Schizophrenia and Complications of Pregnancy and Labor: An Individual Patient Data Meta-analysis

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Abstract

Several epidemiological studies have reported an association between complications of pregnancy and delivery and schizophrenia, but none have had sufficient power to examine specific complications that, individually, are of low prevalence. We, therefore, performed an individual patient meta-analysis using the raw data from case control studies that used the Lewis-Murray scale. Data were obtained from 12 studies on 700 schizophrenia subjects and 835 controls. There were significant associations between schizophrenia and premature rupture of membranes, gestational age shorter than 37 weeks, and use of resuscitation or incubator. There were associations of borderline significance between schizophrenia and birthweight lower than 2,500 g and forceps delivery. There was no significant interaction between these complications and sex. We conclude that some abnormalities of pregnancy and delivery may be associated with development of schizophrenia. The pathophysiology may involve hypoxia and so future studies should focus on the accurate measurement of this exposure.

Key Words: Obstetric complications, aetiology, epidemiology

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Current theories of the etiology of schizophrenia emphasize the early developmental abnormalities that are more frequently observed in individuals who subsequently develop the disorder (Jones et al. 1994; Murray 1994; Weinberger 1995). The neurodevelopmental processes leading to the onset of schizophrenia are probably strongly determined by genetic factors. However, the fact that the concordance between identical twins is approximately 40 percent suggests that environmental factors are causally necessary in at least a proportion of cases, even if they operate via gene–environment interactions. Attention has focused on very early environmental influences that may affect the fetal or neonatal brain.

Complications of pregnancy and labor are among the most extensively studied of putative early risk factors for schizophrenia (Geddes and Lawrie 1995; McNeil 1995). Although pregnancy and labor complications may be independent risk factors for schizophrenia, they could also be themselves an expression of the abnormal developmental processes that eventually lead to the onset of the disease (McGuffin et al. 1994). There would be stronger evidence for a causal association if there was greater clarity about the pathophysiological mechanism by which pregnancy and labor complications affect the fetus. This in turn would be clearer if there was an association between schizophrenia and specific complications, rather than a heterogeneous group of exposures with different effects on the fetus. Unfortunately, there is no consistent evidence that any specific complication is associated with schizophrenia, mainly because studies have had insufficient power to investigate individual complications that occur relatively infrequently.

Meta-analysis of individual studies may provide such power, but we were unable to examine specific complications in our previous meta-analysis because of incomplete reporting in the primary studies. We now report a meta-analysis of individual patient data from 12 case-control studies that used the same scale for measuring exposure. By using individual patient data, we aimed to achieve greater accuracy (Clarke and Stewart 1994; Jeng et al. 1995; Oxman et al. 1995) and sufficient power to detect associations between specific complications and schizophrenia. Furthermore, it has been suggested previously that pregnancy and labor complications may be associated particularly with male gender, early onset, and "sporadic" cases (i.e., with no affected family member) (Lewis et al. 1987; Murray et al. 1992). Our secondary aim in this

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study was to look for interaction between specific complications and sex. The relationship between family history and age at onset could not be investigated using case-control data and is described elsewhere (Verdoux et al. 1997).

Method

Identification of Studies. We searched for case-control studies comparing schizophrenia patients with normal controls using a combination of the following:

1. Electronic MEDLINE search using MeSH headings "labor complications" or "pregnancy complications" or "infant, low birth weight" and "schizophrenia" or "psychotic disorders." This strategy was used to search the database from 1966 to May 1996. A free text search using the same terms and "obstetric complications" was also performed.
2. Survey of references of papers and previous reviews.
3. Personal communication with researchers.

Studies were included in the analysis if the Lewis-Murray scale was used or if we could apply the scale to the study data (Lewis et al. 1989). A total of 13 studies were identified (Eagles et al. 1990; McCreadie et al. 1992; O'Callaghan et al. 1992; Heun and Maier 1993; McNeil et al. 1993; Stöber et al. 1993; Verdoux and Bourgeois 1993; Günther-Genta et al. 1994; Gureje et al. 1994; Rifkin et al. 1994; Kendell et al. 1996; Taylor et al. 1996; Willinger et al. 1996) and individual patient data were obtained from all but one (Gureje et al. 1994) (see table 1). Some studies included patients with other psychotic disorders and several control groups. For this analysis we used only the data from schizophrenia subjects classified according to *ICD–9* (*International Classification of Diseases,* 9th revision; World Health Organization 1978), *DSM–III–R* (American Psychiatric Association 1987), or Research Diagnostic Criteria (RDC; Spitzer et al. 1978) criteria and from the normal controls.

Exposure Measurement. All studies used the scale of Lewis and Murray (Lewis et al. 1989; see table 2) and so there was a reasonable level of uniformity in the measurement of exposure to the individual complications. The scale rates 15 obstetric complications as absent or definitely present; 9 of the exposures can also be rated as equivocally present. Previous studies have often considered either definite or equivocal exposure to any complication of pregnancy or labor as positive exposure, and so we replicated this method in this large dataset. For the main analysis, we investigated the association between each complication of pregnancy or labor and schizophrenia. The Lewis-Murray scale does not differentiate between short and long labor or gestation. To investigate these exposures, we used data only from those studies for which recoded data were available to allow specific examination of the effects of long gestation, short gestation, and long labor. Short labor was not investigated because some recent authors did not include it as a complication, although it was originally classed as such by the scale.

Statistical Analysis. The data were analyzed by unconditional logistic regression using the Epidemiological Graphics, Estimation, and Testing (EGRET) statistical package (Statistics and Epidemiology Research Corporation 1991). Information on pairing was unavailable for the matched studies (in which controls were individually matched with cases on a particular characteristic—details of matching used in individual studies are given in table 1) and so they were analyzed as unmatched. This would be likely to underestimate the study-specific odds ratio (OR) (Breslow and Day 1980). The effect of ignoring matching in the analysis was estimated in the logistic regression model by comparing the estimates from matched and unmatched studies. A pooled weighted estimate of the OR was calculated for each complication by fitting a variable with 12 categories representing each study to the regression model.

Individual complications that were rated as present or absent on the Lewis-Murray scale were treated as dichotomous variables. The main analyses for complications rated as absent, equivocal, or definite considered any degree of exposure as positive, and estimated an OR for the exposed versus the unexposed. An additional subanalysis was performed in which the three-level rating of complications was fitted as a factored variable. This allowed us to assess whether the strength of the association differed according to exposure classification and also whether there was a dose-response. This subanalysis was possible only with data from the small number of studies from which we had full data.

Adjustment for potential confounders including birth order and sex was performed where possible. First order interactions between exposure and sex were also investigated to see if complications of pregnancy or labor were risk factors in only one sex. The population-attributable risk was estimated for each complication that was found to be significantly associated with schizophrenia using the weighted sum approach (Coughlin et al. 1994).

The studies differed in some aspects of design, and we investigated the possibility that these aspects produced different estimates by testing for interaction by the design characteristic. The design features investigated were source and method of rating exposure to complications (contemporaneous birth records vs. maternal/relative

Table 1. Case-control studies included in meta-analysis

No.	Study	Source of obstetric complications	Cases	Controls	Diagnosis
1	Eagles et al. (1990)	Obstetric records	27 patients admitted to Aberdeen hospitals, Scotland; age at onset < 45 years	27 siblings (no schizophrenia)	*DSM–III*
2	McCreadie et al. (1992)	Maternal recall	35 patients living in Nithsdale, SW Scotland area with living mothers	96 siblings (no schizophrenia)	*DSM–III–R*
3	O'Callaghan et al. (1992)	Obstetric records	65 patients on St. John of God Hospital database, Dublin, Ireland, whose obstetric records could be located	65 previous same sex live births at same maternity hospital	*ICD–9*
4	Verdoux and Bourgeois (1993)	Maternal recall	23 schizophrenia subjects under 50 years with living mothers; in Bordeaux, France	23 normal controls drawn from hospital personnel or their children	*DSM–III–R*
5	Heun and Maier (1993)	Maternal recall	47 patients from family study of consecutive admissions to University Department of Psychiatry, Mainz, Germany	70 siblings	RDC
6	McNeil et al. (1993)	Obstetric records	70 hospitalized patients: age at onset before 33 years; born in Malmö, Sweden, 1944–55	70 controls from same hospital matched for maternal parity, social class, age, and marital status at delivery, alive at discharge	RDC
7	Stöber et al. (1993)	Maternal recall	80 patients admitted to Wurztburg University or Lohr District hospitals, Germany, with living mothers	80 healthy, employed controls with no first or second degree relatives with schizophrenia	*DSM–III–R*
8	Günther-Genta et al. (1994)	Obstetric records	23 patients admitted to University of Lausanne Psychiatric Clinic, Switzerland	40 siblings (no schizophrenia)	RDC
9	Rifkin et al. (1994)	Maternal recall	110 consecutive admissions to three hospitals in London, England	100 normal controls from Kings College casualty department, London, UK	*DSM–III*
10	Kendell et al. (1996)	Routine data from obstetric records	115 patients born in Scotland between 1971 and 1974 with a discharge diagnosis of schizophrenia recorded on routinely collected national hospital statistics	115 subjects, birth recorded on routinely collected national hospital statistics, with no hospital diagnosis of schizophrenia matched for obstetric unit, sex, date of birth, maternal age, parental social class, and twin status	*ICD–9*
11	Willinger et al. (1996)	Maternal recall	36 patients with schizophrenia	30 siblings (no schizophrenia)	*DSM–III–R*
12	Taylor et al. (1996)	Maternal recall	76 patients with schizophrenia	29 normal general population controls and 83 normal relatives	*DSM–III–R*

Table 2. Lewis-Murray obstetric complications scale (Lewis et al. 1989)

Definite	Equivocal
Antepartum	
1. Rubella or syphilis	—
2. Rhesus incompatibility	—
3. Preeclampsia: severe and/or leading to early induction or hospitalization	Preeclampsia NOS
4. Ante partum hemorrhage or threatened abortion	—
Intrapartum	
5. Premature rupture of membranes, > 24 hours	—
6. Labor > 36 hours or < 3 hours	Labor > 24 hours or "long"/difficult/"precipitate" NOS
7. *Twin birth, complicated*	*Twin birth* NOS
8. Cord prolapse	Cord knotted or around neck
9. Gestational age < 37 weeks or > 42 weeks	"Premature"/"postmature" NOS
10. Caesarean, complicated or emergency	Caesarean NOS
11. Breech or abnormal presentation	—
12. High or "difficult" forceps	Forceps or other instrumental delivery, NOS
13. Birthweight < 2,000 g	< 2,500 g or "small" NOS
14. Incubator > 4 weeks	Incubator resuscitation/"blue" NOS
15. *Gross physical anomaly*	—
Rating points: definite = 2; equivocal = 1; absent = 0; insufficient information = 9	

Note.—NOS = not otherwise specified.

interview), control type (siblings vs. population controls), and diagnosis (ICD vs. DSM vs. RDC).

The possibility that we selected a biased sample of studies was investigated by using a funnel plot, a plot of the study-specific estimates against the sample size (Dickersin and Berlin 1992).

Results

Individual patient data regarding exposure to complications of pregnancy or labor were available on 700 schizophrenia subjects and 835 controls from 12 case-control studies (see tables 1 and 3). The study, therefore, had 90 percent power of detecting an OR of 2.0 with 95 percent confidence for an exposure with a prevalence among the controls of 5 percent (but only 44% for an OR of 1.5). In some cases, the numbers of subjects given for individual studies deviate from published reports. This is because we used only cases meeting *ICD–9, DSM–III–R,* or RDC criteria for schizophrenia and only one control group from studies with more than one comparison group. Some 325 (46%) cases and 341 (41%) controls were exposed to a broadly defined (i.e., definite or equivocal) complication of pregnancy or delivery. Data subclassifying exposure as definite or equivocal were available in 10 studies. Among these, the weighted mean OR for exposure to at least one equivocal, but no definite complication was 1.01 (95% confidence interval [CI] 0.72–1.42; $p = 0.961$; $p = 0.272$ for heterogeneity). The weighted mean OR for exposure to at least one definite complication was 1.38 (95% CI 1.05–1.84; $p = 0.019$; $p = 0.390$ for heterogeneity). This trend for increasing certainty about exposure to be associated with a larger estimate was significant ($c^2 = 5.20$; $p = 0.023$). Methodological variations between the studies (type of controls, variations in diagnostic criteria, method of rating exposure) had no significant effect on these pooled estimates. There was no significant difference between the estimates from the seven matched and five unmatched studies.

The sex distribution and data on estimated age at onset, birth order, and family history are shown in table 4. Data on these variables were not available from all studies (as indicated in table 4) and were not available for control subjects. Age at onset was estimated as age at first onset of psychiatric symptoms in 56 percent of subjects; otherwise age at first hospitalization was used. Family history of psychosis was based on information obtained from the

Table 3. Frequency of abnormalities of pregnancy and labor for controls and cases in the 12 case-control studies

	Obstetric complications[1]														
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Eagles et al. (1990)															
Controls	0/26	0/25	6/27	1/26	2/25	n/a	2/27	0/27	n/a	0/27	1/27	3/27	2/27	4/27	0/27
Cases	0/27	0/26	7/27	1/27	10/27	n/a	2/27	4/27	n/a	1/27	1/27	5/27	2/27	6/27	0/27
McCreadie et al. (1992)															
Controls	0/96	0/96	5/96	4/96	3/96	9/96	0/96	4/96	n/a	0/96	2/96	9/96	12/89	3/96	1/96
Cases	1/35	0/35	0/35	1/35	4/35	0/35	2/35	1/35	n/a	2/35	4/35	3/35	3/34	3/35	2/35
O'Callaghan et al. (1992)															
Controls	0/66	0/66	3/66	1/66	0/66	n/a	0/66	0/66	n/a	0/66	3/66	1/66	0/66	0/66	0/66
Cases	0/64	0/64	4/64	2/64	0/64	n/a	3/64	1/64	n/a	2/64	3/64	6/64	0/64	5/64	0/64
Verdoux and Bourgeois (1993)															
Controls	0/23	0/23	2/23	2/23	0/23	1/23	0/23	0/23	0/23	1/23	3/23	2/23	1/23	2/23	0/23
Cases	0/23	0/23	2/23	7/23	0/23	2/23	2/23	2/23	3/23	0/23	4/23	5/23	2/23	4/23	0/23
Heun and Maier (1993)															
Controls	0/70	0/70	1/70	3/70	0/70	n/a	0/70	2/70	n/a	1/70	3/70	1/70	2/70	1/70	1/70
Cases	0/47	0/47	0/47	1/47	1/47	n/a	1/47	3/47	n/a	1/46	0/47	1/47	2/47	4/47	0/47
McNeil et al. (1993)															
Controls	1/70	0/70	5/70	1/70	1/70	8/70	0/70	26/70	0/70	0/70	5/70	2/70	0/70	1/70	1/70
Cases	0/70	1/70	9/70	1/70	4/70	14/70	0/70	19/70	3/70	0/70	5/70	3/70	7/70	3/70	1/70
Stöber et al. (1993)															
Controls	0/80	0/80	7/80	5/80	4/80	n/a	3/80	5/80	n/a	0/79	6/80	3/80	3/80	9/80	0/80
Cases	0/80	0/80	2/80	5/80	4/80	n/a	2/80	4/80	n/a	0/80	6/80	9/80	7/80	21/80	1/80
Günther-Genta et al. (1994)															
Controls	0/40	5/40	5/40	0/40	1/40	0/40	2/40	5/40	2/36	1/40	1/40	2/40	2/40	2/40	n/a
Cases	0/23	3/23	3/23	1/23	0/23	0/23	2/23	10/23	2/23	1/23	1/23	1/23	2/23	0/23	n/a
Rifkin et al. (1994)															
Controls	0/99	n/a	12/100	3/100	n/a	6/100	5/100	1/100	4/100	10/90	5/99	16/100	8/100	5/100	n/a
Cases	0/107	n/a	6/106	9/106	n/a	8/93	4/108	1/99	7/102	4/106	1/101	8/104	14/105	7/103	n/a
Kendell et al. (1996)															
Controls	0/115	4/108	2/115	0/114	0/115	18/115	2/115	0/115	4/106	2/115	1/114	2/115	5/115	n/a	n/a
Cases	1/115	7/112	10/115	3/115	0/115	12/115	2/115	0/115	7/108	4/115	4/115	9/115	10/115	n/a	n/a
Willinger et al. (1996)															
Controls	0/36	0/36	0/36	1/36	0/36	n/a	3/36	1/36	n/a	1/36	0/36	2/36	3/36	1/36	0/36
Cases	0/30	1/30	0/30	0/30	1/30	n/a	4/30	1/30	n/a	0/30	1/30	3/30	5/30	2/30	0/30

Table 3. Frequency of abnormalities of pregnancy and labor for controls and cases in the 12 case-control studies—*Continued*

Study	Obstetric complications[1]														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Taylor et al. (1996)															
Controls	0/112	n/a	22/112	7/112	n/a	n/a	1/112	7/112	n/a	0/112	0/112	9/112	8/110	5/112	2/112
Cases	0/76	n/a	12/76	3/76	n/a	n/a	4/76	0/76	n/a	0/76	2/76	8/76	5/68	4/76	2/76

Note.—n/a = not available

[1] Key to obstetric complications: 1 = Rubella or syphilis; 2 = Rhesus incompatibility; 3 = Preeclampsia: severe and/or leading to early induction or hospitalization; 4 = Ante partum hemorrhage or threatened abortion; 5 = Premature rupture of membranes, > 24 hours; 6 = Labor > 24 hours; 7 = Twin birth; 8 = Cord prolapse or cord knotted or around neck; 9 = Gestation < 37 weeks; 10 = Caesarean, complicated or emergency or NOS; 11 = Breech or abnormal presentation; 12 = Any instrument delivery; 13 = Birthweight < 2,500 g; 14 = Use of incubator, resuscitation or "blue"; 15 = Gross physical anomaly

subject or from case notes in 88 percent of subjects; in the remainder it was based on maternal interview.

Publication Bias. The funnel plot (see figure 1) of study size against study-specific OR appears to show a relative absence of small studies finding a negative or small association between obstetric complications and schizophrenia. This may indicate that we have failed to detect these studies or that they have not been published (Dickersin and Berlin 1992). If this is so, the pooled estimate would be an overestimate of the true effect.

Individual Complications of Pregnancy or Labor. The principal analysis used dichotomized exposure (absent vs. present [equivocal or definite]). The weighted average ORs for the individual complications of pregnancy or labor are shown in table 5, in which the ORs are for dichotomized variables. There were significant associations between schizophrenia and premature rupture of membranes (OR 3.11; 95% CI 1.39–6.95; $p = 0.006$), gestational age shorter than 37 weeks (OR 2.44; 95% CI 1.13–5.26; $p = 0.023$), and use of resuscitation or incubator (OR 2.21; 95% CI 1.38–3.54; $p = 0.001$). There were associations of borderline significance between schizophrenia and birthweight lower than 2,500 g (OR 1.51; 95% CI 0.99–2.30; $p = 0.056$) and forceps delivery (OR 1.47; 95% CI 0.99–2.17; $p = 0.056$). There was no statistically significant heterogeneity between studies for any complication of pregnancy and labor, although there was a trend toward between-study heterogeneity for preeclampsia (likelihood ratio statistic [LRS] = 13.88; df = 8; $p = 0.085$). Inspection of the study-specific ORs for this exposure revealed that only one study produced a statistically significant positive association, regardless of the level of exposure (Kendell et al. 1996). Exclusion of this study reduced the evidence for heterogeneity (LRS 5.23; df = 7, $p = 0.631$).

Subanalysis Using 3-Level Exposure (0 = absent, 1 = equivocal, 2 = definite). The OR for definite exposure to short gestational age was 3.1 (95% CI 0.9–11.8; $p = 0.043$), although this estimate was based on data from only three studies. There was a statistically significant linear trend of increasing OR with increasing certainty about this exposure (LRS = 4.78; df = 1, $p = 0.029$). The OR for equivocal exposure to resuscitation or incubator was 2.2 (95% CI 1.3–4.0; $p = 0.003$) and for definite exposure 2.5 (95% CI 0.6–10.5; $p = 0.152$). Again, there was a statistically significant linear trend of increasing OR with increasing certainty about the exposure (LRS = 10.19; df = 1, $p = 0.001$).

Effect of Methodological Variation. The weighted mean odds ratio of exposure to preeclampsia varied sig-

Table 4. Sex distribution and illness characteristics of schizophrenia subjects and number of studies contributing to subgroup analyses

	Male	Female	Total
Total, *n* (%) (*11 studies*)	442 (66)	230 (34)	672
Age at onset, mean yrs (standard deviation) (*9 studies*)	22.7 (5.5)	24.2 (7.3)	23.2 (6.2)
0–14 yrs, *n* (%)	11/374 (3)	6/188 (3)	17
15–24 yrs, *n* (%)	250/374 (67)	108/188 (57)	358
25–34 yrs, *n* (%)	101/374 (27)	52/188 (28)	153
≥ 35 yrs, *n* (%)	12/374 (3)	22/188 (12)	34
Birth order, *n* (*7 studies*)			
Firstborn	90/220	44/134	134/354
Non-firstborn	130/220	90/134	220/354
Positive family history of psychosis, *n* (*7 studies*)	107/320	80/171	187/491

nificantly according to the method of exposure measurement (LRS = 10.25; df = 1; $p = 0.001$). Only studies using contemporaneous birth records found a significant association (OR 2.0; 95% CI 1.1–3.8; $p = 0.032$). This difference remained when the Kendell et al. (1996) study was excluded. There was a significant difference in weighted mean OR of exposure to forceps delivery between studies using maternal recall and those using birth records (LRS = 4.28; df = 1; $p = 0.039$); only the former found a significant association (OR 3.1; 95% CI 1.3–7.0; $p = 0.017$). Differences between studies depending on the type of controls used occurred only with exposure to cord complications: An association was observed in studies using sibling controls (OR 2.4; 95% CI 1.1–5.2; $p = 0.032$) but not in those using population controls (LRS = 5.77; df = 1, $p = 0.016$).

Figure 1. Funnel plot of study-specific estimates against study sample size

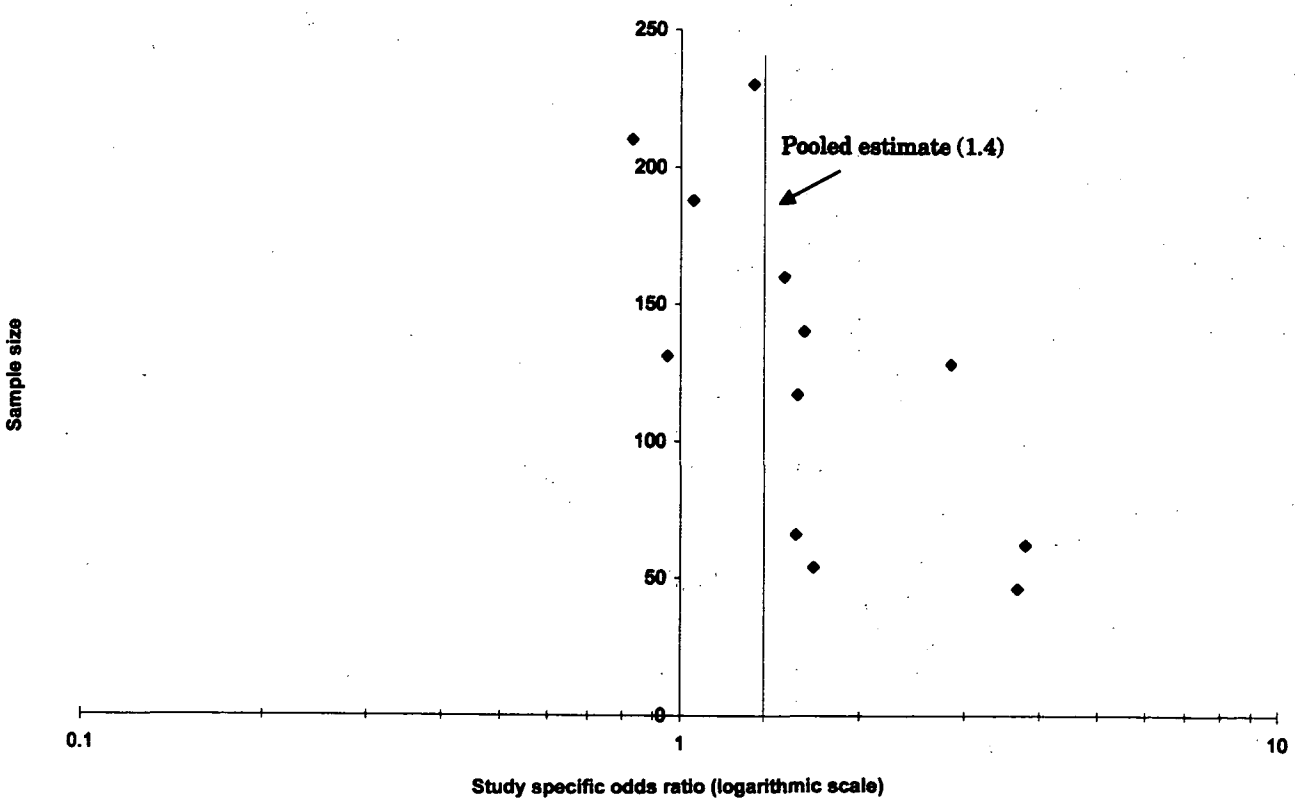

Table 5. Association of individual complications of pregnancy and labor with schizophrenia

	Studies contributing to meta-analysis[1]	Weighted summary odds ratio (95% confidence interval)	*p*	Attributable fraction (95% confidence interval)
Rubella or syphilis	1–12	—	—	—
Rhesus incompatibility	1–8,10,11	1.40 (0.54–3.63)	0.488	—
Preeclampsia	1–12	0.98 (0.67–1.45)	0.934	—
Ante partum hemorrhage	1–12	1.35 (0.78–2.33)	0.285	—
Premature rupture of membranes	1–8, 10, 11	3.11 (1.39–6.95)	0.006	0.07 (0.03–0.12)
Labor > 24 hours	2, 4, 6, 8, 9, 10	0.96 (0.60–1.55)	0.874	—
Twin birth	1–12	1.27 (0.66–2.45)	0.478	—
Cord complications	1–12	1.07 (0.65–1.76)	0.781	—
Gestational age < 37 weeks	4, 6, 8, 9, 10	2.44 (1.13–5.26)	0.023	0.05 (0.02–0.07)
Caesarean section	1–12	0.73 (0.32–1.68)	0.460	—
Abnormal presentation	1–12	1.23 (0.71–2.13)	0.455	—
Forceps delivery	1–12	1.47 (0.99–2.17)	0.056	—
Birthweight < 2,500 g	1–12	1.51 (0.99–2.30)	0.056	0.03 (0.0–0.07)
Incubator or resuscitation	1–9,11,12	2.21 (1.38–3.54)	0.001	0.06 (0.03–0.09)
Gross physical abnormality	1–7, 11,12	2.13 (0.55–8.25)	0.274	—

[1] Numbers refer to studies displayed in table 1.

Confounding. Investigation of confounding could usually be examined on only a subset of the studies. The presence of confounding was assessed by calculating an adjusted OR using the studies for which there were sufficient data. It was usually possible to examine the possibility of confounding by sex and birth order. This made no notable difference to the OR (defined as a greater than 10% change; Greenland 1989) for any potential confounding variable.

Interactions With Baseline Variables. There were no significant interactions by sex for the effect of any individual complication of pregnancy and labor.

Discussion

With the exception of preeclampsia, there was no evidence of statistical heterogeneity between study-specific estimates for any of the abnormalities of pregnancy and labor. It was therefore justifiable to pool the data to produce summary estimates for the other complications. Premature rupture of membranes, prematurity, and use of an incubator or resuscitation were identified as significant risk factors for the subsequent development of schizophrenia. There were weaker associations of borderline statistical significance with low birthweight and use of forceps. The overall heterogeneity in the estimates for preeclampsia was mainly due to one study that had previously reported this association (Kendell et al. 1996). However, there was also a significant difference in the estimates produced by studies relying on maternal recall for measurement of exposure to preeclampsia and those using contemporaneous birth records. Only the studies using birth records detected the association. This finding suggests that the agreement between birth records and maternal recall varies between individual complications. Previous studies reporting good agreement between the two methods have been quite small (O'Callaghan et al. 1990; Franzek and Stöber 1995). It is possible that a genuine association exists between preeclampsia and subsequent development of schizophrenia, and this association is likely to be underestimated in studies using maternal recall.

The meta-analysis using individual patient data allowed us to investigate the association of schizophrenia with specific abnormalities of pregnancy and labor that are, individually, relatively uncommon. Nevertheless, the meta-analysis has several weaknesses. We used only those studies that used the Lewis-Murray scale. This scale has limitations—in particular, it does not measure exposure to maternal influenza and malnutrition, both of which have been implicated in the etiology of schizophrenia (O'Callaghan et al. 1991; Susser and Lin 1992). The selection of studies may have introduced bias—the funnel plot is consistent with the presence of publication bias—therefore, the true magnitude of the association between exposure to any pregnancy and labor complication may be smaller than the pooled estimate obtained in the present study. In this respect, it is also notable that the OR for exposure to any definite complication was 1.38 (95% CI 1.05–1.84), which is smaller than our previous estimate

(2.0; 95% CI 1.6–2.4) calculated from a different sample of studies in which we also found evidence of publication bias (Geddes and Lawrie 1995). Although the overall estimate is useful for estimating the possibility of publication bias, our new finding that some complications appear to be associated with schizophrenia while others do not means that it probably has limited usefulness as an overall measure of exposure. Future studies will need to develop valid methods to adequately measure exposure to specific complications.

Hypoxic brain damage has often been proposed to explain the association between pregnancy and labor complications and schizophrenia (Lewis et al. 1989; Kendell et al. 1996). Our findings are consistent with this hypothesis because fetal hypoxia is a common consequence of premature rupture of membranes, prematurity, and low birthweight and may necessitate the use of an incubator or resuscitation. However, each of these complications arises from a complex series of events that would be likely to have several, possibly differing, effects on the developing brain of the fetus. Further testing of the hypothesis that fetal hypoxia is involved in the pathogenesis of schizophrenia would require a more specific measure of exposure to hypoxia.

The absence of significant interactions between specific complications and sex does not support the hypothesis that there is straightforward etiological heterogeneity between male and female cases (Lewis et al. 1987; Murray et al. 1992). More complicated interactions between component causes are likely to exist but the low prevalence of individual complications limited the power of the study to examine these.

As we have outlined, future studies examining the role of perinatal events and schizophrenia should concentrate on the exposures that we have identified to be associated with the disorder. Our findings suggest that it is particularly important to refine the measurement of exposure to hypoxia. The optimal method used for measuring exposures probably differs for individual complications. Contemporaneous birth records may be more sensitive for recording preeclampsia, but maternal recall may be more sensitive for detecting exposure to the use of forceps. We were unable to satisfactorily examine the interaction of pregnancy and birth complications with family history. It is important that future studies investigating the association with putative environmental risk factors, such as complications of pregnancy and birth, also consider the possibility of gene–environment interaction.

Finally, although the population-attributable fraction for each exposure was quite modest, it remains possible that prevention of at least a proportion of schizophrenia cases could be achieved through improved perinatal care.

Addendum

Since acceptance of this manuscript, Dr R.E. Kendell has informed the authors that the method of selection of controls in Kendell et al. (1996) introduced bias and that the results of the study are probably unreliable. Kendell has submitted a paper to the British Journal of Psychiatry that fully describes the source of the bias and its effects on the results.

We therefore reanalyzed the data excluding the Kendell (1996) study. The exclusion of this study had little material effect on the results. Overall, the confidence intervals (CIs) of the pooled estimates were slightly widened. Otherwise, the only notable change was that the odds ratio for forceps delivery, which had been of borderline statistical significance (1.47, 95% CI 0.99 to 2.17), was reduced (1.3, 95% CI 0.87 to 1.98).

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