Obstetric Complications and Schizophrenia: Historical and Meta-Analytic Review

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Objective: This paper reviews the literature on obstetric complications as a risk factor for schizophrenia. The authors trace the evolution of this literature through different methods and carry out a quantitative review of the results from prospective, population-based studies.

Method: Relevant papers were identified by a MEDLINE search, by examination of reference lists of published papers, and through personal contact with researchers in the field. Studies were grouped in chronological order according to common themes or methods. Meta-analytic techniques were used to summarize the findings of prospective population-based studies.

Results: The meta-analytic synthesis of the prospective population-based studies revealed that three groups of complications were significantly associated with schizophrenia: 1) complications of pregnancy (bleeding, diabetes, rhesus incompatibility, preeclampsia); 2) abnormal fetal growth and development: (low birthweight, congenital malformations, reduced head circumference), and 3) complications of delivery (uterine atony, asphyxia, emergency Cesarean section). Pooled estimates of effect sizes were generally less than 2.

Conclusions: Current methods of investigating the relationship between obstetric complications and schizophrenia are reaching the limit of their usefulness. Lack of statistical power to measure small and interactive effects and lack of detailed information about the prenatal period are major problems with current approaches. A combination of disciplines and approaches will be needed to elucidate the mechanisms underlying these small but important associations.

(Am J Psychiatry 2002; 159:1080–1092)

The much-investigated association between obstetric complications and schizophrenia has provided crucial support for developmental and nongenetic etiological models of the disorder. But does such an association really exist? This review outlines the history of the substantial literature examining this association and provides a quantitative synthesis of selected population-based studies. The limitations of the research methods that are currently used are discussed, and possible new lines of inquiry are suggested.

The first mention of an association between birth complications and schizophrenia occurred in the *American Journal of Psychiatry* in 1934. Rosanoff and colleagues (1) published "The Etiology of So-Called Schizophrenic Psychoses," based on detailed case reports of 142 pairs of twins concordant and discordant for schizophrenia. The authors concluded that schizophrenia could be regarded (at least in part) as a "decerebration syndrome which may result from birth trauma." Somewhat surprisingly, nothing further was published on this topic until 1956 when Pasamanick and colleagues (2) proposed their now-classic thesis of a "continuum of reproductive casualty," whereby pregnancy and birth complications can lead to a gradient of injury extending from fetal and neonatal death through cerebral palsy, epilepsy, mental deficiency, and behavior disorder. The paper by Pasamanick and colleagues initially had its greatest impact on the field of child psychiatry. In the early 1960s, there were reports of significant associations between pregnancy complications (particularly toxemia, bleeding, and severe maternal illness) and childhood psychosis (3–6). However, diagnostic uncertainty about the classification of childhood psychosis seems to have halted research in this area. Even though a review in 1966 concluded that "the need for further research…is strongly indicated by these findings" (7), there was a gap of 10 years before a study by Torrey and colleagues (8) reported an association between bleeding in pregnancy and childhood psychosis.

Research on Low Birth Weight (1966–1970)

In 1966 attention shifted to adult schizophrenia when Lane and Albee (9) reported that the birth weights of 52 hospitalized schizophrenic adults were significantly lower than that of their siblings. Although the difference between the mean birth weights of the patients and their siblings was significant, it was quite small (in the region of 175 g), and few of the patients actually met the criteria for the "low birth weight" category (<2500 g). Rather, there ap-

peared to be a "shift in distribution" of birth weight within a population of cases compared with noncases. In 1967 Stabenau and Pollin (10) published an analysis of birth histories of 100 pairs of monozygotic twins discordant for schizophrenia and reported that significantly more of the schizophrenic (index) twins had been the lighter of the two at birth and had experienced birth complications, particularly asphyxia. However, other investigators subsequently failed to find significant differences in birth weight between schizophrenic subjects and siblings or comparison subjects (11–13). It is likely that these studies were underpowered to find an effect, as the mean difference in birth weights between groups was actually very similar to that originally reported by Lane and Albee (9). The epidemiological concept of a "population shift" did not come to attention again until recent years (14).

Studies of High-Risk Groups (1970–1980)

The next phase of the literature was prompted by an analysis of obstetric complication data from the Copenhagen High-Risk Study (15, 16). The "high-risk" design examined the characteristics of a group of offspring of schizophrenic parents who were at 10–15 times higher risk of developing schizophrenia than individuals from the general population. Mednick (16) found that 70% of the "high-risk" children who were psychiatrically ill by their early 20s had suffered one or more serious pregnancy or birth complications, compared with 15% of the high-risk group who remained well and 33% of the comparison group (i.e., offspring of parents who did not suffer with schizophrenia). Mednick speculated that, given a subject's genetic predisposition, schizophrenia would appear only if the hippocampus was selectively injured by anoxia at birth. Analyses of other high-risk study groups revealed an excess of unexplained fetal and neonatal deaths (17–19), bleeding and swelling during pregnancy (20), and neonatal problems (21). However the research strategy focusing on high-risk children was dealt a severe blow by a series a negative findings (22–25) and, in particular, by two reports that failed to find any differences between the birth histories of schizophrenic women and those of women with other psychiatric disorders (26, 27). A review concluded that there was little evidence for an excess of obstetric complications in births to parents with schizophrenia (28). Although this conclusion was later challenged (29), the era of research focused on high-risk offspring was effectively over by 1980. Indeed, only a handful of papers on the topic of obstetric complications and schizophrenia were published over the next few years (30–32), and interest in the topic seemed to have waned. The development of new brain imaging techniques provided the impetus for the next phase of the literature.

Brain Imaging Studies (1984–1987)

The finding of cerebral ventricular enlargement in schizophrenia was originally thought to reflect neurodegeneration (33). However, investigators found that ventricular enlargement was already present at the onset of the illness (34) and was positively correlated with a history of obstetric complications in groups of high-risk and schizophrenic subjects (35, 36). Murray and colleagues (37) suggested that intraventricular hemorrhage in the newborn infant might be one cause of the ventricular enlargement found in schizophrenia and proposed a distinction between "familial" and "sporadic" forms of the disorder. Andreasen and colleagues (38) found decreased cerebral and cranial size in schizophrenia and suggested that "some type of early developmental abnormality, such as complications of delivery" may be responsible for the findings. A "neurodevelopmental hypothesis" of schizophrenia began to take shape (39–41). This hypothesis or model proposed that schizophrenia was associated with a subtle, static brain lesion that was caused by a combination of genetic or environmental factors and that interacted with the normal maturational processes of the brain. Evidence for an association between obstetric complications and schizophrenia provided important support for the neurodevelopmental hypothesis.

Case-Control Studies (1987–1997)

In 1987, Lewis and Murray (42) published a case-control study reporting that patients with schizophrenia were more likely to have a history of obstetric complications recorded in their case notes than patients with other psychiatric disorders. In another paper (43), the authors divided the overall patient group on the basis of family history, age at onset of illness, premorbid personality, and cerebral ventricular size and compared rates of obstetric complications between the subgroups. The quest for "subgroups" and the search for correlates of obstetric complications were themes that would recur many times during the years that followed. Another consequence of this study was the introduction of the so-called "Lewis-Murray" scale for rating retrospective information on obstetric complications (43). The Lewis-Murray scale could be used for rating information on obstetric complications from case notes, birth records, and maternal interviews. It was derived from a consensus of six previous scales and consisted of 15 complications with thresholds for rating some as "definite" or "equivocal."

The combination of three factors—1) the theoretical framework provided by the "neurodevelopmental hypothesis," 2) the possibility of using maternal recall and case notes as sources of information about obstetric complications, and 3) the availability of an easy-to-use rating scale—gave rise to a veritable flood of case-control studies investigating the association between obstetric complica-

tions and schizophrenia during the early and mid-1990s. Due to limitations of methods, however, this enormous research effort served to confuse rather than elucidate the association. Some studies found a significant overall effect for obstetric complications (44–48), others did not (49, 50). Some studies had no normal comparison group (51–53), while others included a sibling comparison group (44, 47, 49, 50, 54). Different variations of the Lewis-Murray scale were used, but the results were still presented as total scores. Although some studies clearly attempted to use population-based methods (28, 44, 45, 48), the final samples were selected to varying degrees and were prone to bias. Many studies relied solely on maternal recall as the source of information about the exposure (46, 49, 52). Subgroup analyses were common but yielded inconsistent results. Obstetric complications were examined in relation to family history (49, 51, 55–57), premorbid adjustment (51), imaging abnormalities (53, 58), age at onset of illness (45, 55, 59, 60), gender (45, 56, 57, 59), neurological abnormalities (49, 55), ethnicity (61), and season of birth (56), among others. The search for environmental risk factors for schizophrenia had become an example of "circular epidemiology," namely "the tendency to perseverate at one level of evidence, for example, on one type of study design without moving forward" (62).

In 1995, Geddes and Lawrie (63) carried out a meta-analysis of published results from 16 case-control studies and two cohort studies. They concluded that there was a modest relationship between the broad category of obstetric complications and later schizophrenia, with a pooled odds ratio of 2.0 (95% confidence interval [CI]=1.6–2.4). However, they pointed out two important caveats: 1) there was evidence for selection and publication bias in the literature and 2) there was significant heterogeneity between studies with case-control and cohort designs. To examine specific complications, Geddes and colleagues (64) obtained raw data from the investigators of 12 case-control studies that had used the Lewis-Murray scale and carried out a meta-analysis using the data from the individual patients. This analysis, based on data from 700 schizophrenic subjects and 835 comparison subjects, found that the following obstetric complications were significantly associated with schizophrenia: premature rupture of membranes, prematurity, use of resuscitation or incubator, birthweight <2500 g, preeclampsia (birth record data only), and forceps delivery (maternal recall only). However, the problems with selection and information bias among the component studies threatened the validity of the meta-analysis. More robust, population-based methods were needed.

Population-Based Studies (1997–present)

This phase of the literature on obstetric complications and schizophrenia began in earnest in 1997 and continues to date. Studies are characterized by large samples drawn from population-based hospital or case registers, with comparison subjects drawn from the same population, and use of standardized, prospective obstetric data from birth records or registers. Investigators usually report odds ratios for individual obstetric complications and control for demographic confounders by matching or statistical adjustment.

It was hoped (indeed expected!) that these large, methodologically robust studies would provide clear, consistent answers about the relationship between individual obstetric complications and schizophrenia, but this has not proved to be the case. As Table 1 shows, the findings from the population-based studies were mostly negative and surprisingly contradictory. Rather than dealing with each of these studies separately, we have elected to carry out a meta-analytic synthesis of the results. Possible reasons for the discrepancies between studies will be discussed after presentation of the findings from the meta-analysis. The standardized fashion of reporting results and the similarities in the methods of the population-based studies lend themselves to a meta-analytic approach. Meta-analysis provides a method for integrating quantitative data from multiple studies by using a weighted average of the results in which larger studies have more influence than smaller studies. It improves the estimates of effect size, increases the statistical power, and helps to make sense out of studies with conflicting conclusions (65, 66).

The limitations of using a meta-analytic approach for observational studies should be mentioned. Observational studies may yield estimates of association that are influenced to a greater or lesser degree by confounding or bias, and meta-analysis in itself is no defense against such factors ("bias in equals bias out"). The population-based studies in this analysis were relatively free from bias, and the odds ratios were adjusted for confounders such as sex, hospital where the birth took place, and social class. However the samples were drawn from different populations, in terms of geography, age at illness onset, and cohort and period effects, and all these differences could provide sources of confounding factors. Obstetric practices and methods for recording information about different complications vary between countries and over time.

Meta-Analytic Review of Population-Based Studies

Method

Inclusion criteria. Studies were included in the meta-analysis if they fulfilled the following a priori set of criteria: 1) inclusion of a well-defined sample of cases drawn from population-based registers or cohorts, 2) use of standardized, prospectively collected obstetric information from birth records or registers, 3) inclusion of comparison subjects drawn from the general population with information

on obstetric complications collected from the same source, and 4) use of a standardized format for presentation of data on individual obstetric complications, allowing for comparisons between studies. The search strategies used were 1) computerized MEDLINE search, 2) cross-referencing of original studies, and 3) contact with other researchers in the field. We identified eight studies that fulfilled all four criteria (67–73). Two of these studies were reported within one scientific paper (71). The characteristics of the eight studies and a summary of their findings are presented in Table 1. We identified a further five studies that fulfilled the first three criteria but not the fourth—the obstetric data were presented in aggregate form and could not be used in the meta-analysis (74–78). These five studies will be mentioned in the discussion of the results of the meta-analysis where appropriate.

Statistical analysis. Individual obstetric complications were included in the analysis if more than two studies reported on that complication in a comparable way. Two of the studies (69, 70) report on the same data set, although with different sampling frames. Therefore, when both studies report on the same obstetric complication, data from only the larger study (70) were used. A funnel plot showed no evidence for publication bias. Adjusted odds ratios for the associations between individual obstetric complications and later schizophrenia with 95% CIs were extracted from each paper and used as the measures of effect size and the variance of the effect size, respectively. A pooled estimate was calculated for each association by using Woolf's method, with 95% CIs and a test that the true pooled effect was zero (65). The analysis used a fixed-effects model, which assumes that variability between studies is due solely to random variation (66). A homogeneity statistic Q was calculated for each association (79). A significant value for Q indicates that there is heterogeneity between the studies for that complication. Where significant heterogeneity was detected, we calculated a random-effects estimate for the association. The random-effects model assumes a different underlying effect for each study and leads to wider CIs than the fixed-effects model (79). However since the maximum number of contributory studies never exceeded six, there was insufficient power to formally investigate potential sources of heterogeneity (such as age at onset, gender, or period effects) in this analysis. All analyses were performed with STATA 6.0 (Stata Corp., College Station, Tex.)

Results

Results of the meta-analysis for the individual complications are presented in Table 2. Significant differences between schizophrenic subjects and comparison subjects were found for the following variables in order of effect size: diabetes in pregnancy, birth weight <2000 g, emergency Cesarean section, congenital malformations, uterine atony, rhesus variables (comprising rhesus incompatibility, rhesus-negative mother, rhesus antibodies), asphyxia, bleeding in pregnancy, birth weight <2500 g, and preeclampsia. Significant heterogeneity was detected for two of these complications: asphyxia ($Q=10.41$, df=2, $p=0.005$) and birthweight <2500 g ($Q=12.56$, df=4, $p<0.02$). The random-effects estimate for asphyxia was 2.01 (95% CI=0.73–5.49; $z=1.3$, df=2, $p=0.18$) and for birth weight <2500 g was 1.66 (95% CI=0.94–2.95; $z=1.7$, df=4, $p=0.08$). The following three complications just missed formal statistical significance: placental abruption, head circumference <32 cm, and a negative association with nonspontaneous delivery.

Discussion

The significant estimates from the meta-analysis appear to group into three main categories: 1) complications of pregnancy (bleeding, preeclampsia, diabetes, and rhesus incompatibility), 2) abnormal fetal growth and development (low birth weight, congenital malformations, and small head circumference), and 3) complications of delivery (asphyxia, uterine atony, and emergency Cesarean section). The results will be discussed in these categories within the context of relevant findings from other studies that may elucidate these results.

Complications of pregnancy. Bleeding and preeclampsia in pregnancy have been associated with psychosis since the earliest days of such research. Pasamanick and colleagues (2) singled out the "anoxia-producing complications of pregnancy such as toxemia and bleeding" as most likely to be associated with behavior problems.

Preeclampsia came to particular attention in 1996 when Kendell and colleagues (80) reported a very strong association between preeclampsia and later schizophrenia, but, in their attempt to extend the study group and replicate this finding, a flaw in the original study design was uncovered, and a retraction was published (71). The revised analysis found no significant effect for preeclampsia. However, in the largest single population-based study to date, preeclampsia was the only obstetric risk factor that remained significant after the analysis controlled for all potentially confounding factors (70). What could be the mechanism of action of this association? The most popular theory at present involves the mechanism of abnormal fetal blood flow resulting in chronic fetal hypoxia or malnutrition (75).

Bleeding during pregnancy has many causes. Implantation bleeding and abbreviated menses are common in the first month, and placenta praevia and premature separation of the placenta are frequent causes in the last month. The causes of mid-pregnancy bleeding are less well understood. In one study, two-thirds of the cases were found to be due to premature separation, placenta praevia, hydatiform moles, incompetent cervices, and other identifiable causes, while in one-third of the cases, the cause could not be determined (81). In severe cases of bleeding, the pathogenic effect on the fetus is thought to be anoxia, but, in many cases, the amount of bleeding may be slight (8, 20), and anoxic brain damage is unlikely. Another explanation

TABLE 1. Prospective Population-Based Studies Included in a Meta-Analysis of the Association Between Obstetric Complications and Schizophrenia

Study	Year	Country	Study Design	Schizophrenic Subjects: N	Schizophrenic Subjects: % of Female Subjects	Number of Comparison Subjects	Variables Matched or Adjusted For	Diagnostic Criteria	Birth Years
Sacker et al. (67)	1995	U.K.	Follow-up of National Child Development Study cohort[c]	35	39	16,812	N/A	Present State Examination (S+ in the Catego program)[d]	1958
Jones et al. (68)	1998	Finland	Follow-up of 1966 North Finland Birth Cohort	76	32.9	1,074	Adjusted for sex, social class, smoking, maternal depression	DSM-III-R	1966
Hultman et al. (69)	1999	Sweden	Case-control study	167	34.9	835	Matched on sex, year of birth, hospital	ICD-9	1973–1979
Dalman et al. (70)	1999	Sweden	Cohort follow-up	238	41.6	507,278	Adjusted for sex, year of birth, hospital, maternal age, marital status, maternal history of psychosis	ICD-9	1973–1977
Kendell et al. (71)	2000	Scotland	Case-control study	296	24.4	296	Matched on sex, date of birth, hospital, maternal age, parity, social class	ICD-9, ICD-10	1971–1974
Kendell et al. (71)	2000	Scotland	Case-control study	156	24.4	156	Matched on sex, date of birth, hospital, maternal age, parity, social class	ICD-9, ICD-10	1975–1978
Byrne et al. (72)	2000	Ireland	Case-control study	431	40.6	431	Matched on sex, date of birth, hospital, maternal age, parity, social class	ICD-9	Not specified
Dalman et al. (73)	2001	Sweden	Case-control study	524	34	1,043	Matched on sex, hospital, year of birth, parish; adjusted for maternal age, maternal history of psychosis, parity, social class, marital status, attendance at antenatal clinics	ICD-8, ICD-9	1960–1977

[a] Power to detect odds ratios with 95% confidence for an exposure with a prevalence of 10% among comparison subjects.
[b] Odds ratios presented with 95% confidence intervals (CIs).
[c] See Done et al. (74).
[d] Narrow definition of schizophrenia used in the Catego computer program that derives diagnoses from Present State Examination data.

Age at Follow-Up (years)	Power to Detect Odds Ratio of 2.0 (%)[a]	Power to Detect Odds Ratio of 1.5 (%)[a]	Data Source		Variables Associated With Schizophrenia[b]
			Subject Characteristics	Obstetric Data	
16–28	40	10	Mental Health Enquiry 1974–1986	Midwife reports	Low maternal weight (odds ratio=2.4, CI=1.3–4.4), maternal psychological problems (odds ratio=11.4, CI=4.4–29.7), smoking in pregnancy (odds ratio=1.6, CI=0.9–2.8), poor antenatal clinic attendance (odds ratio=2.6, CI=1.5–4.5), rhesus-negative mother (odds ratio=1.8, CI=1.4–6.4), parity >2 (odds ratio=2.4, CI=1.3–4.3), previous births <2500 g (odds ratio=2.4, CI=1.1–4.8), bleeding in pregnancy (odds ratio=3.0, CI=1.4–6.4), untrained person delivered baby (odds ratio=4.9, CI=2.0–12.1), baby's weight <2500 g (odds ratio=3.9, CI=1.9–8.1), antibiotic (streptomycin) given to baby during neonatal period (odds ratio=5.2, CI=1.8–15.2).
27–28	50	15	National Hospital Discharge Register to 1993	Midwife reports	Low birth weight (odds ratio=2.4, CI=1.0–5.6), combination of low birth weight and prematurity (odds ratio=3.5, CI=1.3–9.6), and perinatal brain damage (odds ratio=6.9, CI=2.9–16.3).
15–21	80	35	National Hospital Discharge Register 1987–1994	Birth register entries completed by obstetrician or midwife	Multiparity (odds ratio=2.0, CI=1.0–3.8), bleeding during pregnancy (odds ratio=3.5, CI=1.2–10.3), winter birth (odds ratio=1.4, CI=1.0–2.0), baby small for gestational age (males only, odds ratio=3.2, CI=1.4–7.2), parity >4 (males only, odds ratio=3.6, CI=1.6–7.8)
15–22	95	55	National Hospital Discharge Register 1987–1995	Birth register entries completed by obstetrician or midwife	Preeclampsia (odds ratio=2.5, CI=1.4–4.5), vacuum extraction (odds ratio=1.7, CI=1.1–2.6), malformations (odds ratio=2.4, CI=1.2–5.1), parity=1 (odds ratio=1.3, CI=1.0–1.6), bleeding during pregnancy (odds ratio=2.0, CI=1.0–4.2), threatened premature delivery (odds ratio=2.3, CI=1.0–5.0), gestational age <32 weeks (odds ratio=2.7, CI=1.0–7.0), prolonged delivery (odds ratio=1.6, CI=1.0–2.5), uterine inertia (odds ratio=2.4, CI=1.5–3.9), ponderal index<20 (odds ratio=3.4, CI=1.1–10.1), respiratory illness (odds ratio=1.5, CI=1.1–2.4), birthweight <2500 g (males only, odds ratio=2.2, CI=1.1–4.1), birthweight <1500 g (females only, odds ratio=6.0, CI=1.7–21.4), baby small for gestational age (males only, odds ratio=1.9, CI=1.1–2.6). Preeclampsia remained significant after adjusting for all other complications and confounders (odds ratio=2.1, CI=1.1–4.1).
22–26	78	30	National Hospital Admission Register to 1996	Birth register entries completed by obstetrician or midwife	No association found between any obstetric complication and schizophrenia.
18–21	50	15	National Hospital Admission Register to 1996	Birth register entries completed by obstetrician or midwife	Emergency Cesarean section (odds ratio=3.7, CI=1.0–13.1) and labor >12 hours.
N/A	92	45	Dublin psychiatric case register 1972–1992	Labor ward records	Cesarean section (odds ratio=4.0, CI=1.1–22.1) more common among cases.
29.5 (mean)	99	68	Stockholm county inpatient register 1971–1994	Birth records completed by midwife	Signs of asphyxia at birth (odds ratio=4.4, CI=1.9–10.3) significant after adjusting for other complications and confounders.

TABLE 2. Meta-Analysis of Eight Prospective Population-Based Studies of the Association Between Obstetric Complications and Schizophrenia[a]

Complication[b]	Number of Studies	Number of Schizophrenic Subjects		Number of Comparison Subjects		Fixed Pooled Estimate (Odds Ratio)	95% CI	z	p
		Total	Exposed to Complication	Total	Exposed to Complication				
Diabetes in pregnancy	2	237	3	1,909	3	7.76	1.37–43.90	2.3	<0.03
Placental abruption	2	308	3	508,352	1,643	4.02	0.89–18.12	1.8	0.07
Birth weight <2000 g	2	504	6	10,926	78	3.89	1.40–10.84	2.6	0.009
Emergency Cesarean section	3	818	20	507,863	1,595	3.24	1.40–7.50	2.7	0.006
Congenital malformations	3	737	10	508,781	6,144	2.35	1.21–4.57	2.5	<0.02
Uterine atony	2	659	27	507,703	16,913	2.29	1.51–3.50	3.8	<0.001
Rhesus variables[c]	3	759	18	17,537	2,911	2.00	1.01–3.96	1.9	<0.05
Threatened premature delivery	2	308	8	508,352	6,498	1.98	0.79–4.90	1.5	0.14
Asphyxia[d]	3	1,109	60	2,297	119	1.74	1.15–2.62	2.6	0.008
Bleeding in pregnancy	6	1,223	34	524,972	9,367	1.69	1.14–2.52	2.6	0.009
Birth weight <2500 g[e]	5	1,294	60	536,045	19,343	1.67	1.22–2.29	3.2	0.002
Head circumference <32 cm	2	758	53	508,315	15,388	1.38	0.97–1.91	1.7	0.08
Smoking in pregnancy	2	105	26	17,886	5,752	1.38	0.88–2.14	1.4	0.16
Preeclampsia	6	1,712	75	510,275	18,286	1.36	0.99–1.85	1.9	0.05
Anemia in pregnancy	3	522	20	1,526	96	1.26	0.69–2.28	0.7	0.45
Gestational age <37 weeks	5	1,290	67	536,051	21,710	1.22	0.90–1.65	1.3	0.20
Small for gestational age	5	1,272	86	519,229	23,485	1.21	0.91–1.61	1.3	0.19
Induction of labor	4	689	186	2,361	232	1.18	0.89–1.56	1.1	0.25
Apgar score <7 at 1 minute after birth	2	390	18	507,434	22,771	1.09	0.62–1.92	0.3	0.76
Gestational age >42 weeks	3	1,187	34	508,747	16,065	1.08	0.69–1.68	0.3	0.72
Child stayed in hospital after mother discharged	3	973	110	1,488	99	1.07	0.79–1.44	0.4	0.65
Forceps delivery or vacuum extraction	7	1,724	124	527,058	29,753	1.07	0.85–1.35	0.6	0.48
Birth length <49 cm	3	761	130	51,320	105,205	1.06	0.86–1.31	0.5	0.59
Cephalopelvic disproportion	2	662	10	2,338	42	1.04	0.28–3.82	<0.1	0.95
Cord around neck	2	893	171	1,345	333	1.03	0.81–1.31	0.2	0.83
Cesarean section	5	1,214	63	526,045	42,947	0.99	0.70–1.41	<0.0	0.98
Birth weight <2500 g and premature	4	954	41	11,376	215	0.96	0.62–1.46	–0.2	0.84
Nonvertex presentation	6	1,667	74	510,208	61,130	0.89	0.67–1.20	–0.7	0.45
Breech delivery	3	464	11	508,508	13,580	0.87	0.38–1.97	–0.3	0.74
Urinary tract infection in pregnancy	3	690	20	507,730	7,115	0.86	0.48–1.55	–0.5	0.63
Nonspontaneous delivery	2	331	46	17,108	1,554	0.63	0.39–1.01	–1.9	<0.06

[a] The studies included in the meta-analysis are summarized in Table 1.
[b] Complications presented in order of effect size.
[c] Includes rhesus incompatibility, rhesus-negative mother, and rhesus antibodies.
[d] Random effects estimate=2.01 (95% CI=0.73–5.49); z=1.3, df=2, p=0.18.
[e] Random effects estimate=1.66 (95% CI=0.94–2.95); z=1.7, df=4, p=0.08.

is that bleeding can represent a threatened spontaneous abortion. This is consistent with the striking and as yet unexplained findings of an excess of stillbirths and neonatal deaths among schizophrenic women (17–19). Rieder and colleagues (20) hypothesized that bleeding was "the result of rather than the cause of injury. In other words the process of uterine rejection could have begun but been interrupted." Genetic or autoimmune factors may play a part in such a process.

The association between diabetes in pregnancy and later schizophrenia, although strong, is based on only two studies in this analysis, neither of which provided information on the type of diabetes. Indirect support for the association comes from one report that high prepregnancy body mass increases the risk of schizophrenia in the offspring (82), since high maternal body mass index is associated with non-insulin-dependent diabetes and gestational diabetes. The effects on the developing brain of altered glucose metabolism are not well understood (83). Poorly controlled maternal diabetes is associated with an increased risk of congenital anomalies and impaired intellectual and psychomotor development in offspring (reviewed in reference 82). Insulin-dependent diabetes mellitus has been found to be more common among the first-degree relatives of patients with schizophrenia than among comparison subjects (84, 85), indicating that an autoimmune process might be involved. Autoimmune mechanisms could also be implicated in the association between rhesus incompatibility and later schizophrenia. Rhesus hemolytic disease of the newborn is an illness with neurological consequences secondary to effects of a maternal antibody (86, 87). Hemolytic disease can lead to early spontaneous abortion, chronic fetal hypoxia, neonatal asphyxia and pulmonary edema, and neonatal hyper-

bilirubinemia and kernicterus (86). The association has independent support from a cohort study that found a twofold increase in relative risk of schizophrenia among men from rhesus-incompatible pregnancies (88) and a report that neonatal hyperbilirubinemia is a risk factor for later mental illness (89).

Abnormal fetal growth and development. Low birth weight has been associated with schizophrenia throughout each era of investigation (1, 9, 21, 29, 43, 52), but this association is not invariably found (71–73, 90), and there was significant heterogeneity in the estimate for low birth weight (<2500 g) in this meta-analysis. The concept of a "population shift" in birth weight may account for this heterogeneity, and investigators using an arbitrary cutoff for low birth weight (i.e., <2500 g) will find inconsistent associations depending on the power of the study. Using a quantitative approach, Wahlbeck et al. (91) found that the risk of schizophrenia *decreases* in a linear fashion with increasing birth weight, increasing length at birth, and increasing placental weight. Low birth weight is usually due to prematurity or intrauterine growth retardation. The lack of a significant association between risk of schizophrenia and prematurity in our meta-analysis indicates that the low birth weight is most likely due to intrauterine growth retardation (although there was no association between risk of schizophrenia and being small for gestational age). However, almost any factor adversely affecting the fetus will retard its growth, so these findings do not appreciably narrow our search. Low birth weight may be a proxy variable for some other adverse influence or influences on the developing fetus, whether of genetic or environmental origin. Women with schizophrenia or who later develop schizophrenia have been shown to be at increased risk of behaviors during pregnancy—such as smoking, taking medication, or poor attendance at antenatal clinics—that are associated with low birth weight outcomes (21, 29, 92). The increased prevalence of congenital malformations found in this meta-analysis echoes the extensive literature on minor physical abnormalities and schizophrenia (93, 94) and further implicates pregnancy as a time when potential etiological factors may be operating.

Complications of delivery. The common mechanism for the delivery complications of asphyxia, uterine atony, and emergency Cesarean section found in our meta-analysis appears to be fetal hypoxia or anoxia. This is by no means a new idea, as anoxia has been mentioned since the earliest days of this literature (2). Geddes and colleagues (64) concluded that the underlying mechanism for all the complications associated with schizophrenia in their meta-analysis was likely to involve fetal hypoxia but that a "more specific measure of exposure to hypoxia" was required. The pooled estimate for asphyxia in our meta-analysis demonstrated significant heterogeneity, possibly due to the different definitions of asphyxia used. Three population-based studies that could not be included in the meta-analysis but that fulfilled three of the four inclusion criteria (76–78) provide additional support for the involvement of fetal hypoxia or asphyxia in the etiology of schizophrenia . Individuals from the National Collaborative Perinatal Project with three or more hypoxia-related obstetric complications were more than five times more likely to develop schizophrenia than individuals with no hypoxia-related obstetric complications (76), and this finding was particularly marked among patients with early-onset schizophrenia (77). Siblings of schizophrenic subjects were no more likely to experience these complications than were comparison subjects (76, 77). Cannon and colleagues (76, 77) suggest that these results are consistent with a model of schizophrenia involving interaction of genetic vulnerability and obstetric complications (95, 96) and that the neurotoxic effect of fetal hypoxia leads to an early onset of schizophrenia through premature cortical synaptic pruning (77). Putative hypoxia-related complications have been related to brain structural abnormalities among schizophrenic patients (95, 97).

The major difficulty with proposing hypoxic-ischemic damage as a causal risk factor for schizophrenia is the establishment of independence—it may be related to pregnancy complications, preexisting problems with the fetus (98, 99), or maternal behaviors (29, 92). Although some initial investigations have not found empirical support for this notion (100), few studies have had sufficient power to examine the interrelationships between various obstetric complications in the same individuals.

Why Is It So Difficult to Study Obstetric Complications and Schizophrenia?

Statistical Power

The effect sizes for the relationship between obstetric risk factors and later schizophrenia are generally small, with odds ratios of less than 2 (Table 1 and Table 2). This is the sort of effect size reported for the relationship between passive smoking and lung cancer (101) or the risk of breast cancer among users of the oral contraceptive pill (102). Such small effects are usually controversial (103) and are some way from indicating strong causality. One may be dealing with proxy effects for some other lifestyle or socioeconomic factors or interactive effects with as-yet-unknown genetic or epigenetic factors. The study of individual obstetric risk factors for schizophrenia could be conceptualized as the search for rare risk factors for a rare disease and is therefore truly suitable neither for the classic cohort design nor for case-control designs. The power of even the largest population-based studies to detect odds ratios of 1.5 was less than 70% (Table 1). Methods such as the "nested" case-control design (69, 73) are useful, but, even so, the lack of independence of individual obstetric complications (discussed earlier) and possible interactive effects further erode statistical power. Some

studies have tried to overcome low statistical power by examining only one exposure on the basis of a prior hypothesis. This has proved a relatively fruitful endeavor, showing significant effects for the putative risk-increasing mechanism of hypoxic and ischemic damage (73, 75–78), but each set of researchers has used different combinations of exposures, hindering replication and comparison or pooling of the results between studies.

Definition of Obstetric Complications

No one realized initially just how common the broadly defined Lewis-Murray obstetric complications are in the general population—about 25%–30% of births involve at least one Lewis-Murray complication (see references 68 and 104). So many discrete exposures are wrapped up in the term "obstetric complication" that it is essentially meaningless to consider them as one risk factor (105). Before beginning to judge whether any association should be interpreted as causal, researchers must consider many distinct associations in terms of chance, bias, or confounding. If the field is to progress, advances are needed not only in population-based methods but also in sharpening the definitions of the exposures under scrutiny. A broad definition of obstetric complications should no longer be used as it will not improve our understanding of the field any further. More careful definition of exposures, such as prenatal measurement of maternal antibodies, and more extensive use of quantitative measures, including birth weight or head circumference, are likely to show larger and more consistent effects.

Information on the Prenatal Period

Birth records tend to include detailed information about the delivery and neonatal period, but information about the prenatal period is less reliable (106). Details about the course of the pregnancy are often recorded at the time of admission to the labor ward. Major pregnancy complications, such as preeclampsia, are usually mentioned, but there may be no record of problems such as prenatal stress or there may be insufficient detail about timing of infection or bleeding. Nevertheless, the current meta-analysis shows that many prenatal factors (even with the less-than-optimal data available) are significantly associated with later schizophrenia. Even stronger effects may have been found if detailed, prospective data on the prenatal period were available. Ecological data, cunningly exploited, have provided clues of the existence of other prenatal risk factors for schizophrenia, including prenatal infection (for a review, see references 14, 107, 108), prenatal malnutrition (109), and prenatal stress (110, 111). Such exposures should ideally be incorporated into future studies of obstetric complications and schizophrenia. Another approach would be to follow up a cohort of individuals who have suffered definite specific prenatal (or perinatal) complications and assess a range of outcomes during development—a return to the position advocated by Pasamanick and colleagues many decades ago (2). This approach has already been useful in elucidating some rare prenatal exposures such as rubella infection (112) and rhesus incompatibility (88) and is currently being applied to follow-up studies of subjects with low birth weight and premature birth (113). This approach could also address the issue of specificity of obstetric risk factors for schizophrenia.

Interactive or Subgroup Effects

There has long been interest in whether the effect of obstetric complications may be confined to a subgroup of patients with schizophrenia, such as those with a family history, or male sex, or early onset, but most studies have not had sufficient power to examine this issue reliably. Verdoux and colleagues (114), in an individual-patient data meta-analysis, found a relationship between age at onset of schizophrenia and obstetric complications—the earlier the age at onset of schizophrenia, the more likely a history of obstetric complications—but found no relationship with family history of schizophrenia or gender. Cannon and colleagues (76, 77) also found a relationship between asphyxia and schizophrenia among patients with early-onset schizophrenia. However, in general, the recent population-based studies have tended not to examine subgroups within the population of patients with schizophrenia.

The study of gene-environment interactions is beginning to be applied to schizophrenia (115). There is increasing awareness that "hidden" genetic factors can have a substantial influence on the effect of environmental exposures, such as obstetric complications. An exposure that has a small effect on schizophrenia in general may have a large effect in those with a specific genetic make-up. In the coming decade we may see the first reports of studies that examine precisely measured genetic and environmental causes of schizophrenia in the same population (116). However, to adequately model interactive effects involving rare environmental risk factors (such as individual obstetric complications) and genes of small effect, sample sizes of tens of thousands will be required (14). We also have to take into account the dynamic interplay between genes and environment in utero (117).

Need for Collaborative Approaches

Current methods for studying the relationship between obstetric complications and schizophrenia merely allow us to report associations and, as a result, we have become stuck at the point of reporting risk factors of "vanishingly small effect" over and over again (62, 118). Research in this area will need to move beyond the domain of epidemiology and involve other disciplines, such as developmental biology, neuropathology, and genetics (119, 120). Innovative approaches include the use of animal models to study effects of prenatal infection (121, 122) and the analysis of large cohorts with detailed prenatal data and stored pre-

natal serum (116, 123). As we enter what some researchers have called a new age of epidemiology for schizophrenia (116, 124), the combination of larger cohorts, new paradigms, and modern statistical and molecular techniques provides the opportunity to discover how obstetric complications contribute to the causation of schizophrenia.

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Supported by a Wellcome Trust Advanced Research Fellowship to Dr. Cannon, the EJLB Foundation, and by the Theodore and Vada Stanley Foundation.

The authors thank Dr. Christina Dalman, Dr. Hollie Thomas, Dr. Paul Fearon, Prof. Glyn Lewis, and Prof. Robert Kendell for their help in preparing the paper.

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