Maternal recall bias, obstetric history and schizophrenia

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Background This study sought to clarify the role of obstetric complications (OCs) and maternal recall bias for patients with first episodes of schizophrenia and those at increased risk of the disorder.

Method Subjects at high risk of schizophrenia were compared with people with first-episode schizophrenia and with healthy volunteers. Consenting mothers of subjects were interviewed using a standardised questionnaire for the recall of OCs, and OCs were also measured from records collected at the time of pregnancy and delivery.

Results High-risk subjects and first-episode patients had higher rates of OCs recalled by their mother than controls, but hospital records showed no differences in OCs between groups. The number of OCs recalled by mothers of the high-risk group was not related to whether the mother had schizophrenia or not, but was related to the maternally rated abnormal childhood behaviour as measured by the Child Behaviour Checklist.

Conclusions These results suggest that studies that rely on maternal recall alone are susceptible to bias. The excess of OCs recalled by the mother could be related to abnormal behaviour in their child rather than maternal illness, family history or psychotic symptoms.

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Obstetric complications have been associated with the development of schizophrenia in offspring (Lewis & Murray, 1987; Verdoux et al, 1997) although it remains unclear which complications are most important and when they exert their effects. Furthermore, the direction of the association is uncertain (Goodman, 1988) and maternal recall bias could also be an issue (Cantor-Graae et al, 1998). Studies in which obstetric data are collected prospectively at the time of pregnancy and delivery tend to find less of an association between obstetric complications and schizophrenia than case–control studies where mothers are asked to recall obstetric information after their child has become unwell (Geddes & Lawrie, 1995).

Obstetric data from the Edinburgh High Risk Study provides opportunities for the clarification of these issues. Complications were recorded from the mothers of people with schizophrenia, healthy individuals at high risk of schizophrenia for genetic reasons and healthy controls at no additional risk. Maternal recall data were compared with contemporaneous health service data collected around the time of pregnancy and delivery.

METHOD

All subjects were participants recruited for the Edinburgh High Risk Study. The methodology and sample have been described extensively elsewhere (Hodges et al, 1999; Johnstone et al, 2000). By definition, the high-risk subjects had at least two relatives with schizophrenia, whereas the young people in the control group had no known relatives with psychosis. The control group was recruited through Edinburgh youth groups and from the social network of the high-risk subjects themselves. Efforts were made to balance the groups for age, gender and socio-economic status.

A further control group aged 16–24 years was recruited from patients admitted to psychiatric care in the Edinburgh area with a new diagnosis of schizophrenia. The diagnosis of first-episode schizophrenia according to DSM–IV criteria was confirmed with the Operational Checklist for Psychiatric Disorders (OPCRIT; McGuffin et al, 1991) of hospital case notes and structured psychiatric interviews. Subjects with a family history of schizophrenia were excluded from this group.

All participants were interviewed using the Present State Examination (PSE–9; Wing et al, 1974) to see if they were currently symptomatic. The PSE is a semi-structured clinical interview in which a set of standard questions is asked and augmented by a set of additional questions when necessary. The questions are used to clarify the presence or absence of 140 symptom items that are defined in the text of the PSE and an accompanying glossary. High-risk subjects were further classified on the basis of the PSE into two groups: those who had experienced psychotic symptoms in the first years of the study; and those without such symptoms (Miller et al, 2002).

Assessment of obstetric complications

Each participant's history of obstetric complications was assessed in the same way. After informed consent had been obtained, the mother of each participant was identified wherever possible and invited either to attend for interview or to take part in a telephone interview (depending on their preference). Participants and their mothers were also asked to give consent for examination of their obstetric histories from health service records. For the period from 1971 to 1978 inclusive, obstetric histories were taken from Scottish Morbidity Record data (SMR2 or SMR[M]) collected nationally at the time of pregnancy and confinement by the Information and Statistics Division of the National Health Service in Scotland. The linkage involved probability matching (Kendrick & Clarke, 1993), which pulls together records belonging to the same individual with 98–99% accuracy.

Each obstetric complication, from both sources, was elicited using a standard questionnaire developed from other published reports (Parnas et al, 1982; Lewis et al, 1989; McCreadie et al, 1992; McNeil & Sjöström, 1995). Obstetric data were rated using the McNeil–Sjöström scale for

obstetric complications (McNeil & Sjöström, 1995) and scored according to a standard protocol after the investigators (S.H., A.M.M.) had undertaken a period of training in the use of this instrument. The other historical and personal details of each subject were also recorded using hospital case notes and face-to-face interviews with the participants.

The NcNeil–Sjöström scale categorises obstetric complications according to six severity levels. Level one refers to complications that are not harmful or relevant and level two refers to complications that are not likely to be harmful or relevant. These complications were therefore excluded from further consideration as they described comparatively trivial complications of pregnancy (e.g. haemorrhoids, back pain, heartburn). Complications of pregnancy, labour and delivery and of the neonatal period were all recorded individually. Pregnancy complications were also further classified as occurring in the first, second or third trimesters of pregnancy.

The McNeil–Sjöström scale was used as the principal measure of obstetric complications as it includes the greatest number of complications of potential relevance to the aetiology of schizophrenia. It is likely to be the most sensitive instrument available now and makes fewer assumptions than other commonly used scales.

Statistical analysis

Demographic, neuropsychological and other patient details were compared between groups to examine whether there were any systematic differences. One-way analysis of variance (ANOVA) was used for continuous data, Kruskal–Wallis ANOVA was used for ranked ordinal data and chi-squared (χ^2) was used where data were categorical. Two-tailed significance testing was used throughout. Where data were not normally distributed, descriptive statistics were presented as medians and interquartile ranges rather than means and standard deviations.

Obstetric complications on the McNeil–Sjöström scale with a severity score of three or more were analysed using the Statistical Package for the Social Sciences (SPSS Software, 1999). The numbers of obstetric complications using this scale were compared between high-risk subjects, first-episode patients and healthy controls using the Kruskal–Wallis test. Where a significant association was found,

correction was made for multiple hypotheses testing using the Bonferroni correction.

Where a significantly higher mean number of obstetric complications was found in the high-risk group than in controls, two subsequent further analyses were conducted. The first compared the mean number of obstetric complications for those high-risk subjects in whom the mother was herself affected with those in whom the mother was unaffected. Second, the number of obstetric complications was compared between groups of high-risk subjects where the individual had displayed some psychotic symptoms (not amounting to a diagnosis of schizophrenia; Lawrie *et al*, 2001) with those who were not showing symptoms. Both analyses were conducted using a Mann–Whitney *U*-test.

The relationship of obstetric complications to the degree of genetic risk to schizophrenia was examined using two methods of assessing genetic liability: a continuous measure described elsewhere (Lawrie *et al*, 2001) and a categorical measure of genetic risk according to whether high-risk individuals had two or more first-degree relatives affected, one first-degree relative and one or more second-degree relative affected, or two or more second-degree relatives affected. The numbers of obstetric complications were compared between these three high-risk groups by means of a Kruskal–Wallis test with correction for multiple hypothesis testing. Spearman's rank correlation coefficients were used to compare the continuous measure of genetic risk with numbers of obstetric complications, and χ^2 tests of significance were also calculated for each correlation reported.

Maternal recall bias was examined by comparing obstetric complications between high-risk subjects, controls and first-episode patients using a repeated measures ANOVA for each scale. Where data were not normally distributed, a rank transformation was applied (Conover & Iman, 1981, 1982). For the McNeil–Sjöström scale, the dependent variable used was the frequency of obstetric complications rated as severity level 3 or greater. The dependent variable had two levels: obstetric complications rated by maternal recall and those rated from health service data.

Maternal assessment of childhood behaviour at age 11 and 16 years was recorded at interview using the Child Behaviour Checklist (CBCL; Achenbach, 1991). The scale is a 120-item checklist, which generates 8 syndrome scales (social

withdrawal, somatic complaints, anxiety–depression, social problems, attention problems, delinquent behaviour; aggressive behaviour and other problems). Mothers were asked to complete the CBCL for their child. The relationship of this measure to the number of obstetric complications recalled by mothers was investigated using Spearman's correlation coefficient.

RESULTS

A total 162 subjects at high risk of schizophrenia, 36 with first episodes and 37 healthy controls provided data. Each of the groups was balanced in terms of gender and age of participants. Of the 235 participants, 185 had relatives who gave obstetric information by maternal recall. A total of 138 gave consent for their health service records to be examined and successful linkage to their SMR data was obtained for 110 (80%; 17 controls, 78 high-risk subjects and 15 first-episode patients). The proportions of each group for whom maternal recall data were obtained did not differ significantly ($\chi^2 = 3.6$, d.f.=2, $P = 0.17$). Similarly, the percentage of male participants ($P = 0.23$) and the mean age ($P = 0.45$) was similar to the non-participants. Socio-economic status was, however, significantly lower in the individuals whose mothers did not provide complete maternal recall data ($P = 0.01$). Socio-economic status was also significantly different between the three groups giving maternal recall data ($P < 0.01$; see Table 1), individuals in the control group being more likely to be in a higher socio-economic group.

Maternal recall data

The total number of obstetric complications recalled by mothers was greatest for subjects at high-risk of schizophrenia compared with patients with first-episode schizophrenia which was, in turn, greater than for normal controls (Table 2; Fig. 1; $P = 0.007$). This finding was also significant after a Bonferroni correction. In addition, the number of obstetric complications occurring in the first and second trimesters of pregnancy and in the neonatal period was greater in high-risk subjects compared with controls, although these findings were not robust to controlling for multiple hypothesis testing.

No differences in obstetric complications (as recalled by mothers) were found between high-risk subjects whose mother

had a diagnosis of schizophrenia (*n*=34) and high-risk subjects whose mother had no diagnosis of schizophrenia (*n*=99, *P*=0.85; Table 3). Similarly, no relationship was found between the total number of obstetric complications and either the discrete (*P*=0.44) or continuous (*P*=0.77) measures of genetic liability to schizophrenia used in the study. No associations were found between either measure of genetic liability and any period of pregnancy, once correction for multiple testing had been performed (see Table 4).

Comparison of maternal recall with health service data

The total number of obstetric complications, rated from health service data, did not differ between the groups for any single period of pregnancy either before or after correction for multiple hypothesis testing. The total number of obstetric complications over the entire pregnancy, delivery and neonatal period also did not differ between the three groups.

The distribution of obstetric complications rated at a severity level of 3 or greater was analysed using a histogram and normal probability plot. Data clearly deviated from the normal distribution, and therefore a rank transformation was applied. Using a repeated measures ANOVA, there was a significant interaction between the number of obstetric complications (classified by McNeil–Sjöström scale as having a severity of 3 or more) recalled by the mother and those rated from health service data according to the group membership of the individual (high-risk, first-episode, control; d.f.=2, *F*=3.51, *P*=0.033; Fig. 2).

Relationship of obstetric data to premorbid behaviour

Childhood behaviour at age 11 and 16 years was rated by the consenting mothers of all three groups using the CBCL. If the number of obstetric complications recalled by the mother was related to perceived abnormal childhood behaviour, an explanation for the apparent maternal recall bias found in this study might be provided. Childhood behaviour at age 11 and its correlation with maternally rated obstetric complications was examined using Spearman's correlation coefficient.

Maternally rated obstetric complications were related to somatic complaints (*r*=0.25, *P*=0.019), anxiety–depression (*r*=0.27, *P*=0.01), social problems (*r*=0.24, *P*=0.024), delinquent behaviour (*r*=0.23, *P*=0.031) and aggressive behaviour (*r*=0.32, *P*=0.002) of children at age 11. They were also related to anxiety–depression (*r*=0.24, *P*=0.03) and aggressive behaviour (*r*=0.25, *P*=0.02) of children aged 16. Hospital-record-rated obstetric complications were not related to any of the measures of childhood behaviour.

DISCUSSION

Rationale for the study

This study was originally conducted when only maternal recall data were available to the authors. The positive findings from maternal recall were submitted to the *British Journal of Psychiatry* but were rejected on the grounds that they were likely to result from maternal recall bias. Contemporaneous health service data were subsequently obtained and the presence of maternal recall bias examined.

The current study measured obstetric complications with a sensitive instrument (McNeil & Sjöström, 1995), using both maternal recall and contemporaneous health service records in a well-balanced population consisting of the mothers of patients with first-episode schizophrenia, high-risk subjects and healthy controls.

Table I Characteristics of the sample giving maternal recall data (*n*=185)

	First-episode (*n*=26)	High-risk (*n*=133)	Controls (*n*=26)	*P*
Gender, *n* (% male)	18 (69.2)	67 (50.4)	12 (53.8)	0.21
Social class, median (IQR)	4 (3)	4 (2)	3 (3)	<0.01
Age of participant, mean (s.d.)	21.6 (3.6)	21.1 (2.9)	21.1 (2.3)	0.85

IQR, interquartile range.

Table 2 Obstetric complications recalled by mother for 133 high-risk subjects, 26 first-episode patients and 26 normal controls

Time frame	Group	Median	IQR	χ^2, d.f.=2	*P*
Trimester 1	High-risk	1	1	9.6	0.008
	Controls	0	1		
	First-episode	0	1		
Trimester 2	High-risk	1	1	6.1	0.047
	Controls	0	1		
	First-episode	0	1		
Trimester 3	High-risk	1	1	3.5	0.176
	Controls	0	1		
	First-episode	1	1		
Trimesters 1, 2 and 3	High-risk	3	4	5.9	0.051
	Controls	1	3		
	First-episode	1	3		
Labour and delivery	High-risk	1	1	1.6	0.447
	Controls	1	1.25		
	First-episode	1	2.25		
Neonatal period	High-risk	0	2	6.2	0.045
	Controls	0	0		
	First-episode	0	1		
Total obstetric period	High-risk	5	4.5	9.9	0.007**
	Controls	2.5	4		
	First-episode	3.5	4		

IQR, interquartile range.
**Significant after correction for multiple comparisons.

We were thus able to directly examine the possibility of maternal recall bias in the obstetric histories of high-risk subjects as well as a sample of patients experiencing their first-episode of schizophrenia.

Main findings

The number of maternally rated obstetric complications (classified by the McNeil–Sjöström scale) of potential relevance to the aetiology of schizophrenia was greater in subjects at high-risk of schizophrenia than in patients with first-episode schizophrenia, which was, in turn, greater than in healthy controls. Health service data revealed no overall differences in obstetric complications (classified by the McNeil–Sjöström scale as of potential relevance to the aetiology of schizophrenia) between high-risk subjects, first-episode patients and normal controls. The number of obstetric complications was not related to whether or not the high-risk subject was the child of a mother with schizophrenia or not, or to whether the affected proband displayed subclinical psychotic symptoms. Although the number of maternally rated obstetric complications was elevated for those at increased genetic risk of schizophrenia, the degree of genetic risk was not associated with the number of obstetric complications found in the high-risk group.

A repeated measures ANOVA found differentially higher maternal recall of obstetric complications among the high-risk subjects and first-episode patients compared with the normal controls than would have been expected from health service data. This finding is highly suggestive of maternal recall bias. Furthermore, the number of obstetric complications recalled by the mother was related to measures of abnormal childhood behaviour at age 11 and 16. It is possible that concern about the child's behaviour can affect the mother's recall of obstetric events. The fact that these behaviours have been shown to predict the onset of schizophrenia in these high-risk subjects (Miller *et al*, 2002) is of interest in the general context of the relationship between maternal recall of obstetric events and the development of schizophrenia. It is possible that mothers could be sensitised to recall adverse obstetric events or make false recollections simply because they know that their child is at enhanced risk of developing schizophrenia in the future, and obstetric complications could be a more acceptable
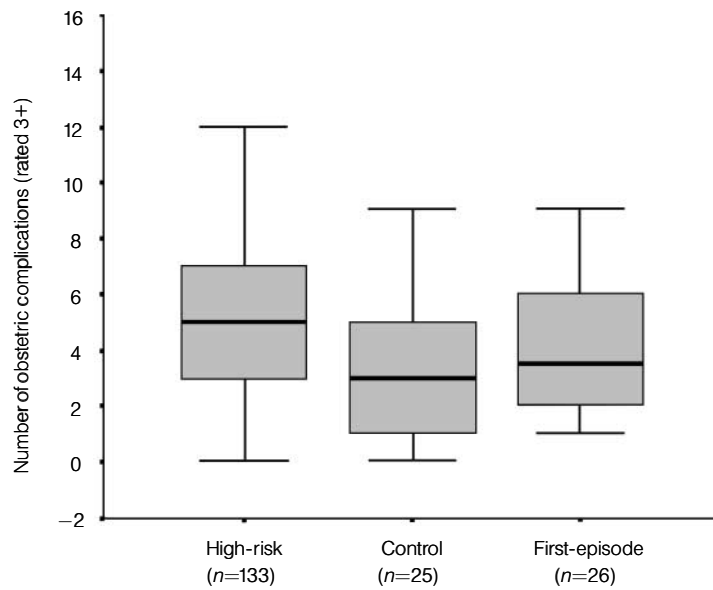
explanation for any abnormal behaviour in their offspring as they might perceive these events to be out of their control.

Strengths and limitations

This study compared obstetric complications in subjects at high-risk of schizophrenia with groups balanced for age, socio-economic status and gender. The degree to which the groups were balanced for age was exceptionally close, although the groups were less similar for gender

and socio-economic status. This could have reduced the reliability of the study findings. As with all case–control studies, confounding may be a significant problem, but some of the main potential confounders were controlled for. Uncorrected confounders of potential relevance include: neuro-developmental genes; maternal compliance with obstetric care; substance misuse; and diet. Complications were also rated by investigators who were not blind to group assignment, and it is possible that this limitation exaggerated the differences between

Fig. I. Box plot showing the number of obstetric complications in first-episode patients, high-risk subjects and healthy controls rated by the McNeil–Sjöström scale at a severity of 3 or more (maternal recall data).

Table 3 Obstetric complications recalled by the mother for high-risk subjects where the mother has had a diagnosis of schizophrenia (affected) compared with high-risk subjects where the mother has not had a diagnosis (unaffected)

Time frame	High-risk group	Median	IQR	U, d.f.=I	P
Trimester I	Mother affected	I	2	1576	0.56
	Mother unaffected	I	I		
Trimester 2	Mother affected	I	2	1552	0.47
	Mother unaffected	I	I		
Trimester 3	Mother affected	I	2	1503	0.32
	Mother unaffected	I	I		
Trimesters I, 2 and 3	Mother affected	0	I	1590	0.62
	Mother unaffected	3	6.25		
Labour and delivery	Mother affected	I	2	1426	0.17
	Mother unaffected	I	I		
Neonatal period	Mother affected	I	1.25	1642	0.82
	Mother unaffected	0	2		
Total obstetric period	Mother affected	4	6.25	1648	0.85
	Mother unaffected	5	4		

IQR, interquartile range.

groups. However, the standardised questionnaire employed in this study is likely to have collected reliable data (Cantor-Graae *et al*, 1998). The rating of obstetric complications from SMR data has obvious advantages as this information is collected prospectively and is unlikely to be subject to differential bias between the three subject groups. However, such information is dependent on the efforts of health service staff and its accuracy and interrater reliability are uncertain. It is likely that any errors in health service data would be random and equally distributed between the groups. Non-systematic errors, and the resulting reduction in power, could therefore have obscured between-group differences in terms of the obstetric complications rated from health service data, although such errors are unlikely to account for the interaction of obstetric complications by group found using a repeated measures ANOVA.

Comparison with other studies

Studies that use data collected prospectively at the time of pregnancy and delivery often fail to find an association between obstetric complications and schizophrenia (Byrne *et al*, 2000; Kendell *et al*, 2000). This fact suggests that studies relying on maternal recall could be biased. Several studies have examined the possibility of maternal recall bias (O'Callaghan *et al*, 1990; Cantor-Graae *et al*, 1998; Buka *et al*, 2000) with varying results. In the first of these studies (O'Callaghan *et al*, 1990), 21 mothers (17 with schizophrenia and four other probands) were interviewed to ascertain obstetric histories by maternal recall. Maternity hospital records were also inspected and generally the level of agreement (on the Lewis–Murray scale) was high. In cases where the maternity records and maternal recall differed, there was a tendency for mothers to recall obstetric complications that could not be confirmed in hospital records. Although the study has many strengths, the numbers involved were small, and no control group was recruited for comparison purposes. To restrict the obstetric complications of interest to those present in the Lewis–Murray scale might have excluded complications of potential relevance to schizophrenia and reduced the power to detect maternal recall bias. The second study (Cantor-Graae *et al*, 1998) obtained obstetric information from structured maternal

Table 4 Relationsip between continuous (ρ) and categorical (*F*) measures of genetic liability to schizophrenia and total number of obstetric complications recalled by mother

Period of pregnancy	ρ	P	F	P
Trimester I	0.01	0.91	0.70	0.93
Trimester 2	0.05	0.55	0.39	0.68
Trimester 3	0.006	0.94	0.07	0.93
All trimesters	0.01	0.87	0.044	0.96
Labour/delivery	−0.04	0.62	0.30	0.74
Neonatal	−0.02	0.86	3.4	0.04[1]
Total obstetric period	−0.03	0.77	0.82	0.44

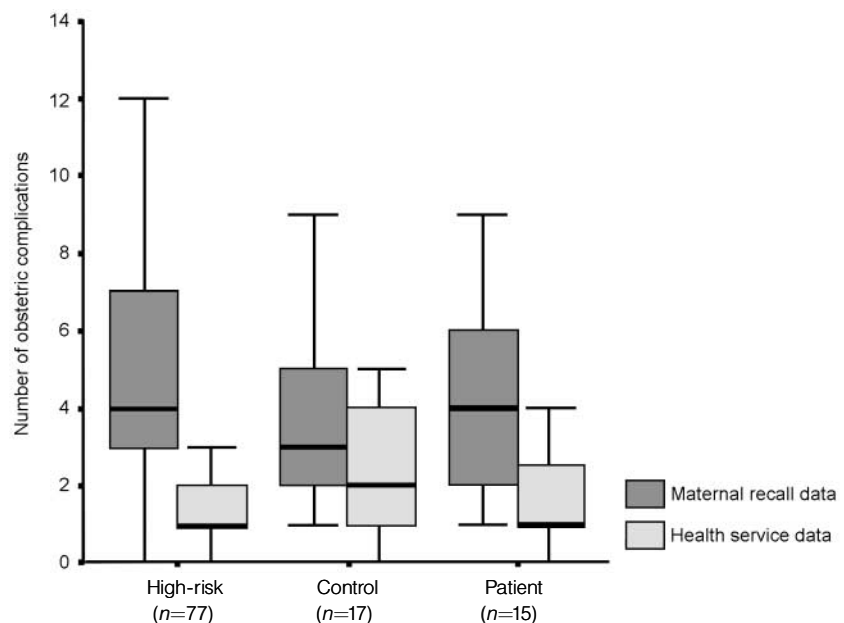1. $P > 0.1$ after correction for multiple comparisons.

Fig. 2. Total numbers of obstetric complications rated from health service records and maternal recall according to the McNeil–Sjöström scale. Complications graded as severity level 3 or greater in subjects providing complete data.

interview and from hospital records in 45 mothers of probands with schizophrenia and 34 control mothers using the McNeil–Sjöström obstetric complications scale. Considerable discrepancies were observed between interviews and maternal records, irrespective of maternal group. No significant differences were found between patients and control mothers in error type or for recall of selected events, but there was a tendency for mothers of probands with schizophrenia to under-report labour and delivery complications. This study included a control group as well as a much broader range of potentially relevant complications, as in the present study. The third study to systematically examine recall bias in the

mothers of probands with schizophrenia (Buka *et al*, 2000) used the Pregnancy History Inventory to rate the obstetric histories of 28 mothers of individuals with schizophrenia and 28 control mothers by both maternal recall and from maternity records. That study, similar to the study by Cantor-Graae *et al* (1998), showed that mothers of affected probands tended to underestimate the frequency of obstetric complications compared with controls. The obstetric histories were, however, elicited solely by telephone interview, a fact which could have limited their accuracy. The current study is the first, as far as we are aware, to find maternal recall bias in subjects at high risk of schizophrenia and relate the degree of bias

to measures of abnormal childhood behaviour in otherwise healthy individuals.

The finding of maternal recall bias in the obstetric histories of the mothers of subjects with schizophrenia suggests that studies that use maternal recall alone could be biased. Studies that rely on maternal recall alone are relatively common outside Scandinavian countries and their inclusion in the meta-analytical reviews in this area (Geddes & Lawrie, 1995; Verdoux *et al*, 1997; Geddes *et al*, 1999) might have falsely elevated the summary effect size.

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CLINICAL IMPLICATIONS

■ Mothers of patients with schizophrenia could be subject to bias in their recall of obstetric complications.

■ Mothers of individuals at high-risk of schizophrenia could also be subject to the same bias.

■ Studies that rely on maternal recall data may overestimate the role of obstetric complications in the aetiology of schizophrenia.

LIMITATIONS

■ Researchers were not blind to the diagnostic status of participants.

■ The quality of health service data (Scottish Morbidity Record) is uncertain.

■ A proportion of those giving maternal recall data could not be linked to their health service records.

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