Patterns of Fetal and Childhood Growth and the Development of Psychosis in Young Males: A Cohort Study

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Factors influencing fetal and childhood growth may affect a person’s risk of developing schizophrenia. Associations of size at birth and body size in young adulthood with schizophrenia and other nonaffective psychoses were assessed in a cohort of 334,577 Swedish male conscripts born in 1973–1980 for whom linked birth, census, hospital admission, and adult height and weight data were available. Complete data on all study variables were available for 246,655 subjects. Over a mean 3.4-year follow-up beginning at age 18 years, 80 subjects developed schizophrenia and 124 developed other nonaffective psychoses. A reverse J-shaped association was found between gestation-adjusted birth weight and schizophrenia. The hazard ratios were 7.03 (95% confidence interval: 1.59, 31.10) for males of low birth weight (<2.5 kg) and 3.37 (95% confidence interval: 1.68, 6.74) for those of high birth weight (>4.0 kg). Birth weight was not strongly related to other nonaffective psychoses. Taller males had a reduced risk of psychosis. The lowest risks were seen for low birth weight males who became tall adults. The associations with birth weight indicate that fetal exposures, including possible effects of gestational diabetes, are important in the etiology of psychosis. The role of childhood exposures, as indexed by adult height and body mass index, appears to be less strong.

birth weight; body height; cohort studies; growth; psychotic disorders; risk factors; schizophrenia

Abbreviations: CI, confidence interval; HBW, high birth weight; ICD, International Classification of Diseases; LBW, low birth weight.

Editor’s note: An invited commentary on this article is published on page 301.

Schizophrenia is thought to be a disorder of neurodevelopment and brain maturation (1). Its etiology is poorly understood, and current models of causation integrate both genetic susceptibility and environmental adversity (2, 3). Because brain development, including remodeling and pruning of neural connections, continues from conception to adulthood (3, 4), environmental exposures operating both pre- and postnatally may influence disease risk. Most studies to date...
have focused on antenatal and perinatal exposures (5, 6). Famine exposure in utero (7), prematurity (8, 9), obstetric complications (9, 10), and low birth weight (LBW) (<2.5 kg) (5, 6, 11) are associated with increased risk.

Few prospective studies of sufficient size to investigate relatively rare illnesses such as schizophrenia have detailed records of childhood exposures. In the absence of such data, proxy measures of childhood development, such as adult height—a marker of both genetically determined growth potential and health/nutrition during childhood (12)—may be useful (13). Short stature may serve as a marker for a range of adverse exposures during childhood. Furthermore, adult height may be used to distinguish LBW infants who are light for gestational age as a result of intrauterine growth retardation from those who are of low weight as a result of genetic influences on growth (small normal babies). LBW infants who become tall adults are likely to have suffered from intrauterine growth retardation prior to conscription (mean age, 18 years) as well as men and women born between 1973 and 1977 and admitted when aged 15–21 years (mean age, 18 years). Our analysis was based on Swedish males born between 1973 and 1980 and diagnosed with incident psychosis. Although the latter category includes those diagnosed by using ICD-9 as having “psychoses with origin specific to childhood” (ICD-9 code 299), only one subject was in this group. Because he was found to be well at his conscription medical examination and had no record of previous psychiatric admissions, we included him among our cases of adult-onset psychoses. To minimize misclassification of diagnosis, if subjects were admitted on more than one occasion, we used the latest diagnosis because we assumed it to be the most accurate. Ethical approval for this study was obtained from the research ethics committee at the Karolinska Institute in Stockholm, Sweden.

Overlap with earlier studies based on Swedish birth registers

Our analysis was based on Swedish males born between 1973 and 1980 and diagnosed with incident psychosis between 1990 and 1997. Mean age at first hospital admission was 21 years. We know of two previous analyses of similar linked Swedish data (8, 10). Dalman et al.’s study (8) focused on men and women born between 1973 and 1977 and admitted to hospital between 1987 and 1995. Hultman et al. (10) examined men and women born in 1973–1979 and admitted when aged 15–21 years (mean age, 18 years). Our data set excluded women and all incident psychosis cases prior to conscription (mean age, 18 years) as well as men considered ineligible for conscription. We had follow-up data on some subjects to age 23 years; therefore, although there was inevitably some overlap, our analysis was based primarily on later occurring psychotic illness among young males considered for military duty. None of the analyses referred to above used information on body size at age 18 years from the Military Service Conscript Registry.

Risk factors investigated

We investigated the risk of psychoses in relation to 1) three markers of fetal growth: birth weight, birth length, and ponderal index (birth weight (kg)/birth length (m)²) obtained from the Medical Birth Registry; and 2) two markers of later childhood growth: the subject’s height and body mass index (weight (kg)/height (m)²) based on clinical measurements made under the supervision of a nurse or physician at the time of conscription. We investigated whether any effect of birth weight on disease risk differed according to adult height by testing for interactions between height and birth weight.

We assessed the effects of the risk factors with and without adjustment for a range of variables found in previous analyses to be associated with an increased risk of schizophrenia. These variables included head circumference; Apgar score at birth; operative (cesarean) delivery; prolonged labor; maternal diabetes; presence of a congenital malformation identified at birth (coded by using ICD, Eighth Revision codes 740–759); preeclampsia and maternal hypertension;
antepartum hemorrhage; maternal age and parity; season of birth (winter: December–February; spring: March–May; summer: June–August; autumn: September–November); urbanicity of area of residence at the time of birth (a four-level variable: main cities and their suburbs (Stockholm, Malmö, and Gothenburg), medium to large cities and industrial areas, rural areas, and other municipalities); and parental education as a measure of the subject’s socioeconomic position (categorized into four groups: < 9 years, 9–10 years, full secondary education, higher education).

Statistical methods

All analyses were carried out by using Stata software, version 6 (15). We used Cox proportional hazards models to assess the influence of measures of fetal and childhood growth on the incidence of nonaffective psychosis. All analyses were controlled for age at the conscription examination. Because of the strong association between gestational age and birth weight and the observation that premature babies are at increased risk of psychosis (8, 16), analyses assessing the influence of birth weight, birth length, and ponderal index were controlled for gestational age by using a three-level categorical variable: £36 weeks, 37–41 weeks, and >41 weeks of gestation. Follow-up was censored at the time of first admission for psychotic illness, death, or emigration. Tests for linear trend were based on the continuous term for the factor examined. To test for nonlinearity, a term for the explanatory variable squared (quadratic term) was added to the factor examined. To test for nonlinearity, a term for the explanatory variable squared (quadratic term) was added to models including a linear term for this variable. Tests for interaction were based on likelihood ratio tests comparing models with and without the relevant explanatory variables.

RESULTS

Subjects included in main analyses

Of the 334,188 males in our original data set, 106 developed schizophrenia and 173 developed other nonaffective psychoses subsequent to their conscription medical examination. The annual incidence of nonaffective psychosis was 0.25 per 1,000 person-years and for schizophrenia was 0.09 per 1,000 person-years.

A total of 87,533 (26 percent) subjects, of whom 26 (0.030 percent) developed schizophrenia and 49 (0.056 percent) developed other nonaffective psychoses, were excluded from the main analyses because data were missing for one or more of the factors investigated. Therefore, 246,655 subjects were included in our main analyses; of these, 80 (0.032 percent) were admitted to hospital with schizophrenia and 124 (0.050 percent) were admitted with a diagnosis of nonaffective, nonschizophrenic psychosis. The most common reason for exclusion was lack of full army medical data (missing for approximately 48,000 subjects). Those for whom data were missing tended to be of lower birth weight (76-g lighter), shorter at birth (0.3-cm shorter), more often born before 37 weeks of gestation (6.3 percent vs. 4.0 percent), and more often born to less-educated parents (28.8 percent vs. 23.5 percent of fathers had received < 9 years of education). At the time of the army medical examination, those subjects for whom data were missing were, on average, 0.3-cm shorter than those for whom data were complete. All of these differences, although generally small, were statistically significant (p < 0.01) because of the large sample size. Subjects were followed up for a mean of 3.40 years (range, 0.03–7.83 years) after their army medical examination.

Characteristics of subjects with schizophrenia and other nonaffective psychoses

Table 1 presents the distribution of birth, conscription, and parental data for the study subjects. Compared with noncases, subjects admitted to hospital for schizophrenic or other nonaffective psychoses tended to be heavier and longer at birth but shorter and lighter as adults. Those with schizophrenia, but not those with other nonaffective psychoses, were more often born in the autumn and winter months. A greater proportion of the parents of those developing psychosis tended to be in the lowest or highest categories of parental education. The prevalence of some obstetric risk factors—preeclampsia, antepartum hemorrhage, and maternal diabetes—was low, indicating that these complications were underrecorded.

Age-adjusted and multivariable models: birth measurements

Table 2 presents age/gestational age and fully adjusted Cox proportional hazards models examining associations of measures of fetal and childhood growth with schizophrenia. A reverse J-shaped association was found between birth weight and schizophrenia; both LBW and high birth weight (HBW) were associated with increased risk (test for nonlinearity using a quadratic term (p = 0.023)). The greatest risk was seen in the LBW category (hazard ratio = 7.03, 95 percent confidence interval (CI): 1.59, 31.10). In models controlling for the possible confounding effects of obstetric complications, other birth measures, and parental education, the strength and direction of associations with birth weight were little different. There was a less marked, but similar-shaped association with ponderal index. In age-adjusted models (without adjustment for gestational age), the same pattern of association with birth weight was observed; the hazard ratios were as follows: < 2.5 kg, 5.07 (95 percent CI: 1.84, 13.95); 2.5–3.0 kg, 2.20 (95 percent CI: 0.96, 5.02); 3.0–3.5 kg, 1.95 (95 percent CI: 1.03, 3.70); 3.5–4.0 kg, 1.0 (reference); and > 4 kg, 3.34 (95 percent CI: 1.77, 6.30). No strong evidence of an association was found between birth weight and other nonaffective psychoses. In particular, there was no evidence of increased risk in the LBW category.

The observed association of LBW with schizophrenia was not due to incomplete adjustment for the confounding effect of prematurity—no schizophrenia cases were born before 35 weeks of gestation, and only three of the cases were born before 37 weeks. No clear relation was evident between birth length and psychosis.
Age-adjusted and multivariable models: adult height and body mass index

The risk of schizophrenia and other nonaffective psychoses decreased with increasing height, but tests for trend were not significant at conventional levels. The hazard ratio for schizophrenia in the top compared with the bottom quartile of height was 0.48 (95 percent CI: 0.23, 1.02); for other psychoses, the hazard ratio for the tallest males was 0.67 (95 percent CI: 0.39, 1.16). These effects were somewhat strengthened in models controlling for birth weight and measures of socioeconomic position. There was evidence that the greatest risk of schizophrenic and other nonaffective psychoses was for conscripts with the lowest body mass index.

Table continues
**Association of birth weight with risk of psychosis across tertiles of adult height**

No evidence of statistical interaction was found between birth weight and height with respect to their association with schizophrenia ($p_{interaction} = 0.23$) or other nonaffective psychoses ($p_{interaction} = 0.92$). Contrary to our expectation, the lowest risks were seen for LBW males who became tall adults, that is, those with some evidence of growth restriction in utero (table 3). In the top tertile of height, risk of schizophrenia increased with increasing birth weight ($p_{trend} = 0.001$). These findings should be interpreted with caution in view of the small number of events in each cell.

**Potential selection bias**

To assess possible selection biases, we repeated all age-adjusted analyses separately for each variable based on those subjects for whom data were available for that variable. Our principal findings were unaltered using this approach. For example, in an analysis based on the 332,945 conscripts for whom we had birth weight and gestational age data, the hazard ratios across the birth weight categories were as follows: $<$2.5 kg, 3.6 (95 percent CI: 1.3, 10.0); 2.5–3.0 kg, 1.7 (95 percent CI: 0.9, 3.5); 3.0–3.5 kg, 1.6 (95 percent CI: 1.0, 2.8); 3.5–4.0 kg, 1.00 (reference); and $>$4.0 kg, 2.6 (95 percent CI: 1.5, 4.4). These hazard ratios are consistent with the increased risk found in the main analyses for HBW and LBW males (see above).
DISCUSSION

Main findings

In this prospective study of Swedish male conscripts, we found that HBW as well as LBW were associated with an increased risk of developing schizophrenia. The associations were independent of a range of possible confounding factors. There was no evidence that small babies who became large adults, that is, those with evidence of intrauterine growth retardation, were at greater risk of developing schizophrenia. However, it is possible that our proxy anthropometric measure of intrauterine growth retardation is a poor marker...
for this phenomenon because it is known that some babies suffering from intrauterine growth retardation become small adults (12). The associations with measures of fetal growth appeared to be specific for schizophrenia rather than the other nonaffective psychoses. In contrast, the (weak) reduction in risk associated with greater adult height and body mass index was evident for both schizophrenic and other nonaffective psychoses.

Study strengths

We used routinely recorded data on birth-related, parental, and adult exposures collected prior to disease onset. Furthermore, because cases were ascertained from a national patient register, the possibility of selection bias was reduced. Linkage between birth and conscription data enabled us to look at an array of measures of fetal and childhood growth. The reasonably large number of cases provided statistical power to detect important etiologic associations and to control for potentially important confounding factors.

Study limitations

This analysis has several limitations. First, case ascertainment was based on hospital-admitted cases whose diagnoses were recorded in an administrative database. Although we missed persons not admitted to hospital, studies in the United Kingdom indicate that, in the 5 years after presentation, over 80 percent of cases are admitted, even in areas with relatively community-oriented services (17). Furthermore, analyses of diagnoses recorded on the Swedish Inpatient Discharge Register indicate that schizophrenia is diagnosed with reasonable accuracy (82 percent specificity and 87 percent sensitivity (18)). To further ensure the validity of case ascertainment, for cases who had several hospital admissions, we used only the diagnosis made at the last admission. Second, our analysis was based on males whose illness onset occurred in early adulthood. Although recent meta-analyses of case-control studies indicate that there are no gender differences in the associations between obstetric complications and schizophrenia, these studies do suggest that associations are stronger for early-onset illness (6, 19). We may therefore have overestimated the effects of these risk factors on the incidence of schizophrenia.

Third, because information on psychotic illness in the parents of cases was not available, we were unable to control for its possible confounding effects in this analysis. A number of studies indicate that parental schizophrenia increases the risk of LBW and obstetric complications (20). However, only about 5–10 percent of cases are likely to have had an affected parent (8, 21). Furthermore, one family-based study reported differences in birth weight between affected and unaffected siblings (22). Fourth, the relatively low prevalence of recorded gestational diabetes, hypertension, and antepartum hemorrhage indicate that data on some obstetric variables were recorded incompletely on the birth registry, raising the possibility of residual confounding. Finally, birth weight, adult height, and body mass index are crude measures of fetal and childhood growth; the exposures influencing growth and underlying the risk of developing psychosis associated with these factors were not discernable in this analysis.

Birth weight and psychosis

The association we found between LBW and schizophrenia is in keeping with that reported in other investigations of Swedish national data (8, 10) and in recent reviews of the literature (5, 6, 11). Because our cases and those included in these earlier analyses overlap, our data provide weak independent new evidence of a LBW effect. Although we found a sevenfold increase in risk for those weighing

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**TABLE 3. Associations of birth weight with schizophrenia and other nonaffective psychoses in males according to tertiles of adult height (controlling for age and gestational age), Sweden**

<table>
<thead>
<tr>
<th>Height tertile (cm)</th>
<th>Birth-weight tertile (g)</th>
<th>No. of cases</th>
<th>Hazard ratio</th>
<th>95% CI†</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>560–3,380</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>147–177</td>
<td>17</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>178–182</td>
<td>10</td>
<td>0.99</td>
<td>0.45, 2.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>183–208</td>
<td>2</td>
<td>0.26</td>
<td>0.06, 1.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.28</td>
<td>0.08, 0.95</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>8</td>
<td>1.01</td>
<td>0.43, 2.37</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>147–177</td>
<td>22</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>178–182</td>
<td>9</td>
<td>0.70</td>
<td>0.32, 1.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>183–208</td>
<td>6</td>
<td>0.62</td>
<td>0.25, 1.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>0.76</td>
<td>0.37, 1.58</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>22</td>
<td>1.08</td>
<td>0.60, 1.97</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-trend 0.40</td>
<td>0.18</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-trend 0.15</td>
<td>0.29</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CI, confidence interval.
† pInteraction = 0.23.
‡ pInteraction = 0.92.
If impaired fetal growth underlies the LBW-schizophrenia association, we might expect that the risk associated with LBW would be greatest for those infants who became tall adults, because subsequent height gives a crude indication of fetal growth potential—large babies tend to become taller adults (23). We found no such evidence. In fact, for LBW babies, greater risks were found for those who remained small. This finding may indicate either that genes that increase the risk of schizophrenia are associated with poor pre- and postnatal growth or that only environmental influences on prenatal growth severe enough to permanently influence an infant’s growth trajectory are associated with disease risk. However, these subgroup findings should be interpreted with caution because the overall test for interaction was not significant ($p = 0.23$). Nevertheless, they are similar to those reported in the only other study to examine associations with fetal and childhood growth, which reported that the greatest risk of schizophrenia was for those who were small at birth and had low body mass indexes at age 7 years (24).

We found an association between HBW, but not increased birth length, and schizophrenia, indicating that the heavier babies are not simply larger but possibly those who have deposited more body fat or have larger body organs. An association with HBW has been reported in one other prospective investigation we are aware of, the Northern Finland 1966 Birth Cohort (25), which found that HBW for gestational age was associated with an almost threefold increased risk of schizophrenia in males, but not females (25). Moilanen et al.’s (25) and our findings are in keeping with a Swedish case-control study reporting a fourfold increased risk for babies more than one standard deviation above mean birth weight (26). Few other studies have examined this issue. In the previous prospective studies based on the Swedish birth registers, more extreme HBW categories were used than that chosen in our analysis. In Dalman et al.’s study (8), those subjects weighing ≥4,500 g ($n = 5$ cases) were compared with those weighing 2,500–4,499 g (as a single group). Hultman et al. (10) compared those whose birth weights were more than two standard deviations from the mean (i.e., >4,800 g ($n = 4$ cases)) with those of all other birth weights. It may be that, in these studies, any possible association with raised birth weight was missed because of the extreme HBW cutoff used. The only other prospective investigation to study birth weight-schizophrenia associations across the range of birth weights was Wahlbeck et al.’s analysis (24) of the Helsinki cohort. They used the same cutoff for their raised birth weight category as we did ($>4,000$ g). In contrast to our finding, they reported that the lowest risks of schizophrenia were found in this HBW group (24). The Helsinki cohort is based on males and females born in 1924–1933, whereas our analysis of Swedish data and the northern Finland cohort included early-onset cases born in the 1960s–1970s, and the positive findings were for males only.

Further indirect evidence that HBW influences the risk of schizophrenia comes from two cohort studies (9, 27) showing that the offspring of overweight mothers (body mass indexes of ≥30 and 29 kg/m², respectively) have a more than twofold increased risk of schizophrenia. High maternal weight is, in turn, one of the most powerful predictors of HBW in the offspring (28).

### Adult height, body mass index, and psychosis

The tallest subjects had a reduced risk of developing psychosis, although these trends did not reach conventional levels of statistical significance. Unlike the associations with LBW, the associations of height with schizophrenia and other nonaffective psychoses were similar. This finding suggests that factors influencing postnatal growth and development, such as diet, infection, psychological stress, poor socioeconomic circumstances, or growth-regulating genes, could also influence the development of psychosis. The trends in risk we observed with decreasing body mass index are in keeping with this suggestion and are consistent with those in the Helsinki cohort (24). Evidence of height-schizophrenia associations from case-control studies is mixed, with some positive (29, 30) and some negative (31) reports. Height associations were not found in one recent prospective investigation (24). Differences between these studies may reflect differences in the populations studied as well as the fact that we were able to investigate associations with only early-onset schizophrenia. Most case-control studies that have examined this issue are limited as a result of control selection biases. Although season of birth is associated with birth weight (32), adult height (33), and schizophrenia risk (34), the associations with these anthropometric variables were not weakened in models controlling for birth season.

### Mechanisms underlying observed associations

Studies investigating the early life origins of schizophrenia have used a wide array of exposure measures (9, 10, 35) characterized as being divided into three broad categories: markers of 1) chronic fetal hypoxia, 2) prematurity, and 3) other complications (9). Possible etiologic pathways increasing susceptibility to later schizophrenia include the permanent effects on brain development of chronic undernutrition at crucial periods of growth, acute brain damage resulting from birth trauma, and the long-term effects of early exposure of either the mother or infant to infectious disease. In our analysis, we used anthropometry at birth as a marker of fetal growth and development; these measures may be influenced by fetal hypoxia as well as a range of other factors, including maternal nutrition, parental body size, and the health of the fetus and mother.

The reverse J-shaped association we found with birth weight is in keeping with similar-shaped associations reported in studies examining birth weight-mortality associations for coronary heart disease (36, 37)—a disorder in which patterns of fetal growth are also thought to be of etiologic importance (38). If the association of raised birth weight with schizophrenia is real, it is likely that the underlying biologic mechanisms are different from those leading to the associations with LBW.
We can conceive of two possible explanations for the association with raised birth weight. First, diabetic mothers and those who develop gestational diabetes tend to produce HBW offspring (39). A recent review of population-based studies investigating obstetric complications and schizophrenia reported that the strongest predictor of risk was diabetes in pregnancy (11). Possible biologic pathways mediating the association of gestational diabetes with schizophrenia are unclear. It is of note, however, that in a study of infants of diabetic mothers, less-optimal neurodevelopment was found in the infants of women whose diabetes was poorly controlled (40). In our study, the low prevalence of maternal diabetes indicates probable underrecording of the less severe forms of maternal glucose intolerance that may nevertheless influence birth weight.

Second, this association could be caused by the increased risk of cerebral anoxia during delivery of HBW infants due to fetal-maternal disproportion (41). The possible importance of disproportion in generating risk is supported by our finding that the risk of developing schizophrenia was lowest for tall conscripts of LBW. Because tall men are more likely to have had tall mothers (correlations between the height of mothers and their male offspring are about 0.50 (12)), they are less likely to have been subject to cephalopelvic disproportion during delivery. Further supportive evidence for this effect comes from the reduced risk for children born by cesarean section who thereby avoided some of the trauma associated with vaginal delivery (refer to table 1). However, this observation should be interpreted with caution because we were unable to distinguish elective from emergency cesarean sections. Infants born by emergency cesarean section are more likely to have suffered birth asphyxia, which itself may be associated with increased risk of schizophrenia (42).

Conclusion

Further detailed research is required to replicate and elucidate the associations with preadult growth observed in this analysis. Although it is not possible to greatly modify birth weight, understanding the factors that lead some LBW and HBW males to develop schizophrenia may help shed light on the etiology of this disorder.

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