A Prospective Cohort Study of Genetic and Perinatal Influences in the Etiology of Schizophrenia

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Abstract

In this study, we examined whether fetal hypoxia and other obstetric complications (OCs) are related to risk for adult schizophrenia; whether such effects are specific to cases with an early age at onset; and whether the obstetric influences depend on, covary with, or are independent of familial risk. Subjects were 72 patients with schizophrenia or schizoaffective disorder; 63 of their siblings not diagnosed with schizophrenia; and 7,941 nonpsychiatric controls, whose gestations and births were monitored prospectively with standard research protocols as part of the National Collaborative Perinatal Project. Adult psychiatric morbidity was ascertained via a longitudinal treatment data base indexing regional public health service utilization, and diagnoses were made by review of all pertinent medical records according to *DSM–IV* criteria. We found that the odds of schizophrenia increased linearly with increasing number of hypoxia-associated OCs and that this effect was specific to cases with an early age at onset/first treatment contact. There were no relationships between schizophrenia and birth weight or other (prenatal/nonhypoxic) OCs. Siblings of patients with schizophrenia were no more likely to have suffered hypoxia-associated OCs than were nonpsychiatric cohort controls. Because the majority of individuals exposed to fetal hypoxia did not develop schizophrenia, such factors likely are incapable of causing schizophrenia on their own. Together, these findings suggest that hypoxia acts additively or interactively with genetic factors in influencing liability to schizophrenia. We propose a model in which the neurotoxic effects of fetal hypoxia may lead to an earlier onset of psychosis because of premature pruning of cortical synapses.

Keywords: Schizophrenia, obstetric complications, fetal hypoxia, age at onset.

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The notion that schizophrenia is a neurodevelopmental disorder has been given impetus by findings of cellular positioning abnormalities and other structural brain changes consistent with a gestational origin (Kovelman and Scheibel 1984; Jakob and Beckmann 1986; Arnold et al. 1991; Akbarian et al. 1993; Cannon et al. 1993). More direct substantiation of this model would be provided by evidence that particular genetic or teratogenic factors adversely affect brain development before or around the time of birth among individuals who develop the condition as adults. Moreover, elucidation of the types of teratogenic factors involved and whether their influences are independent of, covary with, or depend on genetic predisposition could help to isolate the mechanisms by which such factors increase risk for the disorder and suggest strategies for prevention.

Studies using objective measures of prenatal and perinatal history have consistently implicated OCs as risk factors for the disorder, whether the samples were siblings (Lane and Albee 1966; Pollack et al. 1966; Woerner et al. 1971; Eagles et al. 1990; Gunther-Genta et al. 1994; Kinney et al. 1994) and twins (Pollin and Stabenau 1968; Markow and Gottesman 1989; Bracha et al. 1992; Torrey et al. 1994) discordant for schizophrenia, adopted children with schizophrenia (Jacobsen and Kinney 1980), offspring of parents diagnosed with schizophrenia (Parnas et al. 1982; Fish et al. 1992), adults diagnosed with schizophrenia and matched controls (O'Callaghan et al. 1992; McNeil et al. 1994; Kendell et al. 1996; Hultman et al. 1997), or representative birth cohorts (Done et al. 1991; Buka et al. 1993; Dalman et al. 1999; Rosso et al., in press). The two studies reporting null results are not outliers in this respect, only in that the 95 percent confidence intervals of their risk estimates included values of 1 (Done

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et al. 1991; Buka et al. 1993). One of these studies found that odds of schizophrenia were 2.6 times higher among individuals with a history of fetal hypoxia than among those without such a history ($p = 0.13$), but statistical power was limited by a small number of schizophrenia outcomes ($n = 8$) (Buka et al. 1993). The other study found that odds of schizophrenia were 1.4 times higher among individuals exposed to complications predicting stillbirth and neonatal mortality, but this effect was not significant ($p = 0.51$) despite a large sample size (35 schizophrenia cases and 16,945 controls) (Done et al. 1991). The comparability of the OC measure in this latter study to those in other studies is not clear, and, curiously, cases of stillbirth and neonatal death were retained in the prediction analyses. When specific complications were examined in this cohort, bleeding during pregnancy and low birth weight were significantly related to schizophrenia (Sacker et al. 1995).

Most of the studies summarized above employed general summary measures of OCs, making it difficult to determine whether a narrow or broad range of neurally disruptive obstetric mechanisms are potentially implicated in schizophrenia. When particular complications have been examined, both direct and indirect measures of fetal hypoxia have emerged as prominent predictors (see McNeil 1988; Mednick et al. 1991; Cannon 1997 for reviews). This mechanism is clearly suggested in severely cyanotic infants who require prolonged efforts to invoke breathing (and in cases of neonatal apnea), but it also may occur to varying degrees (even in those without diagnostic signs at birth) in association with a variety of prenatal and perinatal complications, including maternal bleeding during pregnancy (Low et al. 1992; Adamson et al. 1995; Low et al. 1995), fetal heart rate/rhythm deviations (Arabin et al. 1993; Adamson et al. 1995), meconium in amniotic fluid (Low et al. 1992; Maier et al. 1994; Adamson et al. 1995; Low et al. 1995), breech presentation (Low et al. 1995), hydramnios (Arabin et al. 1993; Maier et al. 1994), cord knotting/encircling of the neck (Low et al. 1995; Salafia et al. 1995), and placental infarction/hemorrhaging (Maier et al. 1994; Salafia et al. 1995). That most studies have found schizophrenia to be associated with an aggregation of complications, rather than with specific ones in isolation, could reflect involvement of a single mechanism (e.g., hypoxia) that can be produced by a variety of different causes, or the involvement of multiple different mechanisms. Previous studies either did not attempt to differentiate these alternatives or were limited in their ability to do so because of small sample sizes. If fetal hypoxia is the primary mechanism underlying the association between OCs and schizophrenia, given sufficient statistical power, one would expect that odds of schizophrenia would increase with an increasing number of hypoxia-associated complications (i.e., such indicators should aggregate together in the same patients) and that complications implicating other mechanisms would show no association. If multiple obstetric mechanisms are involved, a variety of OCs should be elevated in schizophrenia (with different types of OCs appearing in different patients). Fetal underdevelopment and maternal infection during pregnancy merit special attention in this regard, as each have been found to be associated with schizophrenia outcome in previous studies (see Cannon 1997 for a review), and the association in each case could at least theoretically involve a neurally disruptive mechanism other than fetal hypoxia (e.g., reduced cell proliferation and interference with cell adhesion during neural migration, respectively).

It is also not yet known whether hypoxia and other OCs increase the risk for schizophrenia independently of, or in interaction with, the disorder's genetic diathesis or are themselves consequences of this diathesis (Lewis and Murray 1987; Fish et al. 1992; Cannon et al. 1993). Examining whether OCs occur more or less frequently in the unaffected siblings of patients with schizophrenia than in the general population provides a means to segregate these models. Because risk for schizophrenia is equivalently elevated among offspring of affected and unaffected monozygotic cotwins (Fischer 1973; Gottesman and Bertelsen 1989), it appears that the genetic transmission of this disorder does not depend on overt phenotypic expression in relatives. In addition, some unaffected relatives of schizophrenia subjects show the same neuroanatomical and neurobehavioral deficits seen in schizophrenia, although to a lesser degree (Cannon et al. 1994; Cannon and Marco 1994). Together, these findings indicate that a substantial proportion of the first degree relatives of patients with schizophrenia carry a predisposing genotype without manifesting the disorder phenotypically. It follows that if OCs are consequences of genetic liability to schizophrenia, then the odds of developing schizophrenia *and* of being an unaffected sibling of a schizophrenia subject should be higher among individuals with a history of OCs (i.e., because OCs would then vary with presence of genetic predisposition to schizophrenia regardless of phenotypic expression). Conversely, if OCs act additively or interactively with the disorder's genetic diathesis in increasing risk for phenotypic expression, then unaffected siblings of schizophrenia subjects should be no more likely to have suffered OCs than unaffected individuals from the general population.

The association of OCs and schizophrenia is one line of evidence implicating neurodevelopmental disturbances in the etiology of the disorder. Because OCs suggest brain damage acquired during the prenatal or perinatal period, it is reasonable to suspect they are related to a form of

schizophrenia positive for other indicators of neurodevelopmental compromise, such as delayed motor and cognitive development, poor premorbid social adjustment, and an early age at onset. In support of this view, a recent meta-analytic study integrating individual patient data from 11 different research groups that had employed the Lewis and Murray OC scale (Lewis and Murray 1987) found that patients with an onset before age 22 were about three times more likely to have a history of birth complications than those with later onsets (Verdoux et al. 1997). It is thus possible that OCs are especially or only associated with schizophrenia with an early onset.

We tested these hypotheses in a cohort of 9,236 individuals (including 4,280 siblings) born in Philadelphia from 1959 to 1966, whose gestations and births were monitored with standard research protocols as part of the National Collaborative Perinatal Project (NCPP) (Niswader and Gordon 1972). Psychiatric outcomes were ascertained using a computer data base for registration of treatment contacts in adulthood, with subsequent chart reviews to determine diagnoses according to *DSM–IV* (American Psychiatric Association 1994) criteria.

Methods

Subjects and Psychiatric Diagnoses

Formation of cohort. From 1959 to 1966, the NCPP enrolled for study 9,236 offspring of 6,753 mothers who delivered at two inner-city hospital obstetric wards in Philadelphia—the Pennsylvania Hospital and the Children's Hospital of Philadelphia (Niswader and Gordon 1972). The offspring in over 90 percent of all the deliveries at these two sites during the sampling period were enrolled. Fifty-four percent (n = 4,956) of the cohort members were the only children from their families enlisted in the study, and the remaining 46 percent (n = 4,280) were from families with two or more children participating. The recruitment sites for the Philadelphia cohort were chosen to result in a predominantly African-American cohort (88%), thus permitting ethnic balance across the NCPP study sites taken together.

Diagnostic screening and evaluation. In January 1996, we conducted a search of the Penn Longitudinal Database (Rothbard et al. 1990), a citywide data base for registration of contacts with public mental health facilities in Philadelphia from 1985 to 1995, ascertaining 1,197 individuals whose names and dates of birth matched those of subjects in the birth cohort. In total, 339 (3.7%) of the cohort members had ever had a psychotic disorder diagnosis (194 with schizophrenia or schizoaffective disorder and 145 with affective or drug-induced psychosis) and 858 (9.3%) had ever had nonpsychotic disorder diagnoses (i.e., affective, anxiety, adjustment, developmental, and substance abuse disorders). Thus, this study relied on prevalent rather than incident cases.

Because these register diagnoses were assigned by hundreds of different clinicians in scores of different treatment settings without an explicit attempt to standardize diagnostic procedures and criteria, they are unlikely to have a sufficient degree of precision in differentiating schizophrenia from other psychotic disorder categories. We therefore undertook a diagnostic validation study based on a review of the psychiatric medical records of the psychotic-disordered probands. We reviewed medical records for 144 such probands who had been treated at 15 mental health facilities that agreed to cooperate with the study team in providing access to medical records. The remaining psychotic-disordered probands whose charts were not reviewed (n = 195) had been treated at facilities that no longer existed, refused to cooperate, or were not contacted because only one proband had been treated there. The participating facilities included inpatient services, day treatment clinics, and case management services and were in all apparent ways equivalent to the nonparticipating facilities.

Six diagnosticians (two psychiatrists, two clinical psychologists, and two advanced graduate students in clinical psychology) performed the chart reviews. An initial set of ten charts was used in training to calibrate the less experienced with the more experienced diagnosticians. A standard coding form was used to record information pertinent to *DSM–IV* diagnostic criteria, differential diagnosis of schizophrenia and affective disorders, age at onset (defined as age at first psychotic symptoms or, if not specified, age at first treatment contact), and course. In the vast majority of cases the information present in the records spanned many years of the patient's illness, and a clear picture of the duration and primacy of psychotic symptoms emerged. Of the 144 cases whose charts were reviewed, 72 received a *DSM–IV* diagnosis of schizophrenia or schizoaffective disorder; 41 were diagnosed as having a psychotic form of major depressive disorder or bipolar disorder; and the remaining 31 were given a primary diagnosis of substance abuse, anxiety disorder, atypical psychosis, psychotic disorder caused by a general medical condition, personality disorder, or adjustment disorder. For a randomly selected sample of 94 of the cases (excluding those used in training), charts were evaluated independently by two or more different examiners, with good agreement on the diagnosis of schizophrenia and schizoaffective disorder (κ = 0.85; 41 cases with schizophrenia/schizoaffective disorder according to both diagnosticians; 46 cases without schizophrenia/schizoaffective disorder according to both diagnosticians; 7 cases with schizophrenia/schizoaffective disorder according to

one diagnostician but not the other). There was only moderate agreement between the chart-based *DSM–IV* diagnoses of schizophrenia and schizoaffective disorder with the original register diagnoses ($\kappa = 0.63$; 60 cases with schizophrenia/schizoaffective disorder according to both sources; 57 cases without schizophrenia/schizoaffective disorder according to both sources; 27 cases with schizophrenia/schizoaffective disorder according to one source but not the other).

Demographics of comparison groups. The 72 cases with chart-review-based *DSM–IV* diagnoses of schizophrenia or schizoaffective disorder had 63 siblings not diagnosed with schizophrenia who were also NCPP study participants. (Note that we could include only those siblings who were NCPP participants because only NCPP participants had the relevant obstetric information available.) The 63 siblings included 7 with a history of psychiatric treatment (1 with psychosis not otherwise specified, 1 with mental retardation, and 5 with affective and anxiety disorders) and 56 without such a history. For controls we used the cohort members without a sibling with schizophrenia and who according to our psychiatric screen had not been treated in a public mental health facility in greater Philadelphia as an adult ($n = 7{,}941$). The remaining 1,160 members of the original cohort were excluded from the primary analyses. There were four categories of excluded subjects: (1) 72 cases with a history of treatment for a psychotic disorder who were determined by chart review not to have schizophrenia or schizoaffective disorder, (2) 194 cases with a history of treatment for a psychotic disorder whose charts were not reviewed (i.e., 195 minus 1 included sibling of an included schizophrenia patient), (3) 852 cases with a history of treatment for a nonpsychotic psychiatric disorder (i.e., 858 minus 6 included siblings of included schizophrenia patients), and (4) 42 cases of fetal or neonatal death.

Table 1 gives demographic characteristics of the *DSM–IV* schizophrenia or schizoaffective disorder probands ($n = 72$), unaffected siblings of these probands ($n = 63$), and nonpsychiatric controls ($n = 7{,}941$). The median age at onset—17 years in this sample—was used to categorize the schizophrenia patients into early and later onset groups. There was not a significant difference in age at onset between male and female patients (two-tailed $p = 0.6$).

Obstetric Variables. NCPP obstetric scientists devised an extensive standardized coding scheme that was used to record lab findings, monitoring data, and complications from the first prenatal visit through the neonatal period (Niswader and Gordon 1972). To permit examination of rates of schizophrenia along a continuum of hypoxia likelihood (or severity), we attempted to aggregate those complications associated with fetal hypoxia into a hypoxia-associated OC scale. We used a rationale-empirical approach to constructing this scale. First, we selected complications considered to be either direct (blue at birth, required resuscitation, neonatal cyanosis, neonatal apnea)

Table 1. Demographic characteristics by adult psychiatric outcome

Characteristic	No diagnosis ($n = 7{,}941$)	Schizophrenia ($n = 72$)		Sibling without schizophrenia ($n = 63$)
		Early onset ($n = 34$)	Later onset ($n = 38$)	
Sex				
Males, *n* (%)	3,930 (49.5)	22 (64.7)	25 (65.8)	32 (50.8)
Females, *n* (%)	4,011 (50.5)	12 (35.3)	13 (34.2)	31 (49.2)
Race				
Black, *n* (%)	6,910 (87.0)	34 (100)	36 (97.7)	63 (100)
White, *n* (%)	1,031 (13.0)	0 (0)	2 (5.3)	0 (0)
Season of birth				
Winter, *n* (%)	1,975 (24.9)	6 (17.7)	11 (29.0)	14 (22.2)
Other, *n* (%)	5,966 (75.1)	28 (82.3)	27 (71.0)	49 (77.8)
Birth order, mean (SD)	3.4 (2.4)	4.3 (2.9)	2.9 (2.3)	4.4 (2.7)
SES, mean (SD)	3.4 (1.9)	2.9 (1.8)	3.0 (1.8)	2.6 (2.0)
Mother's age, mean (SD)	23.8 (6.1)	25.4 (7.1)	23.1 (5.9)	22.9 (4.8)

Note.—SD = standard deviation; SES = socioeconomic status.

or indirect (abnormalities of fetal heart rate or rhythm, umbilical cord knotted or wrapped tightly around neck, third trimester bleeding, placental hemorrhaging or infarcts, polyhydramnios, meconium in amniotic fluid, breech presentation) indicators of fetal oxygen insufficiency. The indirect indicators were chosen based on empirical validation against direct hypoxia indicators in prior studies (Low et al. 1992; Arabin et al. 1993; Maier et al. 1994; Adamson et al. 1995; Low et al. 1995; Salafia et al. 1995). Each of the indirect indicators was also predictive of the presence of one or more of the direct hypoxia indicators in this cohort, with the relationships achieving statistical significance for all variables except polyhydramnios: fetal heart rate/rhythm deviations ($\chi^2 = 21.7$, $df = 1$, $p < 0.001$), cord knotting/encircling of the neck ($\chi^2 = 25.7$, $df = 1$, $p < 0.001$), third trimester bleeding ($\chi^2 = 5.1$, $df = 1$, $p < 0.03$), placental infarction/hemorrhaging ($\chi^2 = 8.8$, $df = 1$, $p < 0.003$), polyhydramnios ($\chi^2 = 2.8$, $df = 1$, $p < 0.09$), meconium in amniotic fluid ($\chi^2 = 20.2$, $df = 1$, $p < 0.001$), and breech presentation ($\chi^2 = 5.5$, $df = 1$, $p < 0.02$). We did not weight the indirect indicators according to strength of this association, however, because the direct indicators reflected hypoxia at or shortly after birth whereas many of the indirect indicators could reflect hypoxia prior to birth, sensitivity to which would be reduced if the items were weighted according to their relationship with birth hypoxia. Each complication contributed 1 point to the total hypoxia-associated OC score.

To control for nonspecific obstetric influences, we also created a non–hypoxia-related prenatal OCs scale by aggregating items (each complication contributing 1 to the scale total) that were not significantly predictive of the direct hypoxia indicators in this cohort: maternal infection during pregnancy (including viral, bacterial, and fungal; $\chi^2 = 0.0$, $df = 1$, $p = 0.93$), maternal cardiovascular illness during pregnancy ($\chi^2 = 1.9$, $df = 1$, $p = 0.16$), maternal pulmonary illness during pregnancy ($\chi^2 = 1.0$, $df = 1$, $p = 0.31$), maternal hematologic illness during pregnancy ($\chi^2 = 0.4$, $df = 1$, $p = 0.51$), and maternal endocrine illness during pregnancy ($\chi^2 = 0.0$, $df = 1$, $p < 0.86$). Finally, we evaluated low birth weight (< 2000 g) in relation to diagnostic outcome. Low birth weight was significantly associated with the direct hypoxia indicators in this cohort ($\chi^2 = 23.1$, $df = 1$, $p < 0.001$), but we evaluated it separately because it has traditionally been viewed more prominently in relation to the fetal underdevelopment model rather than to the hypoxia model of schizophrenia.

Statistical Analysis. A logistic regression model was applied to a polytomous measure for diagnostic outcome by method of generalized logits (Proc catmod; Stokes et al. 1995). The outcome measure classified the cohort members into three groups: schizophrenia ($n = 72$), schizophrenia subjects' siblings not diagnosed with schizophrenia ($n = 63$), and no psychiatric diagnosis ($n = 7{,}941$). In the primary analysis, sex, race, season of birth, birth order, socioeconomic status (SES; varying on a scale of 1 [unemployed, on public assistance] to 9 [professional, upper middle class]), mother's age, birth weight, prenatal OCs, and hypoxia-associated OCs were included as predictors. Birth order, SES, mother's age, prenatal OCs, and hypoxia-associated OCs were modeled as interval variables testing for linearity in their predictive relationships with outcome. In the presence of a significant main effect of a predictor variable, odds ratios were computed contrasting each outcome (i.e., schizophrenia, sibling status) with the cohort members with no psychiatric diagnoses. Because the unadjusted odds ratios (i.e., excluding the covariate effects) did not differ from the adjusted odds ratios (i.e., adjusted for the covariates), only the adjusted odds ratios are reported. To determine whether any of the predictive relationships were specific to a form of the disorder with an early age at onset, the above analyses were repeated stratifying the schizophrenia cases into early and later onset groups.

Because it was possible for more than one subject from the same family to be within an outcome group, and because the information on obstetric risk factors in such cases is not independent, we also repeated the primary analyses after averaging the obstetric measures (and covariates) within each family separately for each diagnostic group, thus preserving the assumption of independence of observations. There were 72 unique observations in the proband group, 39 unique observations in the sibling group, and 6,086 unique observations in the control group for these analyses. A conditional logistic regression analysis (Proc phreg; Stokes et al. 1995) was also conducted to test the association between hypoxia and risk for schizophrenia within the families containing a schizophrenia proband. This analysis examines whether hypoxia-associated OCs discriminate schizophrenia cases from the unaffected siblings in their own families, treating family of origin as a stratification variable (thereby controlling for dependency of multiple observations per family unit).

Finally, we evaluated whether the hypothesized relationship between hypoxia-associated OCs and schizophrenia was moderated by gender, prenatal OCs, or birth weight by including the interactions of these three factors with the hypoxia-associated OCs scale in logistic analyses predicting schizophrenia.

Results

Schizophrenia Overall. Table 2 gives the results of the logistic regression analysis predicting outcomes of schizophrenia overall (i.e., regardless of age at first treatment con-

tact). Mother's age, sex, birth order, SES, and hypoxia-associated OCs each contributed significantly to the prediction of adult diagnostic outcome, but there were not significant effects of season of birth, birth weight, or prenatal OCs. The overall effect of race was inestimable because of the absence of racial variation in the sibling group. One of the items in the prenatal OC scale—maternal infection during pregnancy—merits special attention, as this factor has been found to predict schizophrenia in other studies. However, when maternal infection during pregnancy was included in the analysis as a separate variable, it was not significantly related to adult psychiatric outcome ($\chi^2 = 0.8$, $df = 2$, $p = 0.68$) and controlling for it did not alter the significance of the hypoxia effect ($\chi^2 = 6.9$, $df = 2$, $p = 0.03$).

The odds of schizophrenia increased significantly as a function of male gender (odds ratio [OR] = 1.55, 95% confidence interval [CI] = 1.17–2.04), African-American ethnicity (OR = 2.05, 95% CI = 1.01–4.16), and history of fetal hypoxia (OR = 1.41, 95% CI = 1.10–1.80) but were not significantly related to any of the remaining terms in the model (i.e., mother's age, birth order, SES, season of birth, birth weight, prenatal OCs). For each unit increase in hypoxia-associated OCs, risk for schizophrenia increased by 1.41 times, such that individuals with three or more hypoxia-associated complications were 3.84 times more likely to develop schizophrenia than individuals with no hypoxia-associated complications. Odds of being an unaffected sibling of a schizophrenia subject were significantly negatively related to mother's age (OR = 0.88, 95% CI = 0.82–0.95) and SES (OR = 0.82, 95% CI = 0.70–0.96) and significantly positively related to birth order (OR = 1.4, 95% CI = 1.2–1.5), but were not significantly related to history of hypoxia-associated OCs (OR = 0.98, 95% CI = 0.74–1.28) or any of the other terms in the model.

Figure 1A illustrates the linear increase in risk for schizophrenia with increasing number of hypoxia-associated OCs, and figure 1B the lack of relationship with unaffected sibling status.

Schizophrenia With Early Age at Onset/First Treatment. When the schizophrenia cases were divided into those with early versus later ages at onset, the overall pattern of results was the same as in the previous analysis, except that the relationship between hypoxia-associated OCs and schizophrenia was found to be confined to the form with an early age at onset (OR = 1.94, 95% CI = 1.35–2.77). For each unit increase in hypoxia-associated OCs, risk for schizophrenia with an early age at onset increased by 1.94 times, such that individuals with three or more such complications were 7.30 times more likely to develop early-onset schizophrenia than individuals with no such complications. In contrast, there was not a significant relationship between hypoxia-associ-

Table 2. Logistic regression results for demographic and obstetric predictors of adult diagnostic outcome[1]

Source	*df*	χ^2	*p*
Intercept	2	133.3	0.0000
Mother's age	2	11.9	0.0025
Sex	2	9.6	0.0081
Race[2]	1[3]	...	...
Season of birth	2	0.0	0.9841
Birth order	2	20.3	0.0000
SES	2	8.9	0.0114
Birth weight	2	0.8	0.6611
Prenatal OCs	2	0.1	0.9700
Hypoxia-associated OCs	2	7.3	0.0263

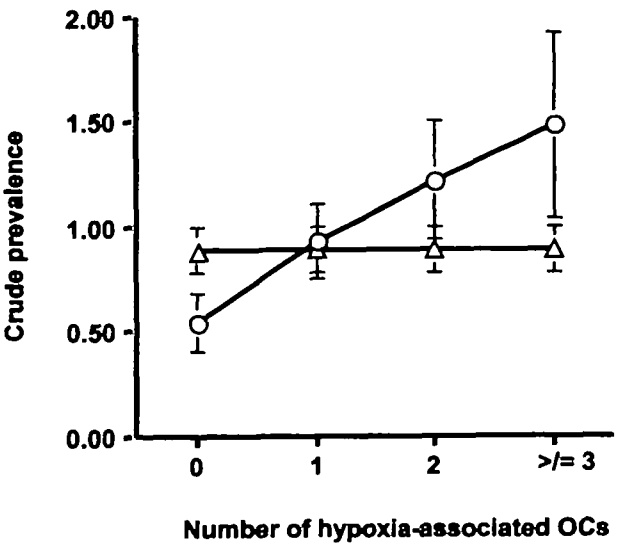
Note.—OCs = obstetrical complications; SES = Socioeconomic status.

[1] The likelihood ratio test for the final model showed an excellent fit ($\chi^2 = 1206.02$, $df = 11709$, $p = 1.0$).

[2] The overall effect of race is inestimable because of the absence of racial variation in the sibling group.

[3] The effect is not estimable.

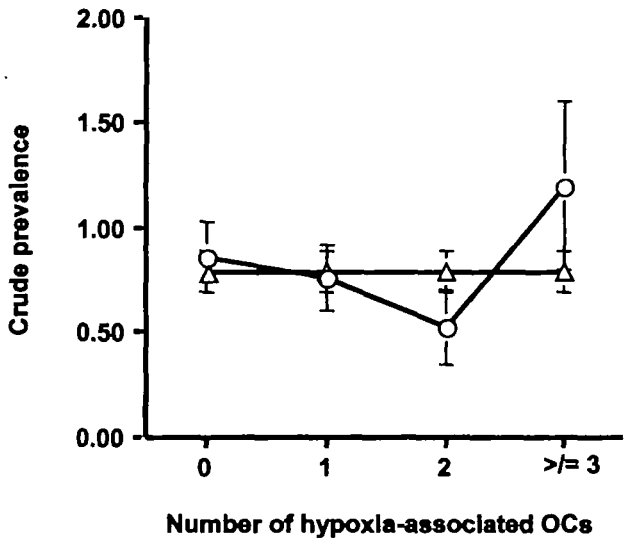
Figure 1A. Crude prevalence (± standard errors) of schizophrenia by number of hypoxia-associated obstetric complications[1]



Note.—OCs = obstetric complications.

[1] The line indicated by circles gives the observed prevalence of the outcome at each degree of hypoxia exposure, and the line indicated by triangles gives the prevalence expected under the null hypothesis of no association between the risk variable and the outcome. Prevalence estimates are "crude" in this context because we can not assure that ascertainment of probands and siblings is complete. The odds of schizophrenia increase by 1.41 times ($p = 0.001$) per unit increase in the hypoxia severity scale. There was not a significant relationship between hypoxia and unaffected sibling status.

Figure 1B. Crude prevalence (± standard errors) of being an unaffected sibling of a person with schizophrenia by number of hypoxia-associated obstetric complications[1]



Note.—OCs = obstetric complications.

[1] See footnote for figure 1A.

ated OCs and schizophrenia with a later age at onset (OR = 1.02, 95% CI = 0.71–1.47).

A limitation of the age at onset variable was that it could reflect either the age at first symptoms or the age at first treatment (if age at first symptoms was not specified in the medical records). Unfortunately, these two alternatives were not coded separately. We did, however, have information from the longitudinal treatment data base reflecting the age at entry into the treatment system in Philadelphia from 1985 onward. A limitation of this definition is that it overestimates the age at first treatment contact for cases with initial treatment before 1985. Nevertheless, the direction of this bias should act to reduce the likelihood of detecting an association between OCs and schizophrenia with an early age at first treatment if such a relationship exists (i.e., because some of the "true" early-treatment cases are incorrectly classified as later-treatment cases). When the schizophrenia cases were stratified into those with early and later ages at initial treatment based on a median split (median = 27.1 years), hypoxia-associated OCs were significantly predictive of schizophrenia with an early age at first treatment (OR = 1.58, 95% CI = 1.12–2.25) but were not significantly related to schizophrenia with a later age at first treatment (OR = 1.17, 95% CI = 0.81–1.70).

Unique Observations and Within-Family Analyses. In the logistic analyses of the obstetric and demographic predictors averaged within families (i.e., whereby each observation in each diagnostic group is unique with respect to family of origin), the overall pattern of results was identical to that reported above. In particular, there continued to be a significant effect of hypoxia-associated OCs on risk for schizophrenia ($\chi^2 = 5.2$, $df = 1$, $p = 0.02$, OR = 1.36, 95% CI = 1.04–1.76) that was specific to the form with an early age at onset ($\chi^2 = 11.8$, $df = 1$, $p = 0.0006$, OR = 1.94, 95% CI = 1.33–2.82).

Further, when the odds of schizophrenia were modeled conditionally within the families containing a schizophrenia proband—after controlling for birth order, sex, mother's age, season of birth, birth weight, and prenatal OCs—the effect of hypoxia-associated OCs was significant ($\chi^2 = 3.8$, $df = 1$, $p = 0.05$), with the odds of schizophrenia increasing by 1.7 times (95% CI = 1.03–3.04) per unit increase in the hypoxia-associated OC scale.

Moderator Variables. In the logistic regression analyses of gender, prenatal OCs, and birth weight as potential moderators of the relationship between hypoxia-associated OCs and schizophrenia, hypoxia-associated OCs did not interact significantly with gender ($\chi^2 = 0.1$, $df = 1$, $p = 0.79$) or prenatal OCs ($\chi^2 = 0.7$, $df = 1$, $p = 0.39$) in the prediction of schizophrenia. It was not possible to conduct a statistical test of the interaction of low birth weight and hypoxia-associated OCs, but the rarity of low birth weight in the schizophrenia group (only one schizophrenia subject had a birth weight below 2000g) indicates that hypoxia-associated OCs were not confined to cases who were excessively light at birth.

Individual Hypoxia-Associated OCs. Table 3 shows the rates of each OC included in the hypoxia-associated OC scale by adult psychiatric outcome. The OCs that were significantly more prevalent at the univariate level in the histories of patients with early-onset schizophrenia compared with controls were third trimester bleeding (OR = 2.6, 95% CI = 1.3–5.3), umbilical cord knotted or wrapped tightly around neck (OR = 2.0, 95% CI = 1.0–4.1), meconium in the amniotic fluid (OR = 2.7, 95% CI = 1.4–5.4), and blue at birth (OR = 2.5, 95% CI = 1.3–5.0). Trends in this direction ($p < 0.15$) were also observed for neonatal cyanosis (OR = 3.9, 95% CI = 0.5–28.7) and required resuscitation (OR = 4.2, 95% CI = 0.6–31.2), for which extremely low base rates limit statistical confidence in the risk estimates.

Discussion

Nature of the Association between OCs and Schizophrenia. Long-term followup of large birth cohorts on which detailed obstetric information is recorded

Table 3. Frequencies (and percentages) of hypoxia-associated obstetric complications by adult psychiatric outcome

Obstetric variable	No diagnosis	Schizophrenia		Siblings without schizophrenia
		Early onset	Later onset	
Abnormal heart rate/rhythm, *n* (%)	732 (10.6)	6 (17.6)	3 (8.3)	2 (3.2)
Blue at birth, *n* (%)	1,360 (19.9)	13 (38.2)	7 (20.0)	19 (30.7)
Required resuscitation, *n* (%)	50 (0.8)	1 (3.0)	1 (2.9)	0 (0)
Neonatal apnea, *n* (%)	111 (1.6)	0 (0)	1 (2.8)	1 (1.6)
Cyanosis, *n* (%)	53 (0.8)	1 (2.9)	0 (0)	1 (1.6)
Cord knotted/wrapped around neck, *n* (%)	1,748 (25.6)	14 (41.2)	9 (25.7)	17 (27.0)
Third trimester bleeding, *n* (%)	1,182 (17.4)	12 (35.3)	5 (14.7)	8 (12.7)
Placental hemorrhaging/infarcts, *n* (%)	354 (5.1)	0 (0)	1 (2.8)	1 (1.6)
Polyhydramnios, *n* (%)	58 (0.9)	0 (0)	2 (5.9)	1 (1.6)
Meconium in amniotic fluid, *n* (%)	1,581 (23.6)	15 (45.5)	10 (28.6)	15 (24.6)
Breech presentation, *n* (%)	136 (1.7)	0 (0)	1 (2.6)	1 (1.6)
Hypoxia scale (sum of above items)				
0	2,777 (35.0)	5 (14.7)	10 (26.3)	24 (38.1)
1	2,885 (36.3)	9 (26.5)	18 (47.4)	22 (34.9)
2	1,544 (19.5)	11 (32.4)	8 (21.1)	8 (12.7)
3 or more	734 (9.2)	9 (26.5)	2 (5.3)	9 (14.3)

prospectively for research purposes offers the potential to resolve the mechanism(s) underlying the association between OCs and schizophrenia. The findings of this study replicate those of other, smaller scale studies (Lane and Albee 1966; Pollack et al. 1966; Pollin and Stabenau 1968; Woerner et al. 1971, 1973; Jacobsen and Kinney 1980; Parnas et al. 1982; Markow and Gottesman 1989; Eagles et al. 1990; Bracha et al. 1992; Fish et al. 1992; O'Callaghan et al. 1992; Buka et al. 1993; Gunther-Genta et al. 1994; Kinney et al. 1994; McNeil et al. 1994; Torrey et al. 1994) in showing that complications representing direct and indirect indicators of fetal hypoxia are associated with an increased risk for schizophrenia. The present results also extend previous findings by demonstrating that odds of schizophrenia increase linearly with an increasing number of such complications. Because the various complications in the hypoxia-associated OC scale aggregated in the prediction of schizophrenia, it appears likely that they are linked with schizophrenia via a common underlying mechanism.

Clinical epidemiologic methods can in most cases suggest causal relationships, without fully proving them, since it is always possible that the association of a given risk factor might be explained by other factors that are related to both disease outcome and the likelihood of the risk exposure. The task is thus to examine all plausible third variables that could account for the exposure-outcome relationship. Consistent with the results of all prior controlled prospective studies of individuals at genetic risk for schizophrenia (Mirdal et al. 1974; Hanson et al. 1976; Rieder et al. 1977; Marcus et al. 1981; Cannon et al. 1993; Gunther-Genta et al. 1994), we found no evidence of covariation between genetic predisposition and hypoxia-associated OCs, as siblings of schizophrenia subjects were no more likely to experience these complications than nonpsychiatric controls from the general cohort. We also could detect no tendency for any of the demographic factors examined (sex, year of birth, season of birth, birth order, parental education, mother's age) to explain or qualify the hypoxia-schizophrenia association. It could be argued that complications before birth (whether they are caused by genetic predisposition to schizophrenia or are independent of it) may have increased the likelihood of hypoxia-associated OCs. However, when we modeled these influences directly (either in the form of an overall prenatal OCs scale or in the form of fetal underdevelopment and maternal infection during pregnancy as unique variables), they were not significantly associated with schizophrenia in this sample, and nonhypoxia-associated OCs did not interact with or modify the significance of the hypoxia-associated OC effect. Further, because the association between OCs and schizophrenia has been observed in adoptees not reared in the same home with their affected relatives (Jacobsen and Kinney 1980), we can rule out that the association is due to covariation between factors predisposing to OCs and subsequent disturbances in the rearing environment.

It would thus appear that hypoxia-associated OCs are in some manner related to the etiology of schizophrenia. Contrary to the predictions of the familial-sporadic model (Lewis and Murray 1987), it is highly unlikely that these factors are sufficient to cause schizophrenia on their own, as the vast majority of individuals exposed to fetal hypoxia—even at the most extreme end of the risk/severity scale—did not become schizophrenia patients. Most of the studies using the family history method have detected no differences in rates of OCs between schizophrenia subjects with and without an affected relative (Mirdal et al. 1974; Hanson et al. 1976; Rieder et al. 1977; Marcus et al. 1981; DeLisi et al. 1987; Nimgaonkar et al. 1988; Foerster et al. 1991; McCreadie et al. 1992; O'Callaghan et al. 1992; Heun and Maier 1993; Roy et al. 1994), but a few studies have found a higher rate of OCs in the patients without a family history of schizophrenia (Reveley et al. 1984; Lewis and Murray 1987), findings widely cited as supporting the familial-sporadic model. Even if we assume that assessments of perinatal history by patient or maternal report are valid, the interpretability of these studies is severely weakened by the inadequate power of the family history design in modeling genetic influences in schizophrenia (i.e., both groups of patients are at elevated risk for carrying a predisposing genotype) and by the fact that the same informants were used to assess family and birth history.

Since most individuals exposed to hypoxia-associated OCs do not develop schizophrenia, other predispositional factors must be required. As the genetic contribution to liability to schizophrenia is on the order of 80 to 85 percent (Cannon et al. 1998*a*), genetic influences represent the single most important determinant of predisposition to this illness. Consistent with the results of all previous prospective studies comparing rates of OCs in schizophrenia subjects and their unaffected siblings or cotwins (Lane and Albee 1966; Pollack et al. 1966; Pollin and Stabenau 1968; Woerner et al. 1971, 1973; Markow and Gottesman 1989; Eagles et al. 1990; Bracha et al. 1992; Gunther-Genta et al. 1994; Kinney et al. 1994; Torrey et al. 1994), in this study, the odds of schizophrenia increased with the number of hypoxia-associated OCs *within families*. Thus, given a genetic background for schizophrenia, individuals exposed to hypoxia have an increased risk for schizophrenia, and individuals without this exposure are much more likely to be unaffected. Taken together, these results support a model in which fetal hypoxia and predisposing genes for schizophrenia act either additively or interactively in increasing risk for phenotypic expression. The present findings do not clarify whether the additive or interactive model is preferable because both models pre-

dict a higher risk for phenotypic expression in the presence of both obstetric and genetic risk factors. However, in other studies we have demonstrated that obstetric and genetic risk factors for schizophrenia interact in the prediction of quantitative indicators of disease liability. In our prospective high-risk study in Denmark, the degree of ventricular enlargement observed in the subjects as adults was predicted by the interaction of degree of genetic risk with OCs (Cannon et al. 1993). Among those without a history of OCs, there was a tendency for ventricular volume to increase linearly with the number of parents affected (neither, one, or both), but this pattern was significantly more pronounced among those with a history of OCs. Notably, there was not an increase in ventricular volume among the low-risk controls as a function of OCs, implying that some degree of genetic risk was required to observe the association. We have recently replicated and extended these findings in a Finnish sample using magnetic resonance imaging (Cannon et al., in review). Taken together, these findings suggest that factors associated with genetic liability to schizophrenia may confer a heightened susceptibility to the neurotoxic effects of hypoxia-associated OCs.

It may thus be possible to prevent schizophrenia in some genetically predisposed offspring through careful prenatal and perinatal monitoring and early intervention. These findings also encourage the search for candidate genes that mediate the brain's vulnerability to hypoxic-ischemic neuronal injury. The list of such candidates is relatively long, but genes participating in N-methyl-D-aspartate (NMDA) receptor formation or membrane dynamics of glutamatergic neurons might be prominent suspects, since overstimulation of glutamatergic NMDA receptors represents an early event in the sequence leading from hypoxia to neuronal death (Choi and Rothman 1990).

Finally, it is important to emphasize that while the pattern of correlations between obstetric risk factors and schizophrenia observed in this study is consistent with the notion that fetal hypoxia represents a unifying neurally disruptive mechanism underlying the association between OCs and schizophrenia, these findings are nevertheless based on clinical indicators rather than molecular markers of fetal blood oxygenation. Further, even if fetal hypoxia is confirmed in the schizophrenia cases in this study, other consequences of fetal distress, such as the induction of proinflammatory cytokines, could be driving some or all of the association. We are currently conducting a screen of maternal and cord blood samples from this cohort to examine these issues further.

Specificity of Effects to Schizophrenia With Early Age at Onset/First Treatment. Our findings are consistent with converging epidemiologic evidence that OCs, hypoxia in particular, confer an increased risk for neurodevelopmental compromise and a form of adult schizophrenia with an early age at onset (Verdoux et al. 1997). There have also been reports of increased rates of OCs in childhood-onset schizophrenia, although most come from a time period when diagnostic comparability with the adult disorder was unclear (Rutt and Offord 1971; Torrey et al. 1975). In the present study, we found a robust association between OC indicators of fetal hypoxia and schizophrenia with an early age at onset/initial treatment contact for both male and female patients, which strengthens the hypothesis that such OCs relate specifically to a neurodevelopmental form of the disorder. Together these lines of evidence for specificity of OCs to early-onset schizophrenia suggest that previous studies that did not separate patients by age at onset may need to be reanalyzed.

While we can only speculate as to the mechanism(s) involved in the timing of schizophrenia onset, a prominent candidate may be the rate of synaptic pruning. Some investigators have proposed that schizophrenia arises because of excessive pruning, such that a reduction of neuronal synapses below a certain threshold produces psychotic symptomatology (Feinberg 1982; Keshavan et al. 1994). Within this framework, variations in the rate of synaptic pruning would vary the age of clinical onset of schizophrenia. Interestingly, an excess of synaptic pruning is consistent with several brain abnormalities documented in schizophrenia, including prominent reductions in neuropil volume (Selemon et al. 1995, 1998) and synaptic protein levels (Glantz and Lewis 1997). Furthermore, since synaptic pruning involves predominantly glutamatergic basal and apical dendrites (Keshavan et al. 1994), exaggerated pruning could result in glutamate receptor hypofunction, which has been posited as a cause of striatal dopaminergic hyperactivity and psychotic symptoms in schizophrenia (Grace 1991; Olney and Farber 1995).

We have recently proposed that the neurotoxic effects of hypoxia-associated OCs may reduce the amount of subsequent postnatal synaptic pruning required to cross the psychosis threshold, leading to an earlier age at onset of schizophrenia (Rosso et al., in press). In support of this hypothesis, the temporal and subcortical brain regions that are most vulnerable to fetal hypoxia (Volpe 1995; Rees et al. 1998) have also been consistently implicated in schizophrenia (Cannon 1996; Nelson et al. 1998). Thus, hippocampal neurons exposed to hypoxia during fetal life have fewer dendrites and are reduced in number and/or density (Kuchna 1994; Yue et al. 1997). These cellular findings are consistent with reports of dendritic spine reduction (Garey et al. 1995; Glantz and Lewis 1995), hippocampal cell loss (Falkai and Bogerts 1986; Jeste and Lohr 1989; Jonsson et al. 1997), and reduced temporal

gray matter volumes in schizophrenia (Suddath et al. 1989; Cannon et al. 1998*b*). Notably, recent in vivo findings from our laboratory indicate that fetal hypoxia is associated with subcortical damage and temporal gray matter deficits among both schizophrenia patients and their unaffected siblings but not among controls at low genetic risk for schizophrenia, which suggests that the schizophrenia genotype heightens susceptibility to hypoxic insult (Cannon et al., in review). High-risk individuals with a history of fetal hypoxia may therefore have a lower baseline number of neurons and synapses in temporal brain regions than those without such a history. A reduced neuronal and dendritic reserve would require less subsequent postnatal synaptic elimination to cross the psychosis threshold, resulting in an earlier age of clinical onset in individuals with the schizophrenia genotype. Furthermore, neuronal loss in temporal-limbic structures would decrease striatal glutamatergic input and modulation (Csernansky and Bardgett 1998). Subsequent pruning of temporal-striatal projection neurons during the postnatal period would then be expected to produce exaggerated mesolimbic dopamine activity and psychotic symptoms *at an earlier age* in preschizophrenia subjects positive for indicators of fetal hypoxia.

Limitations. The procedures used to ascertain and diagnose cases in this study were not ideal. We address the major threats to validity and ability to generalize posed by these methods below.

Are there biases related to the assignment of diagnoses by chart review? We used a two-stage diagnostic procedure whereby we first screened the cohort for any psychotic disorder diagnosis via treatment sources and subsequently performed detailed evaluations of the psychiatric medical records for nearly half of the psychotic-disordered probands for the determination of diagnoses according to *DSM–IV* criteria. Only those cases with chart-review-based *DSM–IV* diagnoses of schizophrenia or schizoaffective disorder were classified as "cases" in the analyses; the remaining psychotic-disordered probands were excluded. The chart-review diagnoses are reliable; independent evaluations of a random sample of medical records by different reviewers produced a high rate of diagnostic agreement ($\kappa = 0.85$, 93% simple agreement). Diagnostic reliability is a necessary but not sufficient condition for diagnostic validity. Optimally, the chart-review diagnoses should be validated against those obtained using direct structured psychiatric interviews, but we have not yet interviewed a sufficient number of cases from this cohort to make this determination. It is important to note that invalid assignment of schizophrenia or schizoaffective diagnoses by chart review would produce a false positive result only if the association between OCs and schizophrenia was restricted to cases whose actual diagnoses were not schizophrenia or schizoaffective disorder. The diagnoses most likely to compete with those assigned are psychotic forms of bipolar or unipolar affective illness. In secondary analyses conducted to address this question—compared with the nonpsychiatric controls—there was no increase in exposure to hypoxia-associated OCs among the 41 psychotic-disordered cases who were screened out of the proband sample because they received *DSM–IV* diagnoses of bipolar or unipolar affective disorder by chart review ($\chi^2 = 0.2$, $df = 1$, $p = 0.68$). Thus, if there are misdiagnosed cases of affective psychosis in the *DSM–IV* schizophrenia/schizoaffective group, the effect on the results should be an under- rather than overestimation of the strength of the association between OCs and schizophrenia.

Are there biases related to incomplete ascertainment of schizophrenia cases? Direct followup of all surviving cohort members in adulthood would provide the most complete ascertainment of outcome, but such an approach is possible only in a country that maintains a central register indexing current residence of all members of its population. A reasonable alternative, and the approach taken in this study, is to screen the birth cohort for a history of local psychiatric service utilization. This approach missed cases who were deceased at the time of followup, who did not come to treatment (or who will come to treatment in the future), or who because of emigration or changes in social class used psychiatric facilities other than those whose patient rolls were screened. We also lost cases who were identified as having a history of treatment for a psychotic disorder but who had been treated at facilities that were no longer operating, did not cooperate with the chart reviews, or had treated only one proband. Incomplete ascertainment of schizophrenia in the cohort could produce biasing effects on the results in two major ways. First, if the identified cases of schizophrenia do not resemble the unidentified cases in terms of demographic factors and obstetric history, selection effects could limit the ability to generalize about the findings. Second, a false positive finding could result if a substantial number of unidentified cases of schizophrenia were included in the sample classified as nonpsychiatric controls *and* if the OC histories of such cases were markedly different from those of the ascertained cases.

In secondary analyses conducted to address the first issue, the 72 cases with chart-review-based *DSM–IV* diagnoses of schizophrenia or schizoaffective disorder were found not to differ significantly from the remaining 121 probands with register diagnoses of schizophrenia or schizoaffective disorder (whose charts were not reviewed) in terms of gender (65% vs. 59% male, respectively; $\chi^2 = 0.9$, $df = 1$, $p = 0.33$), race (3% vs. 6% Caucasian; $\chi^2 =$

0.9, $df = 1$, $p = 0.34$), season of birth (24% vs. 27% winter-born; $\chi^2 = 0.3$, $df = 1$, $p = 0.57$), year of birth (1962 ± 2.2 vs. 1962 ± 1.9; $t = -0.2$, $df = 191$, $p = 0.81$), birth order (3.6 ± 2.7 vs. 3.1 ± 1.9; $t = 1.4$, $df = 191$, $p = 0.16$), mother's age at birth (24.2 ± 6.6 vs. 23.8 ± 6.3; $t = 0.4$, $df = 191$, $p = 0.67$), years of parental education (10.4 ± 2.4 vs. 10.7 ± 2.5; $t = -0.6$, $df = 191$, $p = 0.49$), or number of siblings not diagnosed with schizophrenia enrolled in the NCPP study (0.9 ± 1.1 vs. 0.8 ± 1.0; $t = 1.0$, $df = 191$, $p = 0.34$). The groups also did not differ significantly from each other on the hypoxia-associated OCs scale ($\chi^2 = 2.2$, $df = 3$, $p = 0.54$), on the prenatal OCs scale ($\chi^2 = 0.1$, $df = 2$, $p = 0.94$), or on any of the individual complications included in either scale. Finally, when the primary analysis was repeated using the 194 cases with register diagnoses of schizophrenia or schizoaffective disorder and their siblings, the effect of hypoxia-associated OCs on increasing risk for schizophrenia remained significant (OR = 1.3, 95% CI = 1.1–1.5), and the trend for a negative association between hypoxia-associated OCs and sibling status became significant (OR = 0.8, 95% CI = 0.7–0.9). There thus appears to be no significant biasing effect related to which of the available probands were ascertained for chart review.

In regard to the second issue, it is virtually certain that some cases of schizophrenia were classified as nonpsychiatric controls in the analyses (i.e., female patients whose last names changed at marriage, patients who moved out of Philadelphia before 1985, patients who did not seek treatment, patients who were treated exclusively by private practitioners). The extent of this misclassification cannot be quantified precisely. The prevalence of a treatment-ascertained psychotic disorder diagnosis in this cohort is quite high (i.e., 3.7%) even without taking into account the possibility of unascertained cases. Nevertheless, while we cannot entirely rule out the possibility of an ascertainment bias, there is no reason to suspect that the OC histories of the unascertained schizophrenia subjects in the control group are different from those of the ascertained cases. Given the higher rate of schizophrenia among males in this cohort, an underascertainment of female schizophrenia subjects represents the most plausible candidate for such a biasing effect (but see Hambrecht et al. 1993). However, while males were more likely to have suffered hypoxia-associated OCs than females in the overall cohort (OR = 1.04 per unit increase in hypoxia-associated OCs, $p = 0.08$), the hypoxia effect on risk for schizophrenia was *not* differential according to gender. In view of this result, and considering the fact that the genetic and environmental contributions to liability to schizophrenia are equivalent in males and females (Cannon et al. 1998*a*), the present findings suggest that the gender difference in prevalence of schizophrenia (if not an artifact of our ascertainment methods [Hambrecht et al. 1993]) could be due to a higher frequency of gene-dependent environmental risk exposures in males.

It could be argued that cohort members with a history of OCs were more likely to stay in the vicinity where they were born, in which case our ascertainment methods would have oversampled the schizophrenia cases with a history of OCs. To address this possibility, we compared the schizophrenia cases to the sample of individuals who were identified as having nonpsychotic forms of mental illness in the Philadelphia area treatment data base (whether such cases should have been excluded from the primary analyses as controls is in any case controversial). Any tendency for the subjects with a history of OCs to remain in the locations of their births (and/or for subjects without such a history to have moved out of the area) should have affected our ascertainment of these nonpsychotic cases as well. If a bias toward ascertainment of subjects with positive OC histories exists, the schizophrenia cases should not differ from the nonpsychotic cases ascertained in the register. However, the schizophrenia subjects did in fact have more complications than the nonpsychotic register cases ($\chi^2 = 5.8$, $df = 1$, $p = 0.02$). Moreover, when the primary analyses were repeated including the nonpsychotic register cases with the nonpsychiatric cohort members as controls, the relationship between hypoxia-associated OCs and schizophrenia remained significant ($\chi^2 = 7.1$, $df = 1$, $p = 0.007$).

Are there biases related to higher than typical rates of hypoxia-associated OCs and schizophrenia? Certain of the OCs included in our hypoxia scale occurred at base rates far in excess of that typical for a U.S. cohort. For example, "blue at birth" (defined as a rating of 0 for color in the 1- or 5-minute Apgar score) has a particularly high base rate in this cohort. In fact the base rates for this item varied markedly among the different NCPP study sites (Niswader and Gordon 1972). While we cannot rule out that the high base rate for this item might reflect at least in part measurement error, it is important to emphasize that such error would be expected to be random with respect to adult diagnostic outcome and would thus be unlikely to threaten the validity of the observed association between this variable and schizophrenia. Furthermore, the effects of measurement error are generally to reduce power to detect a true association. This tendency can be overcome at least in part by aggregating multiple indicators (each of which is itself fallible to some degree) into a scale, as was done in this study for hypoxia-associated OCs.

The high prevalence of a treatment-ascertained diagnosis of schizophrenia in this cohort (i.e., 2.1%, even before taking into account the possibility of unascertained cases) raises the question of whether the cohort is unusual with

respect to the distribution of risk factors for schizophrenia. It remains controversial whether rates of schizophrenia vary by factors such as urban residence, social class, and minority status—factors whose variability is greatly limited in this cohort compared with the general population. Unfortunately, the limited racial diversity did not permit us to examine race as a modifier of the hypoxia-associated OC effect. A race-specific effect seems unlikely, however, since hypoxia-related OCs have been found to be associated with schizophrenia in several Scandinavian countries whose populations are nearly entirely Caucasian (Pollack et al. 1966; Woerner et al. 1971, 1973; Jacobsen and Kinney 1980; Parnas et al. 1982; McNeil et al. 1994). Of course, it is also possible that the higher than usual rate of schizophrenia reflects the higher than usual base rate of OCs observed in this cohort (which in turn may reflect its sociodemographic profile). For a further discussion of variations in schizophrenia across place, time, and study design, see Bresnahan et al. (this issue).

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