

Original article

Obstetric complications in patients with schizophrenia and their unaffected siblings

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Abstract

Objective.— We sought to explore whether obstetric complications (OCs) are more likely to occur in the presence of familial/genetic susceptibility for schizophrenia or whether they themselves represent an independent environmental risk factor for schizophrenia.

Methods.— The presence of OCs was assessed through maternal interview on 216 subjects, comprising 36 patients with schizophrenia from multiply affected families, 38 of their unaffected siblings, 31 schizophrenic patients with no family history of psychosis, 51 of their unaffected siblings and 60 normal comparison subjects. We examined the familiarity of OCs and whether OCs were commoner in the patient and sibling groups than in the control group.

Results.— OCs tended to cluster within families, especially in multiply affected families. Patients with schizophrenia, especially those from multiply affected families, had a significantly higher rate of OCs compared to normal comparison subjects, but there was no evidence for an elevated rate of OCs in unaffected siblings.

Conclusion.— Our data provides little evidence for a link between OCs and genetic susceptibility to schizophrenia. If high rates of OCs are related to schizophrenia genes, this relationship is weak and will only be detected by very large sample sizes.

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Keywords: Schizophrenia; Obstetric complications; Siblings; Family study

1. Introduction

There is considerable evidence that exposure to obstetric complications (OCs) is associated with an increased risk of developing schizophrenia in later life [5,18,47]. This risk is small with a pooled odds ratio of approximately 2, and individual studies tend to have insufficient statistical power to implicate specific complications [18,47]. Furthermore, it remains unclear whether OCs represent an independent risk factor for schizophrenia, interact with genetic risk to increase liability, are themselves a manifestation of genetic liability for schizophrenia, or are epiphenomena of developmental compromise in individuals who are already on a trajectory towards psychotic illness in adult life. Previous studies that have attempted to explore whether OCs are linked to genetic susceptibility for schizophrenia have been inconclusive

[34,37,40]. Examining the rate of OCs in patients with and without a family history of illness, and in unaffected siblings of patients can help to clarify the relationship between OCs and schizophrenia.

Unaffected siblings of patients with schizophrenia share 50% of their genes, on average, with their affected relatives and show a significantly increased risk for schizophrenia [44,46]. Given the probable multifactorial nature of schizophrenia [31], it is likely that unaffected first degree relatives of patients share some of the predisposing genes without expressing the disorder, and are therefore more likely to demonstrate some of the biological manifestations of schizophrenia susceptibility genes than normal comparison subjects. Evidence that certain biological markers in individuals without schizophrenia may be related to the schizophrenia genotype comes from reports of increased ventricular size, eye tracking abnormalities, abnormal event related potentials, and an excess of integrative neurological signs and

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neuropsychological deficits among unaffected first degree relatives of patients [10,14,16,19,29].

We set out to examine (i) whether OCs cluster within families, especially those enriched for genetic susceptibility for schizophrenia, and (ii) whether the rate of OCs in the unaffected siblings of patients differs from that in normal controls; which would be expected if genes that increase the risk of schizophrenia also predispose to OCs.

2. Subjects and methods

2.1. Patients and siblings

Subjects consisted of 67 patients who met criteria for DSM-III-R [1] schizophrenia ($n = 62$), schizo-affective disorder ($n = 4$), psychotic disorder NOS ($n = 1$) and 89 of their unaffected siblings, from 59 families. The families were recruited by self referral in response to advertisements, through voluntary organisations or by direct referral from their clinicians. Families were defined as 'familial' if there were two or more first and/or second-degree relatives with schizophrenia or another psychotic disorder. Families were defined as non-familial if the patient had no known family history of psychosis as far as their third degree relatives. Twenty-eight families were classified as belonging to the familial group and 31 families to the non-familial group.

2.2. Normal comparison group

Sixty controls were recruited from the local community via newspaper advertisements and from local staff and were chosen to reflect the combined group of patients and siblings on the basis of age, parental social class and gender. None of the controls had a personal or family history of psychotic illness or a schizophrenia spectrum disorder. A prior history of other psychiatric disorders was not an exclusion factor.

2.3. Clinical assessments

Participants were assessed by a psychiatrist to gather socio-demographic and clinical data. The Schedule for Affective Disorders and Schizophrenia—Lifetime version [45], supplemented by additional clinical information was used to obtain DSM-III-R [1] diagnoses. For those family members who could not be interviewed directly, diagnoses were established using the Family History Research Diagnostic Criteria [13] or the Family Interview for Genetic Studies [35] and conducted with the most reliable family informants available (usually the mother of the subject).

Information on OCs was acquired by maternal interview using the Lewis–Murray Scale [25]. Subjects were rated as having either a definite complication or no complication. Labour <3 hrs was not rated as a definite complication since it can be unreliable [38]. Subjects were also rated as to whether they experienced any complication(s) in the prenatal

and/or perinatal period. The "prenatal" variable was defined as those prenatal events which would produce a score of "definite" on the Lewis–Murray Scale (i.e. rubella, syphilis, rhesus incompatibility, pre-eclampsia: severe and/or leading to early induction or hospitalisation, antepartum haemorrhage or threatened abortion, and birth weight under 2000g). The "perinatal" variable referred to the remaining complications from the Lewis–Murray Scale which occur around the time of labour or in the neonatal period. Some subjects (three patients, two siblings and one controls) had definite complications in both the prenatal and perinatal periods.

Socio-economic status, based on details of parental occupation at birth of the subject, was categorised according to the Office of Population Censuses and Surveys *Standard Occupational Classification* [21].

2.4. Exclusion criteria

All subjects were Caucasian, aged 18–41, and were only included if their mother was available to provide accurate details of their obstetric histories. Only those mothers who were aged 65 or younger at the time of assessment were included in the study. Since an inherent part of the study design was to compare the rates of OCs within sibships, we only included families where there were data available for more than one child.

All participants gave informed consent for their mother to be approached after the details of the study had been explained to them. The study was approved by the local Ethical Committee.

3. Statistical analyses

3.1. Demographic analysis

One way analysis of variance (with Bonferroni post hoc tests) and Pearson's χ^2 tests were used to analyse differences between the groups on demographic characteristics.

3.2. Clustering of OCs in certain families

We assessed for familial clustering of OCs by examining the observed occurrences of OCs (definite complications) and non-OCs (no complications) in all the families via analysis of contingency tables, whose rows were formed by individual families and columns OCs and non-OCs. The Fisher's exact test was used to assess whether occurrences of OCs statistically deviated from random. These analyses were repeated for total definite complications, prenatal and perinatal complications, and were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC 27513, USA).

3.3. Rates of OCs in patients and unaffected siblings

We used logistic (for obstetric complications) and linear (for birthweight) regression analysis to compare the level of

OCs in each group (familial patients, familial siblings, non-familial patients, non-familial siblings) to the control group, controlling for gender, sibship size and age of mother at interview. Since the observations were of individuals within families and thus not independent, a clustered regression analysis was used, with the robust option which uses sandwich estimates of variance to account for possible violations of assumptions of regression (STATA, version 6.0; Copyright 2000 Stata Corporation, 702 University Drive East, College Station, TX 77840, USA). Three measures of OCs were tested; definite complications, prenatal complications and perinatal complications. All tests were two-tailed and used a 0.05 level of significance.

4. Results

4.1. Demographics

The demographic characteristics for the five groups are shown in Table 1. The groups did not significantly differ in measures of parental social class ($\chi^2 = 0.92$, $df = 4$, $p = 0.91$), age of subjects ($F = 1.57$, $df = 4$, $p = 0.18$), maternal age at delivery ($F = 0.14$, $df = 4$, $p = 0.97$) or age of mother at interview ($F = 1.1$, $df = 4$, $p = 0.35$). The “familial group” had slightly larger families than the “non-familial group” ($F = 3.3$, $df = 2$, $p = 0.04$). The groups also differed in gender distribution, with a higher proportion of males in the patient groups ($\chi^2 = 16.10$, $df = 4$, $p < 0.01$).

Table 1
Demographic characteristics of sample

	Familial patients <i>n</i> = 36		Familial siblings <i>n</i> = 38		Non-familial patients <i>n</i> = 31		Non-familial siblings <i>n</i> = 51		Controls <i>n</i> = 60	
	<i>N</i> (%)		<i>N</i> (%)		<i>N</i> (%)		<i>N</i> (%)		<i>N</i> (%)	
Male Gender	28 (79)		16 (42)		21 (68)		21 (41)		32 (53)	
Parental social class (%I & II) ^a	18 (50)		20 (53)		18 (58)		30 (59)		30 (54)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age of subjects	30	(4.2)	29	(5.2)	31	(4.1)	31	(4.7)	29	(6.0)
Age range	20–38		19–40		24–38		18–40		19–41	
	Familial group (<i>n</i> = 74)				Non-familial group (<i>n</i> = 82)				Controls (<i>n</i> = 60)	
	Mean		(SD)		Mean		(SD)		Mean (SD)	
Maternal age at delivery	27		(3.9)		26		(3.9)		27 (4.3)	
Age range	17–37				17–36				18–41	
Current age of mother	56		(4.6)		57		(4.0)		55 (6.3)	
Age range	48–65				48–65				42–65	
Sibship size	3.3		1.0		2.9		0.86		3.2 1.3	

^a Parental social class data not available for four controls.

Table 2
Contingency table analyses for clustering of OCs within families

	Definite complication <i>p</i> ^a	Prenatal complication <i>p</i> ^a	Perinatal complication <i>p</i> [*]
Total sample (familial, non-familial and controls) (<i>n</i> = 222)	0.06	<0.01	0.32
Familial (<i>n</i> = 91)	0.09	0.01	0.06
Non-familial (<i>n</i> = 92)	0.23	0.10	0.79
Normal Comparison subjects (<i>n</i> = 39)	0.27	0.19	0.82

^a *p* refers to the significance level of the Fisher’s exact test to assess whether the distribution of OCs within families deviates from random.

4.2. Familial predisposition to OCs

There was evidence in the total sample for familial clustering of subjects reported to have experienced definite OCs and this was most emphatic for prenatal complications (see Table 2). When the sample was subdivided, such clustering appeared strongest in the “familial group” where it significantly differed from a random distribution for prenatal complications, whereas no significant clustering was detected in the non-familial families, which had a similar number of subjects, or control families.

4.3. OCs in patients and unaffected siblings

The rates of OCs and mean birth weights in each subject group are displayed in Table 3 and Fig. 1 (OC rates), and the results of the regression analysis comparing OCs in each subject group to the control sample are displayed in Table 4. There were significant differences between the groups in rates of definite (Wald $\chi^2 = 21.01$, $p < 0.01$), and perinatal complications (Wald $\chi^2 = 21.52$, $p < 0.01$), which were accounted for by higher rates of these OCs in patients with familial schizophrenia compared to the control group. The subject groups did not significantly differ in rates of prenatal complications (Wald $\chi^2 = 9.34$, $p = 0.23$) or birth weight ($F = 1.64$, $p = 0.13$).

The patient and sibling groups were then collapsed into two groups of “patients” and “siblings” to maximise statistical power. The patient group had a significant excess of definite complications when compared to controls (OR=2.7, CI=1.09–6.8, $p = 0.03$).

Table 3
Number of subjects who experienced at least one obstetric complication and mean birth weights in each subject group

	Familial patients (n = 36)		Familial siblings (n = 38)		Non-familial patients (n = 31)		Non-familial siblings (n = 51)		Controls (n = 60)	
	N	%	N	%	N	%	N	%	N	%
Obstetric complications scored “Definite”	13	36	7	18	8	26	13	26	11	18
Prenatal complication	6	17	5	13	4	13	9	18	6	10
Perinatal complication	9	25	2	5	5	16	6	12	6	10
Birth weight (gms) ^a	Mean 3327	(SD) (520)	Mean 3433	(SD) (610)	Mean 3356	(SD) (568)	Mean 3308	(SD) (546)	Mean 3506	(SD) (585)

^a Birth weight was not available on seven subjects.

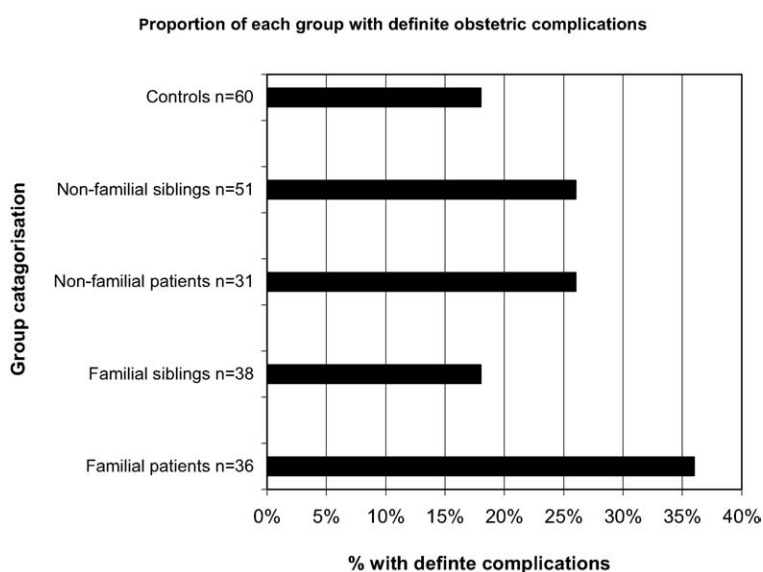


Fig. 1. Proportion of each group with definite obstetric complications.

Table 4

Results of logistic regression analyses comparing pregnancy and birth complications in each group to the control group, controlling for age of mother at interview, parity and gender. Analyses employed multilevel modelling to account for non-independence of obstetric complication histories within individual families

	Familial patients			Familial siblings			Non-familial patients			Non-familial siblings		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Obstetric complications scored “Definite”	3.22	1.15–9.02	0.03	1.21	0.41–3.54	0.73	1.81	0.63–5.22	0.27	2.19	0.78–6.19	0.14
Prenatal complication	1.96	0.56–6.85	0.29	1.57	0.46–5.38	0.47	1.40	0.37–5.34	0.62	2.44	0.72–8.32	0.15
Perinatal complication	3.53	0.99–12.60	0.05	0.57	0.10–3.39	0.54	1.95	0.51–7.50	0.33	1.58	0.42–5.93	0.50
Birth weight (gms)	Coef -214.59	95% CI -481.15 -51.97	p 0.11	Coef -47.09	95% CI -330.24 -236.05	p 0.74	Coef -138.24	95% CI -425.55 -149.08	p 0.34	Coef -156.36	95% CI -461.96 -149.24	p 0.31

There were no significant differences in the rate of definite OCs comparing patients to their own siblings (OR=1.2, CI=0.54–2.72, $p = 0.65$) or siblings to controls (OR=1.5, CI=0.65–3.70, $p = 0.33$).

5. Discussion

In common with most other studies which employ the Lewis–Murray scale [5], we demonstrated higher rates of obstetric complications in patients with schizophrenia than controls, but found little evidence to support the hypothesis

that obstetric complications themselves are a manifestation of genetic liability to schizophrenia, since rates of obstetric complications were not elevated in the unaffected siblings of patients.

Our data does demonstrate that OCs tend to congregate in certain families. This ‘familial’ nature of OCs is not surprising since some OCs are recurrent. The particular tendency of prenatal OCs towards recurrence may indicate that maternal factors are largely responsible for this; for example some mothers have a tendency to develop pre-eclampsia in successive pregnancies [32]. Other maternal factors which can contribute to occurrence of OCs include uterine anomalies,

and a range of medical [26,27] and social factors, such as low social class, poor diet or poor antenatal care [3,39]. Other studies have also reported clustering of OCs in schizophrenic families. DeLisi et al. [11] found birth complications to be significantly concordant in sibling pairs diagnosed with schizophrenia or schizo-affective disorder. Heun et al. [22] reported a minor, but non-significant clustering of OCs in some families of patients with schizophrenia or schizo-affective disorder. It is of interest that such familial clustering appears to be more prominent in our data in multiply affected families which we would expect to be more enriched with predisposing genes for schizophrenia. However, any association between transmission of susceptibility genes for schizophrenia and OCs is of minor effect since we did not find unaffected siblings to have higher rates of OCs than the control group. The lack of difference between unaffected siblings and controls, even in multiply affected families where unaffected siblings are more likely to be gene carriers, is in keeping with other studies which have concluded that OCs are not linked to genetic predisposition for schizophrenia [6,8,20,40].

A number of studies have examined rates of OCs in the relatives of schizophrenic patients. They broadly fall into two study designs. One type examined rates of OCs in the offspring of schizophrenic patients. In a meta-analysis of such studies, Sacker et al. [42] found an increased rate of complications during pregnancy, delivery and the neonatal period in the offspring of mothers with schizophrenia. The authors interpret this as a consequence of adverse socio-environmental conditions associated with schizophrenia, rather than genetic predisposition to complications, and point out the absence of an increased rate of OCs in the offspring of fathers with schizophrenia in support of this.

Indeed there is evidence that risk factors such as smoking, substance misuse and low socio-economic class, all known to be more prevalent in schizophrenic mothers, are associated with increased rates of intrauterine growth retardation, pre-term birth and perinatal death [2]. Howard et al. [23] found an increased risk of stillbirth and neonatal death in the offspring of mothers with psychotic disorders compared to controls, which may have been related to smoking or substance misuse. Nilsson et al. [34] found significantly increased risks for stillbirth, infant death, preterm delivery, low birth weight and small-for-gestational age among offspring of women with schizophrenia compared to controls. These complications were partially accounted for by maternal risk factors such as smoking during pregnancy and single motherhood; but even after controlling for a number of maternal risk factors, the offspring of mothers with schizophrenia had significantly higher rates of preterm delivery and low birth weight, interpreted by the authors as consistent with a common familial vulnerability for pre and perinatal stress and schizophrenia.

The second type of studies examine rates of OCs in the siblings of schizophrenic subjects. Most studies find an increased rate of OCs in patients with schizophrenia compared to their unaffected siblings [11,12,22,24,48]. Only a small

number of sibling studies have used normal controls to examine whether rates of OCs are elevated in siblings themselves [6,8,20,40]. Such studies are better designed for investigating whether OCs may be a manifestation of susceptibility genes for schizophrenia since the confounding effect of schizophrenic illness in the mother is not present. These studies, like our own, generally do not find increased rates of OCs in unaffected siblings of schizophrenia patients. Only one mother in our study herself suffered from a psychotic disorder.

Another study design to assess whether genetic susceptibility to schizophrenia is associated with an increased rate of OCs is to examine whether the morbid risk of schizophrenia is elevated in the first degree relatives of subjects who have experienced OCs. Marcellis et al. [28] have performed such a study and found no significant difference in the rates of schizophrenia or related psychoses among relatives of subjects who had experienced OCs.

5.1. Methodological issues

It has been argued that studies adopting the familial/non-familial (or sporadic) strategy may misclassify patients [41]. We minimised this risk by the use of structured family history interviews utilizing current diagnostic criteria to accurately assess those subjects not directly interviewed. We do not contend that patients without a family history of illness are likely to represent phenocopies of the illness, but rather that more densely affected families are likely to carry a greater load of susceptibility genes, than those families with only one member affected. Indeed such a model of illness is supported by studies which find more extensive brain structural deviations among unaffected relatives from more densely affected families [29,43].

The use of maternal recall as a method of collecting pregnancy and birth information data has been criticised for potential bias. Results from studies examining the reliability of maternal recall using comparisons with contemporary birth records are inconclusive. Two reliability studies found that mothers of patients with schizophrenia tend to underestimate the rate of OCs in their affected offspring compared to controls [4,9]. McIntosh et al. [30] found that mothers of high risk and first episode patients were more likely to recall an OC than mothers of controls: however, birth records for those individuals did not reveal the same finding. On the other hand, O'Callaghan et al. [38] and Franzek and Stober [17] have both reported good agreement between birth records and maternal recall using the Lewis–Murray scale. In both of these studies, the mothers successfully recalled obstetric histories 20–42 years after the birth of their children [17,38], which is similar to the time lag of the present study. The high agreement demonstrated by these studies may be related to the design of the Lewis–Murray scale [25] which targets the retrospective recall of a relatively small number of significant adverse obstetric events. This is consistent with evidence suggesting that the sensitivity of maternal recall improves

with severe or acute events [15] especially those occurring in the perinatal period [49].

The Lewis–Murray scale has been criticised for its “threshold” rating system for defining OCs globally as being either “absent” or “present” (equivocal or definite). A weakness of this approach is that it conflates complications which may be due to maternal factors with those related to the foetus. While this scoring system lacks exactitude, an advantage is that it maximises statistical power in studies which are limited by sample size from examining individual complications. Furthermore the interplay between individual obstetric complications is unclear and they frequently are not independent. Thus, there is evidence that subjects who experience perinatal complications have already experienced other environmental insults earlier in pregnancy [7,33,36].

We cannot discount the possibility of a Type 2 error in our study. Since the rates of OCs in unaffected siblings would be expected to be lower than that found in patients, many studies may lack sufficient statistical power to detect a significant difference and larger samples or meta-analyses may be required to detect a difference, as was the case for offspring [42]. For example, if the subtle odds ratio of 1.5 for a difference between the rate of OCs in siblings of schizophrenic patients and controls in our sample were real, then a sample size of 575 subjects per group would be required to detect this finding with 80% power (using a chi squared test with a 0.05 two-sided significance level). (nQuery Advisor, version 4.0, Copyright 2000, Janet D. Elashoff, Los Angeles, CA, USA). If a gene causes a modest increase in the risk of OCs, and OCs cause a modest increase in risk of schizophrenia, and the overall effect size of the gene on schizophrenia is very small, then one would not expect to see an increase in the rate of OCs in the relatives of schizophrenic patients. On the other hand, if the same gene has modest direct effects on both the risk of schizophrenia and the risk of OCs, then one would expect to see an increase in the rate of OCs among the relatives of schizophrenic patients. The current findings offer evidence against the second but not the first hypothesis.

6. Conclusion

We found evidence for familiarity of OCs which appeared most prominent in those families most likely to be enriched with predisposing genes to schizophrenia. However, possibilities other than genetic susceptibility for schizophrenia, such as maternal factors associated with an increased risk of subsequent OCs, may be responsible for this phenomenon. This study again fails to find evidence that schizophrenia is associated with genetic susceptibility to experiencing OCs since rates in the unaffected siblings and in particular those siblings from multiply affected families did not differ from the control sample. If schizophrenic genes do also predispose to OCs then this effect is weak and would need very large sample sizes to detect it.

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References

- [1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Washington: American Psychiatric Press; 1987 (DC).
- [2] Bennesden B. Adverse pregnancy outcome in schizophrenic women: occurrence of risk factors. *Schizophr Res* 1998;22:1–26.
- [3] Blondel B, Dutilh P, Delour M, Uzan S. Poor antenatal care and pregnancy outcome. *Eur J Obstet Gynecol Reprod Biol* 1993;50: 191–6.
- [4] Buka SL, Goldstein JM, Seidman LJ, Tsuang MT. Maternal recall of pregnancy history: accuracy and bias in schizophrenia research. *Schizophr Bull* 2000;26:335–50.
- [5] Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiat* 2002;159:1080–92.
- [6] Cannon TD, Rosso IM, Hollister JM, Bearden CE, Sanchez LE, Hadley T. A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. *Schizophr Bull* 2000;26:351–66.
- [7] Cannon TD, Van Erp TGM, Rosso IM, Huttunen M, Lonnqvist J, Pirkola T, et al. Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. *Arch Gen Psychiatry* 2002;59:35–41.
- [8] Cantor-Graae E, Ismail B, McNeil TF. Are neurological abnormalities in schizophrenic patients and their siblings the result of perinatal trauma? *Acta Psychiatr Scand* 2000;101:142–7.
- [9] Cantor-Graae E, Cardenal S, Ismail B, McNeil TF. Recall of obstetric events by mothers of schizophrenic patients. *Psychol Med* 1998;28: 1239–43.
- [10] Crawford TJ, Sharma T, Puri BK, Murray RM, Berridge DM, Lewis SW. Saccadic eye movements in families multiply affected with schizophrenia: the Maudsley Family Study. *Am J Psychiat* 1998;155: 1703–10.
- [11] DeLisi LE, Goldin LR, Maxwell EM, Kazuba DM, Gershon ES. Clinical features of illness in siblings with schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1987;44:891–6.
- [12] Eagles JM, Gibson I, Bremner MH, Clunie F, Ebmeier KP, Smith NC. Obstetric complications in DSM-III schizophrenics and their siblings. *Lancet* 1990;335:1139–41.
- [13] Endicott J, Andreasen NC, Spitzer RL. Family history research diagnostic criteria. New York: New York State Psychiatric Institute, Biometrics Research Division; 1975.
- [14] Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT. Neuropsychologic functioning among the nonpsychotic relatives of schizophrenic patients: the effect of genetic loading. *Biol Psychiatry* 2000;48:120–6.
- [15] Filippi V, Ronsmans C, Gandaho T, Graham W, Alihonou E, Santos P. Women’s reports of severe (near-miss) obstetric complications in Benin. *Stud Fam Plann* 2000;31:309–24.
- [16] Frangou S, Sharma T, Sigmudsson T, Barta P, et al. The Maudsley Family Study 4: normal planum temporale asymmetry in familial schizophrenia: a volumetric MRI study. *Br J Psychiatry* 1997;170: 328–33.

- [17] Franzek E, Stober G. Maternal infectious diseases during pregnancy and obstetric complications in the etiology of distinct subtypes of schizophrenia: further evidence from maternal hospital records. *Eur Psychiatry* 1995;10:326–30.
- [18] Geddes JR, Lawrie SM. Obstetric complications and schizophrenia: a meta-analysis. *Br J Psychiatry* 1995;167:786–93.
- [19] Griffiths TD, Sigmondsson T, Takei N, Rowe D, Murray RM. Neurological abnormalities in familial and sporadic schizophrenia. *Brain* 1998;121:191–203.
- [20] Gunther-Genta F, Bovet P, Hohlfeld P. Obstetric complications and schizophrenia. A case-control study. *Br J Psychiatry* 1994;164:165–70.
- [21] H.M.S.O. Office of population censuses and surveys, standard occupational classification. London: HMSO; 1991.
- [22] Heun R, Maier W. The role of obstetric complications in schizophrenia. *J Nerv Ment Dis* 1993;181:220–6.
- [23] Howard LM, Goss C, Leese M, Thornicroft G. Medical outcome of pregnancy in women with psychotic disorders and their infants in the first year after birth. *Br J Psychiatry* 2003;182:63–7.
- [24] Kinney DK, Levy DL, Yurgelun-Todd DA, Medoff D, LaJonchere CM, Radford-Paregol M. Season of birth and obstetrical complications in schizophrenics. *J Psychiatr Res* 1994;28:499–509.
- [25] Lewis SW, Owen MJ, Murray RM. Obstetric complications and schizophrenia: methodology and mechanisms. in: Schulz SC, Tamminga CA, editors, *Schizophrenia: scientific progress*. New York (NY) US: Oxford University Press; 1989. p. 56–68.
- [26] Liu S, Shi Wu W, Demissie K, Marcoux S, Kramer MS. Maternal asthma and pregnancy outcomes: a retrospective cohort study. *Am J Obstet Gynecol* 2001;184:90–6.
- [27] Loffredo CA, Wilson PD, Ferencz C. Maternal diabetes: an independent risk factor for major cardiovascular malformations with increased mortality of affected infants. *Teratology* 2001;64:98–106.
- [28] Marcellis M, Van Os J, Sham P, Jones P, Gilvarry C, Cannon M, et al. Obstetric complications and familial morbid risk of psychiatric disorders. *Am J Med Genet* 1998;81:29–36.
- [29] McDonald C, Grech A, Touloupoulou T, Schulze K, Chapple B, Sham P, et al. Brain volumes in familial and non-familial schizophrenic probands and their unaffected relatives. *Am J Med Genet* 2002;114:616–25.
- [30] McIntosh AM, Holmes S, Gleeson S, Burns JK, Hodges AK, Byrne MM, et al. Maternal recall bias, obstetric history and schizophrenia. *Br J Psychiatry* 2002;181:520–5.
- [31] Moldin SO, Gottesman II. Genes, experience, and chance in schizophrenia—positioning for the 21st century. *Schizophr Bull* 1997;23:547–61.
- [32] Mostello D, Catlin TK, Roman L, Holcomb WL, Leet T. Preeclampsia in the parous woman: who is at risk? *Am J Obstet Gynecol* 2002;187:425–9.
- [33] Nelson K, JH E. Antecedents of cerebral palsy. Multivariate analysis of risk. *N Engl J Med* 1986;315:81–6.
- [34] Nilsson E, Lichtenstein P, Cnattingius S, Murray RM, Hultman CM. Women with schizophrenia: pregnancy outcome and infant death among their offspring. *Schizophr Res* 2002;58:221–9.
- [35] Nurnberger JI, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry* 1994;51:849–59.
- [36] O'Callaghan E, Gibson T, Colohan HA, Buckley P, Walshe DG, Larkin C, et al. Risk of schizophrenia in adults born after obstetric complications and their association with early onset of illness—a controlled-study. *BMJ* 1992;305:1256–9.
- [37] O'Callaghan E, Larkin C, Kinsella A, Waddington JL. Obstetric complications, the putative familial-sporadic distinction, and tardive dyskinesia in schizophrenia. *Br J Psychiatry* 1990;157:578–84.
- [38] O'Callaghan E, Larkin C, Waddington JL. Obstetric complications in schizophrenia and the validity of maternal recall. *Psychol Med* 1990;20:89–94.
- [39] Peacock JL, Bland JM, Anderson HR. Preterm delivery: effects of socioeconomic factors, psychological stress, smoking, alcohol, and caffeine. *BMJ* 1995;311:531–5.
- [40] Rosso IM, Cannon TD, Huttunen T, Huttunen MO, Lonnqvist J, Gasperoni TL. Obstetric risk factors for early-onset schizophrenia in a Finnish birth cohort. *Am J Psychiatr* 2000;157:801–7.
- [41] Roy M, Crowe R. Validity of the familial and sporadic subtypes of schizophrenia. *Am J Psychiatr* 1994;151:805–14.
- [42] Sacker A, Done D, Crow T. Obstetric complications in children born to parents with schizophrenia: a meta-analysis of case-control studies. *Psychol Med* 1996;26:279–87.
- [43] Seidman LJ, Faraone SV, Goldstein JM, Kremen WS, Horton NJ, Makris N, et al. Left hippocampal volume as a vulnerability indicator for schizophrenia: A magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. *Arch Gen Psychiatry* 2002;59:839–49.
- [44] Sham PC, Jones P, Russell A, Gilvarry K, Bebbington P, Lewis S, et al. Age at onset, sex, and familial psychiatric morbidity in schizophrenia—Camberwell collaborative psychosis study. *Br J Psychiatry* 1994;165:466–73.
- [45] Spitzer R, Endicott J. Schedule for affective disorders and schizophrenia—lifetime version. New York: New York State Psychiatric Institute; 1978.
- [46] Tsuang MT, Stone WS, Faraone SV. Genes, environment and schizophrenia. *Br J Psychiatry* 2001;178(Suppl. 40):s18–s24.
- [47] Verdoux H, Geddes JR, Takei N, Lawrie SM, Bovet P, Eagles JM, et al. Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. *Am J Psychiatr* 1997;154:1220–7.
- [48] Woerner MG, Pollack M, Klein DF. Pregnancy and birth complications in psychiatric patients: a comparison of schizophrenic and personality disorder patients with their siblings. *Acta Psychiatr Scand* 1973;49:712–21.
- [49] Yawn BP, Suman VJ, Jacobsen SJ. Maternal recall of distant pregnancy events. *J Clin Epidemiol* 1998;51:399–405.