Obstetric Complications and Age at Onset in Schizophrenia: An International Collaborative Meta-Analysis of Individual Patient Data

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Objective: *An excess of obstetric complications in the histories of schizophrenic patients is a well-replicated finding, but less consistent results have been found concerning the relationships between obstetric complications and family history of schizophrenia, age at onset of schizophrenia, and gender. Small sample size limited the power of previous studies that attempted to assess such relationships. The aim of this study was to use data on individual patients from all available studies to examine the links between a history of obstetric complications and family history of schizophrenia, age at onset, and gender.* *Method:* *Raw data from 854 schizophrenic patients concerning history of obstetric complications rated according to the Lewis and Murray scale were obtained from 11 different research groups. Weighted average estimates were calculated with the use of regression techniques.* *Results:* *A significant association was found between age at onset of schizophrenia and obstetric complications: the earlier the age at onset, the more likely the history of obstetric complications. Subjects with onset of schizophrenia before age 22 were 2.7 times more likely than those with onset at a later age to have had a history of abnormal presentation at birth and 10 times more likely to have had a history of complicated Cesarean birth. No association was found between obstetric complications and family history of schizophrenia or gender.* *Conclusions:* *The association between obstetric complications and early age at onset of schizophrenia indicates that the pathophysiology of early-onset schizophrenia involves neurodevelopmental impairment.*

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Converging epidemiologic evidence implicates early environmental hazards in the etiology of schizophrenia (1). A well-replicated finding is the excess of obstetric complications in the histories of schizophrenic patients compared to normal control subjects, nonschizophrenic psychiatric control subjects, or siblings (2, 3). A meta-analysis of published case-control and cohort studies recently confirmed this association and showed that a history of obstetric complications is twice as frequent among schizophrenic subjects as among control subjects (4).

However, the pathophysiological link between a history of obstetric complications and the subsequent emergence of schizophrenia is obscure. To clarify the relation between obstetric complications and schizophrenia, several studies have assessed whether schizophrenic patients with a history of obstetric complications have distinctive characteristics compared to those

without such a history. An early research strategy used by these studies was based on the dichotomy of familial and sporadic schizophrenia (5, 6). The hypothesis that persons with sporadic schizophrenia are more likely to have experienced adverse early environmental hazards such as obstetric complications has been tested by a number of studies, with conflicting results (3, 7). In the framework of the neurodevelopmental model of schizophrenia, a complementary hypothesis further predicted that a history of obstetric complications should be more frequent among male patients with an early age at onset, prominent negative features, and poor outcome (8, 9). Inconsistent results have been obtained by studies exploring the associations between these variables and a history of obstetric complications among persons with schizophrenia, except for the association with early age at onset, which has been found by most, but not all, studies (10).

Small sample size limited the power of most previous studies and may explain some of the inconsistent findings, as negative results might be due to type II errors. Meta-analysis is one way of synthesizing results from several small studies, but the assessment of such relationships through a meta-analysis of the literature is difficult because of incomplete reporting in the primary studies (4). Meta-analysis of the raw data on individual patients from different studies (11, 12) can be used to overcome these limitations. Therefore, the aim of the present study was to examine, in a large sample pooling raw data from studies on obstetric complications and schizophrenia carried out by different research groups, the relationships between a history of obstetric complications and 1) family history of schizophrenia or psychotic disorder, 2) age at onset, and 3) gender.

TABLE 1. Design Characteristics of 11 Studies Included in a Pooled Sample of Patients With Schizophrenia

Study Design Characteristic	Number of Subjects	Number of Informative Studies	Subjects	
			N	%
Method used to collect obstetric history[a]	854			
Obstetric record		4	272	31.9
Maternal recall		7	558	65.3
Other family members' recall		2	21	2.5
Case notes		1	3	0.4
Diagnostic criteria	854			
DSM-III/DSM-III-R		5	364	42.6
RDC		4	311	36.4
ICD-8/ICD-9		2	179	21.0
Family history method	682			
Standardized[b]		3	415	60.9
Unstandardized[c]		5	267	39.1
Definition of age at onset of schizophrenia	526			
Appearance of first symptoms		5	381	72.4
First medical treatment		1	30	5.7
First hospitalization		2	115	21.9

[a]The total number of studies is greater than 11 because in two studies, other family members' recall or case notes were used when the mother could not be interviewed.
[b]Personal interview of at least one family member with a structured interview.
[c]Information mainly obtained from the proband or from case notes.

METHOD

Published case-control studies on obstetric complications and schizophrenia were previously identified by a MEDLINE search, a survey of references of papers and previous reviews, and personal communications with researchers (4). Researchers involved in this field were then personally invited to collaborate in a study on the association between schizophrenia and individual obstetric complications. The researchers from nine different groups that had used the scale of Lewis and Murray (13) agreed to contribute to this study and sent their raw published and unpublished data on obstetric complications in the histories of schizophrenic patients and control subjects. It was not possible to obtain the raw data from a study conducted in Nigeria (14). Most studies had already been published (15–23). Data that were unpublished at the beginning of this study have meanwhile been published or presented at conferences (24–27). For the two remaining studies (28, 29), the raw data on obstetric complications could be scored by the researchers according to the scale of Lewis and Murray. Written informed consent was obtained from all subjects and their relatives who agreed to participate in the studies mentioned above after the procedures had been fully explained.

For this study, only data on schizophrenic patients were analyzed. The results of the individual patient meta-analysis of case-control studies are reported in another paper (30). Published and unpublished individual data were collected on the 15 specific obstetric complications rated by the scale of Lewis and Murray. Definite and equivocal obstetric complications were defined according to this scale. One level of severity is defined for seven complications (only definite for six; only equivocal for one) of the 15 specific obstetric complications listed in this scale, and two levels (definite and equivocal) are defined for the remaining eight.

Where available, data on gender, birth order, age at onset of schizophrenia, and family history of schizophrenia and/or psychotic disorder were also collected. Age at onset was categorized into a binary variable according to the median in the sample of patients (<22 years versus ≥22 years). Birth order was categorized as firstborn and not firstborn, since more precise information was not available from most studies. The design characteristics of the 11 studies included in the pooled sample of schizophrenic patients are shown in table 1. For the analyses, the obstetric history method was divided into retrospective (family members' recall or case notes) versus prospective (obstetric record). Age at onset was dichotomized by combining the two definitions "age at first medical treatment for psychotic symptoms" and "age at first hospitalization." The criteria for positive family history varied widely from one study to another. Therefore, different definitions were used in the pooled analyses: 1) family history of schizophrenia in first-degree relatives, 2) family history of psychosis in first-degree relatives, and 3) family history of psychosis in first- or second-degree relatives. In addition, "family history however defined" was used when there was a positive family history according to at least one of the three definitions just mentioned.

Logistic regression analyses were performed to examine the relationships between the response variable (obstetric complications) and the three explanatory variables (family history, age at onset, and gender). Pooled weighted estimates of the odds ratios were calculated with the use of regression techniques (31). For this purpose an 11-level variable, "STUDY," was encoded to stratify the study sample by different research groups. (Data on distinct samples of patients from independent studies recently carried out with the same method at the Institute of Psychiatry, London, were incorporated into one STUDY.) Regression models were fitted with the variable STUDY to obtain weighted average odds ratios (according more weight to the larger studies). Unless they differ from crude odds ratios, only weighted average odds ratios are reported for most analyses. Study design char-

TABLE 2. Characteristics of Patients With Schizophrenia Included in a Pooled Sample From 11 Studies

Characteristic	Number of Subjects	Number of Informative Studies	Value			
			Mean	*SD*	*Median*	*Range*
Age at onset of schizophrenia (years)	507	8	22.8	6.5	22	8–53
			N		%	
Gender	854	11				
Male			569		66.6	
Female			285		33.4	
Birth order	462	7				
Firstborn			180		39.0	
Not firstborn			282		61.0	
Positive family history however defined[a]	674	8	225		33.4	
Schizophrenia in first-degree relatives	419	5	65		15.5	
Psychotic disorder in first-degree relatives	224	4	52		23.2	
Psychotic disorder in first- or second-degree relatives	307	4	102		33.2	

[a]Includes schizophrenia or psychotic disorder in first-degree relatives and/or psychotic disorder in second-degree relatives.

acteristics (diagnostic criteria, obstetric history method, family history method, definition of age at onset) were also encoded. Odds ratios and 95% confidence intervals were calculated from the results of the logistic regressions. The statistical significance of the association of an explanatory variable with the response variable was assessed by the likelihood ratio statistic. These procedures were implemented with SPSS (32).

RESULTS

The characteristics of the 854 schizophrenic patients are given in table 2. A positive history of broadly defined obstetric complications (definite or equivocal according to the Lewis and Murray scale) was reported for 408 (47.8%) of the patients. The presence or absence of narrowly defined obstetric complications (definite obstetric complications according to the Lewis and Murray scale) was recorded for 716 patients, of whom 227 (31.7%) had a positive history of such complications; differentiation between definite and equivocal obstetric complications was not available for 138 patients.

Family History

No significant association was found between a history of definite obstetric complications and family history however defined (table 3). The finding of no significant associations with a history of definite obstetric complications held when the three more specific definitions of family history were used (the reference level was negative family history): for family history of schizophrenia in first-degree relatives, weighted average odds ratio=0.84 (95% confidence interval=0.46–1.56; likelihood ratio=0.30, df=1, p=0.60); for family history of psychotic disorder in first-degree relatives, weighted average odds ratio=1.10 (95% confidence interval=0.56–2.13; likelihood ratio=0.07, df=1, p=0.79); for family history of psychotic disorder in first- or second-degree relatives, weighted average odds ratio=0.99 (95% confidence interval=0.59–1.66; likelihood ratio=0.001, df=1, p=0.97).

We found no negative confounding effects (i.e., masking the association) of study design (family history method, obstetric history method, diagnostic criteria) on the association between family history and narrowly defined obstetric complications. No significant association was found when the analyses were repeated for the relationships between broadly defined obstetric complications and family history. Neither significant association nor consistent direction was found in the analyses of the relationships between family history and each of the 14 definite specific obstetric complications rated by the Lewis and Murray scale.

Age at Onset

In the crude analysis, a significant association was found between age at onset of schizophrenia (<22 years versus ≥22 years) and a history of definite obstetric complications (crude odds ratio=1.52; 95% confidence interval=1.04–2.22; likelihood ratio=4.65, df=1, p=0.03). The crude odds ratio estimate indicates a 52% increase in definite obstetric complications among schizophrenic subjects with earlier age at onset compared to those with late onset. The weighted average odds ratio indicates a 43% increase in definite obstetric complications among schizophrenic subjects with early onset, but the association falls outside a conventional significance level (weighted average odds ratio=1.43; 95% confidence interval=0.97–2.12; likelihood ratio=3.12, df=1, p=0.07). Further inclusion of the interaction between age at onset and STUDY did not significantly improve the model (likelihood ratio=12.60, df=7, p=0.08), indicating that the assumption of no heterogeneity across different studies was supported.

Since schizophrenic subjects with earlier onset were more likely to have a history of definite obstetric complications, age at onset was subsequently categorized into quartiles (<19, 19–21, 22–25, and >25 years) in order to assess the possible presence of a "dose-response" relationship, which would add evidence for a cause-effect relationship between obstetric complications and early onset. A significant linear trend was found in the association between age at onset and defi-

TABLE 3. Associations Between History of Definite Obstetric Complications and Characteristics of Patients With Schizophrenia

Variable	Subjects With Definite Obstetric Complications		Crude Odds Ratio	95% Confidence Interval	Likelihood Ratio (df=1)	p	Weighted Average Odds Ratio	95% Confidence Interval	Likelihood Ratio (df=1)	p
	N	%								
Gender (N=716)			1.03	0.74–1.44	0.03	0.86	1.00	0.71–1.40	0.00	0.98
Male (N=473)	151	31.9								
Female (N=243)[a]	76	31.3								
Age at onset (years) (N=507)										
≤18 (N=123)	44	35.8	1.33	0.96–1.85			1.22	0.86–1.73		
19–21 (N=130)	44	33.8	1.22	0.89–1.69			1.26	0.90–1.75		
22–25 (N=137)	45	32.8	1.17	0.85–1.61			1.18	0.85–1.64		
>25 (N=117)[a]	21	17.9	1.00				1.00			
Odds ratio for linear trend[b]			0.77	0.65–0.92	8.19	0.004	0.80	0.67–0.97	5.41	0.02
Family history however defined[c] (N=647)			0.92	0.65–1.43	0.24	0.63	0.96	0.67–1.36	0.06	0.80
Positive (N=225)	69	30.7								
Negative (N=449)[a]	146	32.5								

[a]Baseline.
[b]Summary odds ratio for moving from one quartile to the next.
[c]Schizophrenia or psychotic disorder in first-degree relatives and/or psychotic disorder in second-degree relatives.

nite obstetric complications (table 3), indicating that there was a 20% decrease in the likelihood of having a history of definite obstetric complications when age at onset was delayed by one quartile.

The strong linear relationship between definite obstetric complications and age at onset remained almost constant after adjustment for 1) diagnostic criteria (adjusted odds ratio for linear trend=0.78; 95% confidence interval= 0.65–0.94; likelihood ratio=7.15, df=1, p=0.007); 2) obstetric history method (adjusted odds ratio for linear trend= 0.78; 95% confidence interval=0.65–0.93; likelihood ratio=7.82, df=1, p=0.005; and 3) onset definition (adjusted odds ratio for linear trend=0.77; 95% confidence interval=0.65–0.92; likelihood ratio=8.21, df=1, p= 0.004), indicating that study design had little confounding effect (unstratified odds ratios are presented because it is not possible to calculate weighted average odds ratios in a model fitted with a variable encoding for study design).

The effect of adjustment for birth order could be assessed for only a subsample of patients (N=362). The linear relationship between definite obstetric complications and age at onset was not modified after adjustment for birth order (adjusted weighted average odds ratio for linear trend=0.81; 95% confidence interval= 0.65–1.01; likelihood ratio=3.58, df=1, p=0.06).

A significant linear trend was also found in the association between age at onset with four levels and broadly defined obstetric complications (weighted average odds ratio for linear trend=0.80; 95% confidence interval=0.67–0.97; likelihood ratio=5.47, df=1, p=0.02).

We subsequently explored the associations between age at onset, defined as a dichotomous variable (<22 years versus ≥22), and each of the 14 definite specific obstetric complications. We found significant associations of early age at onset with "Cesarean, complicated, or emergency delivery" and "breech or abnormal presentation" (table 4). Although nonsignificant, most of the other associations were in the same direction; that is, exposure to most of the specific definite obstetric complications was associated with earlier age at onset.

Gender

No significant association was found between a history of definite obstetric complications and gender (table 3). The association between obstetric complications history and gender remained nonsignificant after adjustment for obstetric history method and for diagnostic criteria. The association between broadly defined obstetric complications and gender was not significant (weighted average odds ratio=1.14; 95% confidence interval=0.85–1.55; likelihood ratio=1.04, df=1, p=0.36). The associations between the 14 definite specific obstetric complications and gender were neither significant nor in a consistent direction.

Interaction Between Gender, Age at Onset, and Family History

In the same logistic regression model, with history of definite obstetric complications as the response variable and with dichotomized age at onset and/or family history however defined and/or gender as explanatory variables, no significant interactions were found, after stratification by different studies, between gender and age at onset (likelihood ratio=0.03, df=1, p=0.87), gender and family history (likelihood ratio=0.52, df=1, p=0.47), or age at onset and family history (likelihood ratio=0.24, df=1, p=0.63). Therefore, there was no evidence of effect modification of the association between history of definite obstetric complications and age at onset by the two other variables.

DISCUSSION

A significant association was found between age at onset and history of definite obstetric complications:

TABLE 4. Associations Between Age at Onset of Schizophrenia and History of 14 Definite Obstetric Complications[a]

Type of Obstetric Complication and Age Group of Subjects	Subjects With Complication		Weighted Average Odds Ratio	95% Confidence Interval	Likelihood Ratio (df=1)	p
	N	%				
Rubella/syphilis			—[b]	—	—	—
<22 years (N=249)	1	0.4				
≥22 years[c] (N=249)	0	0.0				
Rh incompatibility			—[b]	—	—	—
<22 years (N=162)	0	0.0				
≥22 years (N=175)	1	0.6				
Severe preeclampsia			1.71	0.61–4.81	1.06	0.30
<22 years (N=250)	10	4.0				
≥22 years (N=253)	6	2.4				
Threatened abortion/antepartum bleeding			1.62	0.68–3.87	1.23	0.27
<22 years (N=251)	18	7.2				
≥22 years (N=252)	9	3.6				
Premature rupture of membranes			1.26	0.40–3.97	0.16	0.69
<22 years (N=209)	7	3.3				
≥22 years (N=223)	6	2.7				
Labor length >36 hours or <3 hours[d]			1.18	0.72–1.94	0.43	0.51
<22 years (N=244)	44	18.0				
≥22 years (N=245)	39	15.9				
Twin birth, complicated			0.66	0.20–2.21	0.47	0.49
<22 years (N=253)	5	2.0				
≥22 years (N=253)	7	2.8				
Cord prolapse			—[b]	—	—	—
<22 years (N=248)	2	0.8				
≥22 years (N=249)	0	0.0				
Gestational age <37 weeks or >42 weeks[e]			1.32	0.04–22.30	0.62	0.43
<22 years (N=248)	22	8.9				
≥22 years (N=250)	15	6.0				
Cesarean, complicated, or emergency delivery			10.05	1.21–83.32	7.41	0.007
<22 years (N=251)	8	3.2				
≥22 years (N=253)	1	0.4				
Breech/abnormal presentation			2.67	1.01–7.04	4.38	0.04
<22 years (N=249)	18	7.2				
≥22 years (N=249)	6	2.4				
"High" or difficult forceps delivery			0.73	0.20–2.65	0.24	0.62
<22 years (N=250)	4	1.6				
≥22 years (N=250)	6	2.4				
Birth weight <2000 g			1.11	0.37–3.33	0.03	0.86
<22 years (N=248)	8	3.2				
≥22 years (N=247)	6	2.4				
Incubator used >4 weeks			0.75	0.18–3.21	0.15	0.70
<22 years (N=250)	4	1.6				
≥22 years (N=251)	4	1.6				

[a]Coded on the Lewis and Murray Scale (13).
[b]Not calculable owing to empty cells.
[c]Baseline.
[d]The association with long labor (excluding short labor) could only be assessed for a subsample of patients (N=138) and was not significant (weighted average odds ratio=0.39; 95% confidence interval=0.08–1.88; likelihood ratio=1.21, df=1, p=0.23).
[e]The association with prematurity (excluding postmaturity) could only be assessed for a subsample of patients (N=111) and was not significant (weighted average odds ratio=1.71; 95% confidence interval=0.40–7.35; likelihood ratio=0.45, df=1, p=0.47).

the earlier the age at onset, the more likely the history of obstetric complications. The direction of the association with age at onset was similar for the majority of the 14 definite specific obstetric complications rated on the Lewis and Murray scale. Early age at onset was significantly associated with a history of breech or abnormal presentation and with a history of complicated Cesarean delivery. No association was found between obstetric complications and family history of schizophrenia or psychotic disorder. Male and female schizophrenic subjects did not differ with regard to the frequency of a history of obstetric complications.

Although we attempted to identify all of the researchers who had carried out studies on obstetric complications and schizophrenia in order to obtain published and unpublished data, our search may have missed some studies. Evidence compatible with a publication bias against small studies with negative findings was found in a previous meta-analysis of the literature on obstetric complications and schizophrenia (4). However, a systematic publication bias related to the variables of interest in the present study (i.e., gender, age at onset, and family history) seems very unlikely. For example, we have no reason to suspect that schizophrenic subjects included in unpublished negative studies would specifically differ in the association between age at onset and history of obstetric complications from those included in published studies.

No statistically significant between-study heterogeneity was found with regard to the association between age at onset and history of obstetric complications. However, the result of the test for statistical heterogeneity between studies was close to the conventional significance level. Taking into account the low power of this test (31), some degree of heterogeneity between studies cannot be definitely dismissed. No evidence was found for interstudy variation linked to the study design (diagnostic criteria, obstetric history method, definition of age at onset). Nevertheless, potential confounding factors such as parental social

class, chronicity of disease, and ethnicity could not be controlled in this study.

Since the late-onset patients were more likely to have been ascertained for study when older than the early-onset patients, the observed link between early onset and history of obstetric complications could in theory be artifactual. First, the validity of maternal recall might be better for younger patients; however, the association between early onset and obstetric complications remained significant after adjustment for obstetric history method, and it is unlikely that such a bias would operate for obstetric records. Second, since the improvement in obstetric care in the latest decades is associated with an increased survival of infants exposed to obstetric complications, the incidence of some obstetric complications may be rising in the population as a whole, and we cannot definitely exclude the possibility that there is a secular trend operating.

No association was found between obstetric complications and broadly or narrowly defined family history of schizophrenia. However, this negative finding might be linked to the limitations of the familial-versus-sporadic dichotomy that was used to define family history. This method does not take into account confounding factors such as family size and age and gender of the relative. Therefore, it does not allow a precise assessment of the familial loading, and some "familial" schizophrenia might have been misclassified as "sporadic," especially when the family was small and/or the relatives were young (7). Furthermore, the quality of the information concerning relatives was variable; only three studies had interviewed one or more relatives in a standardized way.

We found no relation between obstetric complications and the familial/sporadic dichotomy of schizophrenia. Taking into account the limitations of the family history method, we cannot be dogmatic on this issue, which remains to be further explored. However, there is probably no straightforward relation between family history and obstetric complications; previous studies have reported that a history of obstetric complications increased the risk of subsequent schizophrenia in patients with familial schizophrenia (33, 34), indicating that obstetric complications might be a risk factor for the emergence of schizophrenia by interacting with a genetic liability.

Against expectations, no difference was found in the frequency of exposure to obstetric complications among male and female schizophrenic subjects. The median for age at onset was rather low in the present sample for both males (21 years) and females (22 years). This might have favored the inclusion of schizophrenic females presenting with the neurodevelopmental form of illness and lessened the differences between males and females with regard to obstetric history. This probably does not fully explain our negative findings. The excess of males among patients with narrowly defined schizophrenia has been linked to the greater vulnerability of males to neurodevelopmental insults (8). In other words, among subjects from the general population exposed to early environmental hazards, the risk of subsequent schizophrenia may be higher among males than females. This does not necessarily imply that the reverse association holds true, i.e., that among subjects with narrowly defined schizophrenia, a greater proportion of males should have a history of neurodevelopmental disturbance. It may be noted that an excess of early environmental hazards has been found among schizophrenic females by some studies (29, 35, 36).

A growing body of evidence suggests that age at onset is a key characteristic for subtyping the psychotic disorders currently included in the schizophrenia diagnostic category. To better characterize the etiological and pathophysiological heterogeneity of schizophrenia, Murray et al. (9) have proposed the subdivision of schizophrenic disorders into three main groups according to age at onset: "congenital" schizophrenia, "adult-onset" schizophrenia, and "late-onset" schizophrenia. Such a strategy based on age at onset has been successfully used in other diseases (diabetes mellitus, Alzheimer's disease) to distinguish etiologically unrelated disorders (37). Murray et al. (9) hypothesized that early neurodevelopmental abnormalities linked to genetic and/or early environmental factors were more likely to have occurred in patients with early-onset schizophrenia. The fact that a history of obstetric complications is a risk factor for early onset demonstrates the heuristic value of this hypothesis. Moreover, the existence of a "dose-response" relationship between a history of obstetric complications and age at onset provides evidence for a cause-effect relationship between obstetric complications and early onset. Since early-onset schizophrenia is more likely to show a chronic course of illness than late-onset schizophrenia (9), the present findings also indirectly support the hypothesis that neurodevelopmental forms of illness are characterized by poor outcome.

The association between early age at onset and history of obstetric complications was significant for only two definite individual obstetric complications (abnormal presentation and complicated Cesarean section). Both of these obstetric complications can provoke birth asphyxia. Therefore, perinatal brain lesions induced by anoxia may be one of the pathophysiological factors leading to early onset of schizophrenia. On the other hand, since the associations between age at onset and the majority of the other individual obstetric complications were in the same direction, early onset might be a final common pathway for a range of early obstetrical hazards.

Briefly, the main findings of the individual patient meta-analysis of case-control studies looking for etiological associations between exposure to obstetric complications and schizophrenia were significant associations between schizophrenia and premature rupture of membranes, prematurity, low birth weight, forceps delivery, and use of resuscitation or an incubator (30). These findings suggest that the specific obstetric complications etiologically related to schizophrenia might be different from those associated with early onset.

However, the fact that fetal hypoxia is a potential common effect of all of these obstetric complications may be emphasized.

The hypothesis of a pathophysiological link between obstetric complications and age at onset should be cautiously considered, taking into account that a multifactorial determination of age at onset is probable. Indeed, it has been hypothesized, on the basis of familial studies showing a strong correlation for age at onset among affected relatives, that age at onset in schizophrenia is mainly determined by genetic factors (38). The association between early age at onset and high genetic risk of schizophrenia (37, 39) also suggests a genetic influence on age at onset.

Thus, we cannot exclude the possibility that the association between early age at onset and obstetric complications is linked to a third risk factor. Goodman (40) speculated that the excess of histories of obstetric complications among individuals with schizophrenia might be the consequence of a preexisting neurodevelopmental abnormality, which could result from some defect in the genetic control of neurodevelopment (41). The same genetic factors might be independently implicated in early age at onset and occurrence of obstetric complications, or obstetric complications might be on the causal pathway between genetically determined neurodevelopmental abnormalities and early age at onset. With regard to the putative role of a third risk factor, another possibility is exposure to other early environmental hazards linked to schizophrenia, such as prenatal influenza, which may be associated with an increased risk of obstetric complications (27, 42).

The pathophysiological link between a history of obstetric complications and age at onset of schizophrenia remains to be clarified. Although fetal hypoxia may be a risk factor for early age at onset, no definite conclusion can be drawn from the present findings concerning the exact mechanisms involved in this process. Nevertheless, our findings strongly suggest that environmental factors such as obstetric complications play a role in the pathophysiology of early-onset schizophrenia, either alone or by interacting with other factors.

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