Fetal Growth Restriction and Schizophrenia: A Swedish Twin Study

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Obstetric complications increase the risk of schizophrenia. However, it is not known whether there is a causal relation or whether the association is mediated by genetic and/or shared environmental effects. The aim of this study was to investigate the associations between birthweight, other birth characteristics, and schizophrenia. Twin pairs discordant for schizophrenia will also control for unmeasured genetic and shared environmental effects. Prospectively filed obstetric records were used for a cohort analysis of 11,360 same-sexed twins, and within–twin pair analyses were conducted on 90 twin pairs discordant for schizophrenia. The results from the cohort study showed that low birthweight (less than or equal to 1999 grams; odds ratio [OR] 1.67, 95% confidence interval [CI] 0.88–3.14 and 2000–2299 grams; OR 1.79, 95% CI 1.07–3.01) and small head circumference (less than or equal to 31.5 cm; OR 1.61, 95% CI 1.03–2.51) were associated with later development of schizophrenia. The associations remained in the within-pair analyses. The association between low birthweight and schizophrenia is partly a function of reduced fetal growth. Fetal growth restriction seems to be associated with risk of schizophrenia independently of familial factors.

Schizophrenia is thought to be a neurodevelopmental disorder, and results from epidemiological, neuropathological and postmortem studies suggest that at least a portion of adult schizophrenia results from aberrant brain development in early life (Murray, 1994). This may have its origin in genetic defects in the control of early brain growth, or in early environmental hazards, such as prenatal exposure to maternal influenza or perinatal complications.

There is growing evidence that obstetric complications and particularly low birthweight and other measures of fetal growth restriction are risk factors for schizophrenia (Cannon et al., 2002; Geddes & Lawrie, 1995; Hultman et al., 1997; Kunugi et al., 2003; McNeil, 1995). However, we do not know whether low birthweight and/or fetal growth restriction is causally related to risk of schizophrenia or whether the association is mediated by genetic and/or shared environmental effects. Twin studies can illuminate this issue. Studying birthweight within same-sexed twin pairs discordant for disease allows matching for gestational age as well as genetic and environmental factors shared by the twins.

In the present study the associations between birthweight adjusted for gestational age and sex ('birthweight ratio') and other birth characteristics and schizophrenia in a cohort of Swedish twins are investigated. In order to control for genetic and shared environmental effects, the importance of fetal growth within twin pairs discordant for schizophrenia is also investigated.

Materials and Methods

Setting

The population-based Swedish Twin Registry includes information about all twins born in Sweden since 1886 in principle. In 1972, the cohort of same-sexed twin pairs born 1926 to 1958 was approached and both members of 14,000 twin pairs completed a questionnaire (Lichtenstein et al., 2002).

The Swedish Twin Registry is updated by individual record linkages to the Swedish Hospital Discharge Registry and the Cause of Death Registry through the 10-digit individual national registration numbers assigned to Swedish residents. The Hospital Discharge Registry includes data on individual hospital discharges from inpatient care in Sweden and has a nationwide coverage of psychiatric diagnoses from 1973 onwards. The Hospital Discharge Registry includes information on the national registration number, main diagnoses and up to five secondary diagnoses (if occurring) classified by the treating physician at the time of discharge from hospital.

Fetal Growth and Other Pre- and Perinatal Characteristics

In Sweden, information on hospital and home deliveries has been recorded on obstetric records since the beginning of the 20th century. The files are archived in maternity hospitals, regional counties, or in city archives. Information was collected on conditions during pregnancy, delivery and the neonatal period from these prospectively filed obstetric records in which systematic notations have been recorded by the attending midwives and obstetricians at birth.

The following information was retrieved from the obstetric records: maternal age, maternal complications during pregnancy, birth order (first- or secondborn twin), birth year, birth place (at home or at hospital), sex of the child, gestational age (in completed gestational weeks based on the last menstrual period), birthweight, head circumference and complications of the infant in the neonatal period. In the analysis, birthweight was divided into three categories (less than or equal to 1999, between 2000 and 2299, and greater than or equal to 2300 grams, including 10%, 15% and 75% of the cohort, respectively). Categories of small head circumference and preterm delivery were chosen to approximate the lowest quartile. Small head circumference was defined as smaller than or equal to 31.5 cm (including 22.6% of the cohort) and preterm delivery as delivery before 37 completed weeks (including 28.9% of the cohort). As measures of fetal growth, birthweight ratio and head circumference ratio were used. Birthweight ratio was defined as the ratio of the observed to the expected birthweight for gestational age and sex. The birthweight ratio was divided into three categories: very low, moderately low and normal birthweight ratio, including 10%, 15% and 75% of the cohort, respectively. Head circumference ratio was defined in the same manner and small head circumference ratio was chosen to approximate the lowest quartile.

Information on birth order (first- or secondborn twin) is essential in order to get correct information on birth characteristics. Information about birth order was available if the twin was baptized and named at birth, and/or if the twin responded to a question about birth order in the telephone interview. Information on birth order has been validated in two subsamples of same-sexed twin pairs born 1926 to 1958. In 2713 twin pairs who were baptized at birth, both twins also were in mutual agreement regarding the question on birth order in the telephone interview. In all, there was a 95% agreement between birth order as assessed by Christian names at birth and self-reported birth order later in life. In another 1762 twin pairs who were baptized at birth, only one twin in a pair responded to the question on birth order in the telephone interview. Here there was a 92% agreement between birth order by Christian names at birth and self-reported birth order. It was therefore decided to include information about birth order, firstly, from Christian names given at birth and, secondly, from self-reported birth order,

provided that both twins responded with mutual agreement, or that only one twin in a pair responded to the question. In 49 cases, birth order was assessed by Christian names given at baptisms at birth and in 41 cases the birth order was given in telephone interviews.

Case Identification

The study population comprises all same-sexed twin pairs born since 1926 included in the Swedish Twin Registry. Potentially eligible cases were all same-sexed twins diagnosed with schizophrenia (the diagnoses are coded according to the 8th and 9th revision of *International Classification of Diseases* [World Health Organization, 1967, 1977], code no 295) in the Hospital Discharge Registry until 1996. Three hundred and two eligible cases with schizophrenia were identified and the diagnosis verified by contacting the doctors responsible for each patient and requesting permission to contact the twins with schizophrenia. Two hundred and forty-nine doctors accepted contact with cases (46 doctors responsible were not found and seven doctors responsible did not accept contact with cases) and 111 cases accepted (71 cases were not found, eight cases were not interviewable and 59 cases did not want to participate). Among these, information on birth order was obtained in 106 cases. Delivery records were obtained for 90 twins diagnosed with schizophrenia (85% of 106).

Cohort Study of Unaffected Unrelated Twins

In the cohort analyses, 11,360 same-sexed twins born between 1926 and 1958 were used whose birth records had been retrieved in an ongoing birth size project in the Swedish Twin Registry. These twins were all alive in the year 2000. Twins with schizophrenia born between 1926 and 1958 (88 cases) were included.

Case-Control Study With Unaffected Co-Twins as Controls (Within-Pair Comparisons)

The second part of the study was a within-pair comparison of same-sexed twin pairs. Individuals included in this analysis were 90 cases born between 1927 and 1974 with schizophrenia, and their co-twins without a history of schizophrenia at the time the case was diagnosed. Unfortunately, the analysis was not able to be subdivided into monozygotic (MZ) and dizygotic (DZ) twin pairs to investigate whether there are genetic or shared environmental factors that explain the familial mediation of the association between fetal growth restriction and schizophrenia. Eight pairs concordant for schizophrenia were excluded.

Statistical Analysis

Analyses with nonrelated twins were performed using logistic regression and the SAS System version 8.2 (SAS, 2000). In order to take into account the dependence within twin pairs, the data was analysed using Generalized Estimation Equation models (GEE) and PROC GENMOD, which provides a correlation structure for related observations (Diggle et al., 1994). The

within-pair analyses were performed with conditional logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were calculated as measures of relative risk.

Results

Table 1 shows the distribution of birth characteristics and crude ORs of schizophrenia in the cohort. Individuals with a birthweight of less than 2300 grams faced an almost doubled risk of developing schizophrenia compared to individuals with higher birthweight. Children with a small head circumference (31.5 cm or less) had a 60% higher risk of developing schizophrenia compared to children with a larger head circumference. Compared to children born at term (37 gestational weeks or more), children born preterm (36 weeks or less) had a 70% increased risk of developing schizophrenia.

Next, the analyses were restricted to pairs where birth order was confirmed in written documents (i.e., baptized and named at birth). In all, 47 twins with schizophrenia and 11,272 twins without the diagnosis were included in these analyses. Compared to children with a birthweight of 2300 grams or more, the risk of schizophrenia was increased among children with a birthweight below 2000 g (OR 2.34, 95% CI 1.16–4.72), and also for children with a birthweight between 2000 and 2299 g (OR 1.42, 95% CI 0.64–3.13). Similarly, small head circumference and preterm delivery were also associated with increased risks of schizophrenia (data not shown).

There were no statistically significant differences between individuals with and without schizophrenia with regard to maternal age, maternal complications during pregnancy, birth year, sex of the child, birth order (first- or secondborn) or birthplace (at home or at hospital; data not shown). The only infant complication in the neonatal period that differed significantly between twins with and without schizophrenia was the neonatal diagnosis *congenital debility* (15.9% of the twins with schizophrenia compared to 9.2% of the twins without the diagnosis; $\chi^2 = 4.76$, $p = .029$). This diagnosis was used before the introduction of the Apgar score and reflects hypotonia and other signs of asphyxia immediately after birth. Debility was therefore controlled for in the subsequent analysis.

In the comparison with external unrelated twins, we also wanted to investigate whether the associations between birth characteristics and risk of schizophrenia reflect an association between fetal growth restriction and schizophrenia. Compared to individuals with normal birthweight ratio, children with very low birthweight ratio had a 40% increased risk of developing schizophrenia, although not statistically significant (Table 2). Similarly, individuals with a small head circumference ratio faced a nonsignificantly increased risk of schizophrenia. After adjusting for debility these risks were further attenuated.

Table 1

Distribution and Crude Odds Ratios (OR) and 95% Confidence Intervals (CI) of Birthweight, Head Circumference, and Gestational Age Among Individuals With and Without Schizophrenia

| | Schizophrenia | | | |
| | Yes | No | OR | 95% CI |
	n (%)	n (%)		
Birthweight (grams)				
≤ 1999	13 (14.8)	1119 (9.9)	1.67	(0.88–3.14)
2000–2299	20 (22.7)	1690 (15.0)	1.79	(1.07–3.01)
≥ 2300	55 (62.5)	8463 (75.1)	Ref	
Head circumference (cm)				
≤ 31.5	27 (31.8)	2476 (22.6)	1.61	(1.03–2.51)
≥ 32.0	58 (68.2)	8499 (77.4)	Ref	
Missing	3	297		
Gestational age (weeks)				
≤ 36	34 (40.5)	2998 (28.8)	1.68	(1.05–2.69)
≥ 37	50 (59.5)	7416 (71.2)	Ref	
Missing	4	858		

Note: Ref = reference group.

Table 2

Crude and Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for the Associations Between Birthweight Ratio and Head Circumference Ratio and Risk of Schizophrenia

| | Crude | | Adjusted[†] | |
	OR	95%CI	OR	95% CI
Birthweight ratio				
Very low birthweight	1.43	(0.75–2.73)	1.33	(0.68–2.62)
Moderately low birthweight	1.11	(0.63–1.97)	1.04	(0.58–1.84)
Normal birthweight	Ref		Ref	
Head circumference ratio				
Small head circumference	1.36	(0.85–2.20)	1.26	(0.76–2.10)
Normal	Ref		Ref	

Note: [†]Adjusted for congenital debility.
Ref = reference group.

Table 3

Odds Ratios (OR) and 95% Confidence Intervals (CI) for Schizophrenia in Same-Sexed Twin Pairs, Discordant for Schizophrenia

| | Crude | |
	OR	95% CI
Birthweight		
≤ 2299	1.50	(0.61–3.67)
≥ 2300	Ref	
Head circumference		
≤ 31.5	1.67	(0.61–4.59)
≥ 32.0	Ref	

Note: Ref = reference group.

Within-pair analyses were also performed to be able to take into account unmeasured familial factors (genetic and/or shared environmental). The within-pair analyses of pairs discordant for schizophrenia are presented in Table 3. Since twin pairs share gestational age, differences in birthweight and head circumference within same-sexed twin pairs mirror differences in fetal growth. Low birthweight and small head circumference were not significantly associated with increased risks of schizophrenia, although the point estimates for both variables remained increased.

Interestingly, an association was found between congenital debility and the risk of schizophrenia. When external controls were used, children with debility had, in the crude analysis, an almost doubled risk of developing schizophrenia compared to children without debility (OR 1.87, 95% CI 0.99–3.53; Table 4). After adjustment for gestational age the risk decreased, but was still elevated (not statistically significant). In the within-pair analysis, debility was associated with a doubled, although not statistically significant, increased risk of schizophrenia.

Discussion

The results from this cohort study of 11,360 same-sexed Swedish twins lend further support for the hypothesis that low birthweight is associated with later development of schizophrenia. This finding was also supported by the restricted analysis, where only pairs whose birth order was confirmed in written documents were included. Also, in the cohort analyses as well as in the within-pair analyses, the measures of fetal growth restriction were associated with schizophrenia. In the cohort analyses the risk estimates generally decreased when debility was adjusted for, a diagnosis reflecting signs of asphyxia immediately after birth. Thus, this study suggests that the previously reported association between low birthweight and schizophrenia partly is a function of reduced fetal growth and also partly due to infant-specific characteristics. The results from the cohort study were supported by the analyses within twin pairs discordant for disease, indicating that the association between fetal growth restriction and the risk of schizophrenia is independent of familial factors. In other studies on MZ twins discordant for schizophrenia, there was no clear-cut evidence for lower birthweight in twins with

schizophrenia compared with their unaffected co-twins (Gottesman & Shields, 1976; Kunugi et al., 2003; McNeil et al., 1994; Onstad et al., 1992; Pollin & Stabenau, 1968; Torrey, 1977). However, most of these twin studies obtained their obstetric data from maternal or other relatives, recall rather than hospital records (Kunugi et al., 2001).

An association was also found between a small head circumference and schizophrenia, both in the cohort and in the within-pair analyses, again suggesting that the association between obstetric complications and schizophrenia is not confounded by familial effects. An association between small head circumference at birth and the later development of schizophrenia was confirmed in a number of previous studies (Cantor-Graae et al., 1998; Hultman et al., 1999; Ichiki et al., 2000; Kunugi et al., 1996; McNeil et al., 2000). In accordance with our results, three of these studies showed a reduction in the risk related to small head circumference, after controlling for gestational age (Cantor-Graae et al., 1998; Kunugi et al., 1996; McNeil et al., 2000). Moreover, a study by Gilmore et al. (1996) showed that there is a significant difference in head circumference measured *in utero* by ultrasound among MZ twin pairs. The authors conclude that the difference in brain development may contribute to the observed discordance rate in MZ twins with schizophrenia.

Our results also suggest that there is an association between preterm delivery and schizophrenia, even though Cannon et al. (2002) did not find any association between prematurity and schizophrenia in a recent meta-analysis.

The twins in this study were born between 1926 and 1974, and neonatal complications of the infant were classified differently from today. Signs of asphyxia at birth, weakness after delivery and the need for a child to remain under care after birth were noted with the diagnosis 'congenital debility' (coded according to the *Manual of International Statistical Classification of Diseases, Injuries, and Causes of Death*, 6th and 7th revision [World Health Organization, 1948, 1956] code no 772.0 and 773.0). This diagnosis was used as a proxy for Apgar score, which is the current standardized assessment of asphyctic signs at 1, 5 and 10 minutes after delivery. In agreement with our finding of an association

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Table 4

Odds Ratios (OR) and 95% Confidence Intervals (CI) for the Diagnosis Congenital Debility Among Individuals With and Without Schizophrenia

	Crude		Adjusted for gestational age		Within-pair analysis	
	OR	95% CI	OR	95% CI	OR	95% CI
Congenital debility						
Yes	1.87	(0.99–3.53)	1.55	(0.80–2.98)	2.00	(0.18–22.05)
No	Ref		Ref		Ref	

Note: Ref = reference group.

between debility and the later development of schizophrenia, four population-based studies reported a trend towards increased frequency of low Apgar scores among infants who later developed schizophrenia (Dalman et al., 1999; Dalman et al., 2001; Hultman et al., 1999; Jones et al., 1998), although the association was only statistically significant in one study (Dalman et al., 2001). Similar ideas have been suggested from earlier twin studies; Torrey et al. (1994) found two subgroups of twins with schizophrenia, an early and a late divergence group. In the early divergence group, the affected and the unaffected twins became permanently different from each other in motor skills or unusual behavior at the age of 5 years or before. A recent case report by Kunugi et al. (2003) showed that the discordant MZ twin pair analyzed in that study clearly belonged to the early divergence group. The author suggested that there may be a subtype of schizophrenia originating from prenatal underdevelopment, leading to poor premorbid functioning caused by perinatal hypoxia brain damage, and subsequently resulting in the development of schizophrenia in adolescence or early adulthood. Thus, it is possible that early signs of weakness (e.g., debility) may, in addition to low-birthweight and/or fetal growth restriction, be important predictors of later development of schizophrenia.

This population-based twin study offers several methodological advantages. Information of conditions during the neonatal period was gathered from prospectively filed pediatric records. Systematic notations have been recorded at delivery and neonatally by the attending midwives and obstetricians. The twin design guarded against the confounding effects of earlier suggested risk factors for schizophrenia, such as maternal lifestyle factors and conditions during pregnancy. Birthweight was categorized and the lowest quartile was regarded as the low birthweight babies. The same principle was used regarding small head circumference. This is in line with Cannon et al. (2002), who argue that arbitrary cut-offs in birthweight may account for the heterogeneity in the association between low birthweight and schizophrenia in previous studies.

There are at least four limitations to consider in this study. First, the diagnoses studied were those made by the treating physicians, and are thus dependent on the judgment of different doctors. However, psychiatric diagnoses listed in the Hospital Discharge Registry are reliable, as Swedish diagnostic practice is generally considered to be good (Dalman et al., 2002; David et al., 1997). Moreover, the Swedish concept of schizophrenia is narrow and reflects diagnostic caution rather than overinclusiveness (Kristjansson et al., 1987). Therefore, some individuals with schizophrenia who are not registered in the Hospital Discharge Registry are likely to have been misclassified to the control group. A concordant pair may have been treated as discordant in the analysis, and this

may have led to an underestimation of the true risks. Second, higher risk estimates were obtained when the analyses were restricted to pairs whose birth order was confirmed in written documents (i.e., baptized and named at birth) compared to analyses where all pairs were included. This indicates that birth order may have been misclassified among cases and their co-twins and the true risk may have been underestimated. Third, although the confidence intervals are relatively wide, the consistent pattern of an increased risk for schizophrenia among twins with low birthweight and small head circumference supports the hypothesis of a casual effect of restricted fetal growth on schizophrenia. This study highlights the difficulty in twin studies, even in quite large samples, to analyze discordant pairs in disorders with very high heritability estimates (Sharp et al., 2003). Only 90 birthweight discordant pairs were identified in which one of the twins met the criteria for schizophrenia. Consequently we were not able to subdivide the analysis with MZ and DZ twin pairs to elucidate whether there are genetic or shared environmental factors that explain the familial mediation of the association between fetal growth restriction and schizophrenia. Fourthly, affected twins discordant for schizophrenia are considered phenotypically comparable with affected singletons (Sharp et al., 2003), but the problem of generalization cannot be fully excluded from twins to singletons.

We have replicated previous association between low birthweight and schizophrenia. The within-pair analyses indicated that the association between fetal growth restriction and risk of schizophrenia is probably independent of familial factors. We also found an independent effect of debility (previously used as a measure of asphyxia in the neonatal period) associated with schizophrenia. Thus, it is possible that early signs of weakness (e.g., debility) may, in addition to low birthweight and/or fetal growth restriction, be important predictors of later development of schizophrenia. This study highlights the importance of continuous search for such early indicators.

Acknowledgments

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