. Results from retrospective case-control studies on schizophrenia may be distorted or inflated because of bias in case selection or ascertainment of risk factor information. However, in the present population- and register-based study, all data on risk factors for schizophrenia were ascertained before an outcome was known.

One limitation of our study is that it excluded both schizophrenia subjects who were never hospitalized and those hospitalized in young adulthood only before 1971.

In an extensive cross-sectional health survey of a representative sample of the Finnish adult population between 1978 and 1980, 86% of those with psychosis were currently receiving treatment. In Finland, treatment of schizophrenia almost always includes hospitalization. The cumulative incidence of 1.6% in our cohort, born between 1924 and 1933, is compatible with the findings of a declining incidence of schizophrenia in Finnish birth cohorts and the 1-month prevalence of schizophrenia of 1.3% in the population study from 1978 to 1980.

Like another population-based cohort study, we failed to replicate the finding of small head circumference at birth made in retrospective case-control studies of clinical samples. Those studies may include more severely ill patients, with a stronger connection to premorbid brain abnormalities. A similar discrepancy between cohort and case-control studies has been described concerning obstetric complications as a risk factor for schizophrenia. Together these observations may indicate a true difference between clinical- and population-based samples, and they suggest the need for caution when interpreting findings from retrospective case-control studies.

The association between small birth size and schizophrenia was not due to shortened gestation and must therefore be caused by reduced rates of growth. We suggest that the associations with reduced fetal growth, small placental size, and late-pregnancy maternal thinness indicate that schizophrenia may originate through fetal undernutrition. This conclusion is strengthened by findings among people who were conceived during the height of the Dutch famine in 1945, whose risk for a schizophrenia-spectrum disorder was increased almost threefold. Although there was no acute food shortage in Finland during the years of cohort birth, the nutritional situation of the lower classes was not good. About half of an average blue-collar worker’s wages was spent on food, and food shortage was common in working-class families with many children. The primary source of protein was cereal products, mainly bread.

In a previous analysis of this semirural cohort, we found that high maternal BMI in late pregnancy was associated with a high rate of coronary heart disease in men. We now find that low late-pregnancy maternal BMI increased the child’s risk of subsequent schizophrenia. Mothers’ late-pregnancy BMI reflects both weight gain during pregnancy

Table 3. Odds Ratios (95% Confidence Intervals) for Schizophrenia According to Tertiles of Birth Weight and Length, and Body Mass Index (BMI) at Age 7 Years, in 7086 Subjects

<table>
<thead>
<tr>
<th>BMI at Age 7 y, kg/m²</th>
<th>≤14.8</th>
<th>&gt;14.8 and ≤15.7</th>
<th>&gt;15.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3180</td>
<td>2.5 (1.3-5.0)</td>
<td>0.9 (0.4-2.3)</td>
<td>1.5 (0.7-3.5)</td>
</tr>
<tr>
<td>3190-3590</td>
<td>1.9 (0.9-3.9)</td>
<td>1.0 (0.4-2.4)</td>
<td>0.5 (0.1-1.4)</td>
</tr>
<tr>
<td>≥3600</td>
<td>1.5 (0.7-3.5)</td>
<td>1.1 (0.5-2.6)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤49</td>
<td>4.0 (1.8-8.8)</td>
<td>1.2 (0.4-3.2)</td>
<td>2.2 (0.9-5.4)</td>
</tr>
<tr>
<td>49.5-50.5</td>
<td>2.7 (1.2-6.3)</td>
<td>2.3 (0.9-5.6)</td>
<td>1.2 (0.4-3.4)</td>
</tr>
<tr>
<td>≥51</td>
<td>2.1 (0.8-5.1)</td>
<td>1.1 (0.4-3.0)</td>
<td>1.0 (Reference)</td>
</tr>
</tbody>
</table>

*The total number of schizophrenia cases was 114.

In a later Finnish general-population cohort of subjects born in 1966, when the socioeconomic circumstances in Finland had improved, a high prepregnancy maternal BMI was associated with schizophrenia. In a secondary analysis of that cohort, the heaviest fifth percentile (BMI ≥ 29) of mothers had a doubled risk of offspring with schizophrenia when compared with the middle 90%, but the finding was not statistically significant. The differing findings between our study and the later Finnish cohort may reflect societal changes. A low BMI in the late 1920s or early 1930s, in a society without developed welfare structures, was linked to malnutrition or illness, whereas in 1966, when the population’s nutritional status was good, it was more a matter of choice. In current Western populations, a high rather than low maternal BMI is more likely to be associated with adverse outcomes, such as late fetal death, neural tube defects, and other congenital malformations. However, it does protect against the delivery of an infant that is small for its gestational age. We suggest that our cohort’s independent association between thinness in childhood and schizophrenia may reflect childhood undernutrition. Our data indicate that children with a length of 49 cm or less at birth, and who were below the lowest BMI tertile at age 7 years, had a fourfold risk of developing schizophrenia when compared with children who were above upper BMI tertile at age 7 years and were longer at birth (Table 3). In 1932, only 29% of children were offered meals in primary schools. The cohort experienced a food shortage during adolescence in 1942, but there was no wartime famine in Finland because of organized food rationing. In the Dutch famine study, periconceptional famine was associated with an increased risk of schizophrenia. The current study associates indicators of continued undernutrition with schizophrenia.

Epidemiologic studies have found that schizophrenic patients usually belong to lower socioeconomic groups. However, the classic study by Goldberg and Morrison found that the social class distribution of the fathers of schizophrenic subjects did not differ from that of the general population, which indicates that the excess of persons with schizophrenia in the lowest socioeconomic group may be more the result of a downward drift, or a decrease in social status, than of a socioeconomic causative factor. In the present study, those original findings were replicated: we found no significant difference between groups in socioeconomic distribution according to fathers’ occupation. Schizophrenia developed in 1.5% of children of laborers and in 2% of children of nonlaborers. A similar trend of association between schizophrenia and high social class at birth was reported in the British 1946 cohort. Thus, the association with nutritional status does not seem to be mediated by socioeconomic status of the family.

In conclusion, low late-pregnancy maternal BMI, small placental size, and small size at birth, possibly indicating fetal undernutrition, are associated with increased lifetime risk of schizophrenia. Subjects who subsequently developed schizophrenia remained lean during childhood, which may indicate continued malnutrition.

REFERENCES

(Reprinted) Arch Gen Psychiatry/Vol. 58, Jan 2001 www.arcgenpsychiatry.com