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.

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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 1971.12,13 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.14 Using the father’s occupation, the subjects were grouped according to a social classification used by the Central Statistical Office of Finland.15 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.12,13 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.16 Accuracy of primary diagnoses in the HDR is acceptable; a 96.3% agreement between HDR data and case notes has been reported in a schizophrenia sample.17 The predictive power of an HDR diagnosis in a broad schizophrenia spectrum is 0.93 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.17

Diagnoses have been entered in the HDR according to the International Classification of Diseases, Eighth Revision (ICD-8) until 1986, according to 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.18 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. The mothers of schizophrenic subjects were similar to the other mothers regarding their age and parity.

In the unaffected control group (n=6,097), mean±SD maternal BMI was 26.8±3.2 kg/m², mean birth weight was 3,383±508 g, mean birth length was 50.0±2.0 cm, and average BMI at age 7 years was 15.3±1.2 kg/m².

MATERNAL BODY 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.

BIRTH SIZE

Men and women who were born small had an increased risk of schizophrenia. Both low birth weight and a short length at birth increased the risk (Tables 1 and 2). Schizo-
Mothers' late-pregnancy BMI (OR, 1.07; 95% CI, 1.00-1.12; \(P = .03\)) was related to schizophrenia. As expected, size at birth was related to childhood body size (OR, 1.11; 95% CI, 1.01-1.22; \(P = .06\)). Length of gestation (days) was not associated with increased risk of schizophrenia (OR, 1.01; 95% CI, 0.99-1.02). There was no difference in the proportion of preterm births (11.2% of births) when compared with the rest of the cohort (10.9% of births) when birth length was of borderline significance (OR, 1.07; 95% CI, 0.97-1.02). There was no difference in the proportion of preterm births (11.2% of births) when compared with the rest of the cohort (10.9% of births) when birth weight was associated with an increased risk of schizophrenia (OR, 1.01; 95% CI, 0.97-1.02).

**CHILDHOOD GROWTH**

Table 1 indicates that at age 7 years, boys and girls who later developed schizophrenia had below-average weight and BMI. These differences were statistically significant and remained so at each age up to 15 years (Figure). The height of boys and girls who developed schizophrenia did not differ significantly from the average between ages 7 and 15 years. Table 3 presents the simultaneous effect of birth length and BMI at 7 years on risk of schizophrenia. The highest risk was in people who were short at birth and thin in childhood. In a simultaneous regression with mothers' late-pregnancy BMI, birth length, and offspring's BMI at age 7 years, only lower birth length and BMI at age 7 years remained significantly associated with schizophrenia (OR, 1.37; 95% CI, 1.13-1.66; \(P = .001\)). Shortness at birth was of borderline significance (OR, 1.10; 95% CI, 1.00-1.20; \(P = .06\)), and lower late-pregnancy maternal BMI was not significant (OR, 1.05; 95% CI, 0.97-1.12; \(P = .22\)). Findings in men and women were similar.

**CHILDLHOOD 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, 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. 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.
Factors exert their maximum effect early in life, and thus assume that adverse maternal, pregnancy, and childhood events gain strength from the prospectively collected growth and 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 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 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 and obstetric complications as a risk factor for schizophrenia.
and BMI before pregnancy. Body mass index in late preg-
nancy is highly correlated with BMI before pregnancy
($r = 0.86$; Keith Malcolm Godfrey, BM, PhD, MRCP, unpublished

In a later Finnish general-population cohort of sub-
jects born in 1966, when the socioeconomic circum-
stances in Finland had improved, a high prepregnancy ma-
ternal BMI was associated with schizophrenia. In a sec-
ondary analysis of that cohort, the heaviest fifth per-
centile (BMI $\geq 29$) of mothers had a doubled risk of off-
spring with schizophrenia when compared with the middle
90%, but the finding was not statistically significant.28 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 wel-
fare 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 popu-
lations, a high rather than low maternal BMI is more likely
to be associated with adverse outcomes,27 such as late fe-
tal death,28 neural tube defects,29 and other congenital mal-
formations.30 However, it does protect against the deliv-
eration of an infant that is small for its gestational age.

We suggest that our cohort’s independent association be-
tween thinness in childhood and schizophrenia may re-

clect childhood undernutrition. Our data indicate that chil-

dren 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 chil-

dren who were above upper BMI tertile at age 7 years and
were longer at birth (Table 3). In 1932, only 29% of chil-
dren were offered meals in primary schools. The cohort ex-
perienced a food shortage during adolescence in 1942, but
there was no wartime famine in Finland because of orga-
nized food rationing.38 In the Dutch famine study,25 peri-
conceptional 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 pa-

tients usually belong to lower socioeconomic groups.

However, the classic study by Goldberg and Morrison31
found that the social class distribution of the fathers
of schizophrenic subjects did not differ from that of the gen-

eral 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 so-
cioeconomic 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 asso-
ciation between schizophrenia and high social class at birth
was reported in the British 1946 cohort.8 Thus, the asso-
ciation with nutritional status does not seem to be medi-
ated by socioeconomic status of the family.

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