Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study

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Abstract

Objective To examine prenatal and perinatal risk factors for subsequent development of schizophrenia and affective and reactive psychosis.

Design Three population based, case-control studies conducted within a Sweden-wide cohort of all children born during 1973-9. This was done by linking individual data from the Swedish birth register, which represents 99% of all births in Sweden, to the Swedish inpatient register.

Subjects Patients listed in inpatient register as having been first admitted to hospital aged 15-21 years with a main diagnosis of schizophrenia (n = 167), affective psychosis (n = 198), or reactive psychosis (n = 292). For each case, five controls were selected.

Main outcome measures Risks of schizophrenia and affective and reactive psychosis in relation to pregnancy and perinatal characteristics.

Results Schizophrenia was positively associated with multiparity (odds ratio 2.0), maternal bleeding during pregnancy (odds ratio 3.5), and birth in late winter (odds ratio 1.4). Affective psychosis was associated with uterine atony (odds ratio 2.2) and late winter birth (odds ratio 1.5). Reactive psychosis was related to multiparity (odds ratio 2.1). An increased risk for schizophrenia was found in boys who were small for their gestational age at birth (odds ratio 3.2), who were number four or more in birth order (odds ratio 3.6), and whose mothers had had bleeding during late pregnancy (odds ratio 4.0).

Conclusions A few specific pregnancy and perinatal factors were associated with the subsequent development of psychotic disorder, particularly schizophrenia, in early adult life. The association of small size for gestational age and bleeding during pregnancy with increased risk of early onset schizophrenia among males could reflect placental insufficiency.

Introduction

Evidence from epidemiological and neuropathological studies indicates that pathogenic processes that culminate in the development of schizophrenia are initiated early in life.[1] The neurodevelopmental hypothesis that schizophrenia has its origins in aberrant brain development receives support from the evidence of an association between obstetric complications and schizophrenia,[2–4] especially schizophrenia with an early age of onset.[5] However, there is still controversy concerning the specificity of this association for schizophrenia, the existence of specific risk factors, and the possibility of a bias in the literature towards publication of positive findings.[4] In a recent hospital based case-control study of 107 schizophrenic patients with age of onset up to 45 years only aberrations in size at birth remained significantly associated with schizophrenia in a multivariate analysis.[3]

We undertook the present nationwide Swedish study to examine the association between size at birth and other prenatal and perinatal factors and the risk of developing schizophrenia in early adult life. Additionally, we addressed the question of whether disturbance in prenatal development is specific to schizophrenia or whether it also occurs in affective and reactive psychoses.[3 6–9]

Subjects and methods

We linked individual data from the Swedish birth register, which represents 99% of all births in Sweden,[10] to the nationwide inpatient register by means of the unique 10 digit personal identification number assigned to each Swedish resident. Complications during pregnancy, delivery, and the neonatal period were classified according to the ICD-8 (international classification of diseases, eighth revision). These assessments had been completed by obstetricians on a standard form at the time each infant was discharged from hospital. The Swedish inpatient register provides data on individual hospital discharges, including the diagnosis assigned by the treating physician, according to ICD-9 (international classification of diseases, ninth revision) from 1987 onwards. The registers provide nationwide coverage for the study.[11 12]

Method of selecting cases and controls

We selected subjects who were registered in the birth register as born between 1973 and 1979 and who were subsequently listed in the inpatient register as having

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Table 1 Prenatal and perinatal characteristics of subjects with schizophrenia, affective psychosis, or reactive psychosis and matched controls. Values are numbers (percentages)

	Schizophrenia		Affective psychosis		Reactive psychosis	
	Cases (n=167)	Controls (n=835)	Cases (n=198)	Controls (n=990)	Cases (n=292)	Controls (n=1460)
Maternal factors						
Age at delivery (years):						
⩽19	10 (6.0)	59 (7.1)	11 (5.6)	60 (6.1)	25 (8.5)	94 (6.4)
20-29	112 (67.1)	595 (71.2)	126 (63.6)	686 (69.3)	181 (62.0)	1020 (69.9)
⩾30	45 (26.9)	181 (21.7)	61 (30.8)	244 (24.6)	86 (29.5)	346 (23.7)
Parity:						
1	80 (47.9)	372 (44.5)	95 (48.0)	483 (48.8)	135 (46.2)	675 (46.2)
2-3	71 (42.5)	419 (50.2)	92 (46.5)	458 (46.3)	128 (43.9)	713 (48.9)
4	16 (9.6)	44 (5.3)	11 (5.6)	49 (5.0)	29 (9.9)	72 (4.9)
Pregnancy and delivery factors						
Hypertensive diseases	9 (5.4)	27 (3.2)	9 (4.5)	30 (3.0)	8 (2.7)	53 (3.6)
Diabetes	2 (1.2)	2 (0.2)	1 (0.5)	6 (0.6)	2 (0.7)	3 (0.2)
Bleeding during pregnancy	6 (3.6)	13 (1.6)	6 (3.0)	23 (2.3)	6 (2.0)	29 (2.0)
Uterine atony	15 (9.0)	51 (6.1)	17 (8.6)	41 (4.1)	17 (5.8)	74 (5.1)
Preterm rupture of membranes	2 (1.2)	7 (0.8)	2 (1.0)	12 (1.2)	5 (1.7)	0.9 (1.3)
Fetopelvic disproportion	3 (1.8)	23 (2.8)	4 (2.0)	26 (2.6)	11 (3.8)	43 (2.9)
Vacuum extraction	15 (9.0)	57 (6.8)	15 (7.6)	55 (5.6)	17 (5.8)	76 (5.2)
Caesarean section	9 (5.4)	51 (6.1)	14 (7.1)	75 (7.6)	26 (8.9)	109 (7.5)
Traumatic delivery	7 (4.2)	31 (3.7)	9 (4.6)	40 (4.0)	11 (3.8)	48 (3.3)
Twin birth	3 (1.8)	6 (0.7)	4 (2.0)	23 (2.3)	6 (2.0)	22 (1.5)
Child characteristics						
Gestational age (weeks):						
36	12 (7.2)	40 (4.8)	16 (8.2)	66 (6.7)	22 (7.6)	85 (5.8)
37-41	132 (79.5)	658 (79.2)	160 (81.6)	774 (78.7)	223 (76.9)	1172 (80.6)
42	22 (13.3)	133 (16.0)	20 (10.2)	143 (14.6)	45 (15.5)	197 (13.6)
Birth weight (g):						
<2500	11 (6.6)	31 (3.7)	11 (5.6)	37 (3.7)	16 (5.5)	59 (4.1)
2500-4499	153 (91.6)	779 (93.3)	183 (92.4)	930 (94.0)	267 (91.4)	1367 (93.8)
⩾4500	3 (1.8)	24 (2.9)	4 (2.0)	23 (2.3)	9 (3.1)	32 (2.2)
Birth length (cm):						
<49	25 (15.1)	117 (14.2)	33 (16.8)	177 (18.1)	60 (20.9)	251 (17.3)
49-51	87 (52.4)	415 (50.4)	111 (56.6)	507 (51.8)	138 (48.1)	722 (49.9)
52-54	47 (28.3)	257 (31.2)	48 (24.5)	270 (27.6)	78 (27.2)	439 (30.3)
>54	7 (4.2)	35 (4.2)	4 (2.0)	24 (2.5)	11 (3.8)	36 (2.5)
Head circumference (cm):						
⩽31	6 (3.7)	24 (2.9)	11 (5.6)	46 (4.7)	11 (3.9)	48 (3.3)
32-33	28 (17.1)	151 (18.3)	44 (22.2)	239 (24.5)	56 (19.6)	271 (18.9)
34-35	74 (45.1)	406 (49.3)	102 (51.5)	455 (46.7)	138 (48.3)	720 (50.2)
⩾36	56 (34.2)	243 (29.5)	41 (20.7)	235 (24.1)	81 (28.3)	396 (27.6)
Birth weight for gestational age:						
Small (⩾2 SD below mean)	12 (7.2)	41 (4.9)	11 (5.6)	45 (4.6)	22 (7.6)	93 (6.4)
Mean	150 (90.4)	756 (91.0)	178 (90.8)	906 (92.2)	258 (89.0)	1313 (90.4)
Large (⩾2 SD above mean)	4 (2.4)	34 (4.1)	7 (3.6)	32 (3.3)	10 (3.4)	46 (3.2)
Ponderal index (centiles)*:						
⩽5	12 (7.2)	35 (4.2)	7 (3.5)	49 (5.0)	15 (5.2)	71 (4.9)
6-94	146 (88.0)	751 (90.5)	181 (91.4)	886 (89.0)	257 (88.9)	1319 (90.8)
⩾95	8 (4.8)	44 (5.3)	10 (5.1)	50 (5.1)	17 (5.9)	62 (4.3)
Apgar score at 1 minute:						
0-6	10 (6.1)	39 (4.9)	12 (6.2)	33 (3.4)	15 (5.3)	50 (3.5)
7-10	154 (93.9)	762 (95.1)	183 (93.8)	928 (96.6)	267 (94.7)	1378 (96.5)
Apgar score at 5 minutes:						
0-6	4 (2.4)	9 (1.1)	0	10 (1.4)	4 (0.8)	12 (0.8)
7-10	159 (97.6)	784 (98.9)	192 (100)	943 (98.9)	278 (98.6)	1413 (99.2)
Asphyxia	21 (12.6)	91 (10.9)	28 (14.1)	91 (9.2)	30 (10.3)	146 (10.0)
Neonatal jaundice	1 (0.6)	9 (1.1)	0	8 (0.8)	1 (0.3)	8 (0.5)
Season of birth						
January-April	73 (43.7)	303 (36.3)	87 (43.9)	358 (36.2)	113 (38.7)	517 (35.4)
May-December	94 (56.3)	532 (63.7)	111 (56.1)	632 (63.8)	179 (61.3)	943 (64.6)

*$(100\times(\text{birth weight (g)})/(\text{birth length (cm)})^3$

been first admitted to hospital aged 15-21 years with a main diagnosis of schizophrenia (ICD-9 code 295), affective psychosis (ICD-9 code 296), or reactive psychosis (ICD-9 code 298). For each case, we selected five controls from the birth register who were individually matched by sex, year of birth, and hospital of birth and who were alive at the time the case subject's psychotic disorder was diagnosed. The mean ages at admission were similar for the three patient groups (17.7 or 17.8 years).

Risk factors

The effects of the following potential risk factors for psychotic disorders were studied.

Maternal factors were mothers' age (⩽19, 20-29, or ⩾30 completed years at infant's birth) and parity (1, 2-3, or >3).

Pregnancy and delivery factors were hypertensive diseases during pregnancy (ICD-8 codes 401, 637), diabetes (ICD-8 code 250), bleeding during pregnancy (ICD-8 codes 632, 651), uterine atony (weak contractions during labour) (ICD-8 codes 657.0, 657.1), preterm rupture of the membranes (ICD-8 codes 635.95, 661.0), fetopelvic disproportion (ICD-8 codes 654, 655), vacuum extraction, caesarean delivery, traumatic delivery (ICD-8 code 772), and twin birth.

Child characteristics were gestational age (in completed gestational weeks since last menstruation), birth weight, birth length, head circumference, small or large size for gestational age (2 SD below or above the mean birth weight for gestational age according to the Swedish birth weight curve[13]), ponderal index ($100 \times (\text{birth weight (g)})/(\text{birth length (cm)})^3$), Apgar scores at one and five minutes, asphyxia (ICD-8 codes 661.7, 661.8, 776), and neonatal jaundice (ICD-8 codes 774, 775).

Season of birth was categorised into the periods January-April and May-December.

Statistical analysis

We performed tests for independence between cases and controls for all categorised variables, assuming a χ^2 distribution. Variables showing any dependence ($P<0.10$) were modelled in a conditional logistic regression model, taking into account the matched design. We calculated odds ratios and 95% confidence intervals as measures of relative risk[14] using the PHREG procedure in the SAS statistical package (version 6.11). We also derived tests for trend for categorical variables with more than two categories. As ponderal index correlates with birth weight ($r=0.47$-0.56, $P=0.0001$), we entered ponderal index and birth weight for gestational age in separate models.

Results

Table 1 shows the characteristics of the cases and controls. Univariate analyses showed that distributions of parity, maternal diabetes, bleeding during pregnancy, and season of birth were different between the cases with schizophrenia and their controls ($P<0.10$). Uterine atony, low Apgar score at one minute, asphyxia, and late winter birth differed between the cases with affective psychosis and their controls. Maternal age and parity were the only factors that differed between the cases with reactive psychosis and their controls.

We made separate analyses for males and females (data not shown). In males, parity, hypertensive diseases, birth weight for gestational age, and ponderal index were associated with subsequent increased risk of schizophrenia, while in females the same was true only for maternal diabetes. Affective psychosis was associated with uterine atony and late winter birth in males and with a low Apgar score at one minute in females. Reactive psychosis was associated with maternal parity in males and with maternal age in females.

Table 2 Odds ratios (95% confidence intervals) for incidence of psychotic disorders in relation to prenatal and perinatal characteristics. Values derived from conditional logistic regression model

	Schizophrenia (n=163)	Affective psychosis (n=193)	Reactive psychosis (n=281)
Maternal factors			
Age at delivery (years):			
⩽19	0.8 (0.4 to 1.7)	1.0 (0.5 to 2.0)	1.3 (0.8 to 2.2)
20-29*	1.0	1.0	1.0
⩾30	1.2 (0.8 to 1.8)	1.4 (0.9 to 2.0)	1.3 (0.9 to 1.8)
Parity:			
1	1.3 (0.9 to 1.9)	1.0 (0.7 to 1.4)	1.1 (0.9 to 1.5)
2-3*	1.0	1.0	1.0
4	2.0 (1.0 to 3.8)†	1.0 (0.5 to 2.2)	2.1 (1.3 to 3.5)
Pregnancy and delivery factors			
Hypertensive diseases	1.3 (0.6 to 3.1)	1.6 (0.7 to 3.5)	0.8 (0.4 to 1.7)
Diabetes	7.8 (0.9 to 67.6)	0.7 (0.1 to 6.8)	3.4 (0.5 to 21.5)
Bleeding during pregnancy	3.5 (1.2 to 10.3)	1.1 (0.4 to 2.9)	1.2 (0.5 to 3.0)
Uterine atony	1.4 (0.7 to 2.6)	2.2 (1.2 to 4.1)	1.0 (0.6 to 1.8)
Child characteristics			
Birth weight for gestational age:			
Small (⩾2 SD below mean)	1.5 (0.7 to 3.1)†	1.3 (0.7 to 2.7)	1.0 (0.6 to 1.7)
Mean*	1.0	1.0	1.0
Large (⩾2 SD above mean)	0.5 (0.2 to 1.6)	1.2 (0.5 to 2.9)	0.9 (0.4 to 2.0)†
Ponderal index (centiles)‡:			
⩽5	2.1 (0.8 to 4.3)	0.6 (0.3 to 1.4)	1.1 (0.6 to 2.0)
6-94*	1.0	1.0	1.0
⩾95	1.0 (0.4 to 2.2)	1.0 (0.5 to 2.2)	1.4 (0.8 to 2.5)
Apgar score at 1 minute:			
0-6	0.97 (0.4 to 2.3)	1.3 (0.6 to 2.7)	1.8 (0.9 to 3.7)
7-10*	1.0	1.0	1.0
Asphyxia	1.0 (0.6 to 1.8)	1.4 (0.9 to 2.3)	0.8 (0.5 to 1.3)
Season of birth			
January-April	1.4 (1.0 to 2.0)	1.5 (1.1 to 2.0)	1.2 (0.9 to 1.5)
May-December*	1.0	1.0	1.0

*Reference category.
†Significant interaction with sex ($P<0.05$).
‡$(100\times(\text{birth weight (g)})/(\text{birth length (cm)})^3$. Entered in a separate model in place of birth weight for gestational age.

We entered all of the above variables in the multivariate analyses (table 2). These showed that increased risk of schizophrenia was associated with multiparity, bleeding during pregnancy, and late winter birth, but the association with maternal diabetes did not reach significance. Increased risk of affective psychosis was associated with uterine atony and late winter birth, while risk of reactive psychosis was associated only with multiparity.

Because of previous suggestions of sex differences in the association between perinatal complications and schizophrenia,[2] we analysed the interaction of the subjects' sex with the independent variables included in the multivariate analyses. For schizophrenia, we found significant interactions between sex and multiparity and small size for gestational age (table 2). For affective psychosis, we found no significant interaction with sex. Surprisingly, reactive psychosis was related to large size for gestational age in girls but not in boys.

Table 3 shows the results of sex specific regression analyses for schizophrenia. Among males, increased risk of schizophrenia was significantly associated with multiparity, bleeding during pregnancy, small size for gestational age, and low ponderal index. In females none of the variables analysed was significantly related

Table 3 Odds ratios (95% confidence intervals) for incidence of schizophrenia in relation to prenatal and perinatal characteristics for male and female subjects. Values derived from conditional logistic regression model

	Male subjects (n=106)	Female subjects (n=57)
Maternal factors		
Age at delivery (years):		
⩽19	0.7 (0.3 to 2.0)	0.9 (0.3 to 2.9)
20-29*	1.0	1.0
⩾30	1.5 (0.9 to 2.5)	1.1 (0.5 to 2.3)
Parity:		
1	1.4 (0.9 to 2.3)	1.2 (0.6 to 2.2)
2-3*	1.0	1.0
4	3.6 (1.6 to 7.8)†	0.5 (0.1 to 2.5)†
Pregnancy and delivery factors		
Hypertensive diseases	1.6 (0.6 to 4.3)	0.7 (0.1 to 6.2)
Diabetes	No exposure	13.5 (0.8 to 239.4)
Bleeding during pregnancy	4.0 (1.1 to 13.7)	4.4 (0.3 to 65.2)
Uterine atony	1.3 (0.6 to 2.9)	1.3 (0.3 to 4.1)
Child characteristics		
Birth weight for gestational age:		
Small (⩾2 SD below mean)	3.2 (1.4 to 7.2)†	0.3 (0.03 to 2.4)†
Mean*	1.0	1.0
Large (⩾2 SD above mean)	0.6 (0.2 to 2.4)	0.3 (0.03 to 3.3)
Ponderal index (centiles)‡:		
⩽5	3.1 (1.4 to 7.1)	0.5 (0.1 to 5.1)
6-94*	1.0	1.0
⩾95	0.5 (0.2 to 2.0)	1.5 (0.5 to 4.3)
Apgar score at 1 minute:		
0-6	1.4 (0.5 to 4.1)	0.6 (0.1 to 2.8)
7-10*	1.0	1.0
Asphyxia	0.8 (0.4 to 1.7)	1.6 (0.5 to 4.9)
Season of birth		
January-April	1.4 (0.9 to 2.3)	1.6 (0.9 to 2.8)
May-December*	1.0	1.0

*Reference category.
†Significant interaction with sex (P<0.05).
‡(100×(birth weight (g))/(birth length (cm))^3. Entered in a separate model in place of birth weight for gestational age.

to schizophrenia. The number of females with schizophrenia was small (n=57), but the non-significant increase in risk associated with maternal diabetes (odds ratio 13.5) was confined exclusively to females. In males risk of affective psychosis was associated with uterine atony (odds ratio 2.6, 95% confidence interval 1.0 to 6.7) and late winter birth (odds ratio 2.2, 1.3 to 3.8). In females these associations were weaker and non-significant (data not shown). Risk of reactive psychosis was associated with high parity (odds ratio 3.1, 1.6 to 5.9) in males, and in females with maternal age of ⩾30 years (odds ratio 1.8, 1.1 to 2.8) and a low Apgar score at one minute (odds ratio 3.6, 1.3 to 10.1).

Discussion

The overall picture presented by our study is that adverse prenatal and perinatal characteristics were primarily associated with increased risk of schizophrenia of early onset only in male subjects: multiparity, bleeding during pregnancy, and small size for gestational age were all associated with increased risk. Associations were weaker for females with schizophrenia, and for affective psychosis in both sexes. However, the role of maternal diabetes in increasing risk of schizophrenia in females, and weak contractions during pregnancy and late winter birth in affective psychosis merit further investigation.

Methodological issues

Our population based, case-control study fulfils many of the suggested methodological criteria proposed for the study of the relation between obstetric complications and psychotic diseases.[2] Data on exposure to potential risk factors were obtained before outcome was ascertained, which precludes recall bias. The number of cases is large, and the relatively short inclusion period for the samples optimises similarity in prenatal and obstetric practices.

The study was restricted to patients first presenting with psychotic disease between the ages of 15 and 21 years. Since other studies have suggested that schizophrenia of early onset is particularly associated with an excess of obstetric complications,[5] a higher genetic load,[15] and male sex,[16] our results may not apply to patients with psychosis of a later onset.

The diagnoses listed in the Swedish inpatient register are reliable as Swedish diagnostic practice is generally considered to be good[17] and the Swedish concept of schizophrenia is narrow and reflects diagnostic caution rather than overinclusiveness. Scandinavian psychiatrists have a reasonably reliable concept of reactive psychosis,[18] but we suspect that some of the cases of reactive psychosis in our study might have been diagnosed as schizophrenia in other countries.

Interpretation of results

Ours is the first study that we know of which directly addresses the question of whether obstetric complications are risk factors for reactive psychosis in a large sample. Patients with reactive psychosis have generally been considered to be subject to more precipitating stress and fewer familial risk factors and to have a more favourable outcome than patients with schizophrenia.[19] Consequently, reactive psychoses, as their name suggests, are often thought to be psychogenic rather than organic in origin. Our findings suggest that the influence of perinatal factors on reactive psychosis remains doubtful or, at least, not strong enough to produce independent effects of single complications.

We hypothesised, on the basis of a recent, hospital based, case-control study,[3] that aberrations in birth size would be the most consistent difference between preschizophrenic infants and controls. In a recent population based study from Finland low birth weight and the combination of low birth weight and short gestation were more common among schizophrenic subjects than controls.[20] Our present study showed that small size for gestational age (or a low ponderal index) and bleeding during pregnancy were associated only with increased risk of schizophrenia among boys. Bleeding, especially during late pregnancy, is often a sign of placental insufficiency, which in turn is associated with retardation of intrauterine growth.[21]

Asphyxia has often been considered the single most influential event causing adverse developmental sequelae.[22] Indeed, it has been proposed as the common denominator underlying the different obstetric complications associated with schizophrenia,[23] possibly through producing hypoxic-ischaemic damage to the brain. Although we did not find a direct association between neonatal asphyxia and schizophrenia, intra-

uterine asphyxia commonly occurs in pregnancies with retarded intrauterine growth or placental complications.[24 25] Thus, it may be that it is relatively long term exposure to intrauterine asphyxia rather than short term neonatal asphyxia that is important.

Our results fail to confirm recent case-control studies of clinical samples which reported small head circumference in preschizophrenic neonates.[3 26] The reason why we did not replicate these findings in our present study may have been because of differences in composition of the studies' samples: the earlier studies were more heterogeneous with regard to year of birth and age at onset of disease and so may have included subjects with more severe illness than in the present study.

A possibility which deserves attention is whether differences in maternal health, lifestyle, or compliance with routines for antenatal care may account for the differences in the pregnancy and birth histories of infants who later develop schizophrenia compared with the rest of the population.[8] Schizophrenic mothers are reportedly more likely to have low birthweight infants than healthy mothers[27]; unfortunately, we did not have reliable information about psychiatric illness in the mothers. It is also possible that the mothers of the schizophrenic patients smoked more than the mothers of control subjects.[27] Unfortunately, smoking, which is causally related to retardation of fetal growth,[28] was not included in the information recorded in the birth register. Other maternal factors reported to increase risk of schizophrenia include prenatal malnutrition[29] and stress or depression during pregnancy.[20 30] Antenatal care was standardised in Sweden in 1970, and practically all pregnant women follow these routines.[31] It is possible that the mothers of schizophrenic patients, less than 10% of whom would have been schizophrenic themselves, might have been less likely to have followed these routines. However, the influence of antenatal care routines on outcome such as bleeding during pregnancy, uterine atony, small size for gestational age, and season of birth is not known.[32]

Conclusion

This study suggests that prenatal and perinatal factors were more important in the development of schizophrenia of early onset than in that of affective or reactive psychosis. Multiparity, bleeding during pregnancy, and small size for gestational age status were associated with increased risk of early onset of schizophrenia in males. The pathological mechanisms that underlie such associations are not yet established, and little can be said about the relation of these findings to other risk factors for schizophrenia such as family history, maternal nutrition,[29] prenatal exposure to infections,[33] or prenatal concentrations of sex hormones.[34]

Contributors: CMH initiated the study, contributed to the study hypothesis and design and data analysis, and was mainly responsible for writing the paper. PS participated in discussing the study design, data analysis, and writing the paper. NT helped in statistical analysis and in writing the paper. RMM participated in interpreting the data, discussing core ideas, and writing the paper. SC initiated the study and its design and participated in data analysis and in writing the paper. CMH is guarantor for the paper.

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Key messages

- The role of prenatal and perinatal risk factors in the development of schizophrenia and affective and reactive psychosis in early adult life were investigated by linking individual data from the Swedish birth and inpatient registries
- Adverse prenatal and perinatal factors were more common in patients with schizophrenia of early onset than in controls and seemed more important in the aetiology of schizophrenia than in that of affective and reactive psychosis
- Multiparity, bleeding during pregnancy, and small size for gestational age were associated with a threefold to fourfold increased risk for schizophrenia among males
- There was no support for previous claims that head circumference is small in preschizophrenic infants
- Late winter birth was associated with increased risk of both schizophrenia and affective psychosis

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Prenatal and perinatal risk factors for early onset schizophrenia, affective psychosis, and reactive psychosis

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The psychotic disorders schizophrenia and bipolar disorder accounted for a total of more than 27 million disability adjusted life years worldwide in 1990, placing them among the 30 leading causes of disability.[1] There is little reliable information about their causes. Genetic factors are probably important in both disorders, but twin studies consistently show that up to half of monozygotic twins do not develop the disorder.[2] This suggests that environmental exposures may increase the risk for the disorders, possibly via interaction with genetic factors. With the prevailing view of schizophrenia as a neurodevelopmental disorder, there has been particular interest in environmental exposures early in life, including adverse events during pregnancy and labour, maternal viral infections, and fetal malnutrition. Epidemiological investigation of these putative risk factors has proved challenging: psychotic disorders are rare conditions that usually appear at least two decades after exposure to prenatal and perinatal events. There have been no large scale prospective studies.

Hultman and colleagues report the findings of a population based, nested case-control study of the association between prenatal and perinatal events and psychotic disorders. Although an association between perinatal events and schizophrenia has been reported for three decades, the early studies in this area were small and of variable quality, with the suggestion that there was bias towards publication of positive findings.[3] The current study marks a methodological advance for several reasons. It is larger than previous studies, including 167 patients with schizophrenia, 198 with affective psychosis, and 292 with reactive psychosis. Each case was matched with five controls. The analyses are straightforward, and interpretation is appropriately cautious. Inclusion of non-schizophrenic psychoses allowed the authors to investigate the specificity of the association with schizophrenia.

Overall, it seems that adverse perinatal events may be more strongly associated with schizophrenia than with other forms of psychosis. The associations are not particularly strong even though the cases of schizophrenia were of early onset, in which there is some evidence of an increased association with perinatal events.[4] Misclassification of diagnosis and exposure may have attenuated the observed size of effect.

Although the available evidence suggests that there are moderate associations between adverse perinatal events and schizophrenia, the inconsistencies between studies mean that there is still considerable uncertainty about which specific exposures, and, hence, which pathophysiological mechanisms, are involved. To clarify this issue, the design of future studies will need to move away from the opportunistic use of routinely collected data, which probably limits the reliability of measurement of exposures and diagnosis. Recent studies, including the present one, have attempted to limit the influence of the systematic biases that plague this kind of research.[5 6] Future studies will not only need to avoid systematic bias but also need to be large enough to limit random error and to provide reliable estimates of risk factors. Perhaps the first step should be to take stock of the current crop of studies by investigating the feasibility of pooling the data. This may help to answer two questions: which exposures need to be accurately measured in the next phase of research, and do the findings so far warrant the time and expense of large scale studies?

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