20 Meade TW, Dyer S, Browne W, Townsend J, Frank OA. Low back pain of mechanical origin: randomised comparison of chiropractic and hospital outpatient treatment. *BMJ* 1990;**300**:1431-6.
21 Gilbert JR, Taylor DW, Hildebrand A, Evans C. Clinical trial of common treatments for low back pain in family practice. *BMJ* 1985;**291**:791-4.
22 Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. *N Engl J Med* 1990;**322**:1627-34.
23 Manniche C, Hesselsoe G, Bentzen L, Christensen I, Lundberg E. Clinical trial of intensive muscle training for chronic low back pain. *Lancet* 1988;ii:1473-6.
24 Evans C, Gilbert JR, Taylor DW, Hildebrand A. A randomized controlled trial of flexion exercises, education, and bed rest for patients with acute low back pain. *Physiotherapy Canada* 1987;**39**:96-101.
25 Coxhead CE, Inskip H, Meade TW, North WRS, Troup JDG. Multicentre trial of physiotherapy in the management of sciatic symptoms. *Lancet* 1981;i:1065-8.
26 Waterworth RF, Hunter IA. An open study of diflunisal, conservative and manipulative therapy in the management of acute mechanical low back pain. *N Z Med J* 1985;**95**:372-5.
27 Stankovic R, Johnell O. Conservative treatment of acute low back pain: a prospective randomized trial. *Spine* 1990;**15**:120-3.
28 Nwuga VCB. Relative therapeutic efficacy of vertebral manipulation and conventional treatment in back pain management. *Am J Phys Med* 1982;**61**:273-8.
29 Farrell JP, Twomey LT. Acute low back pain: comparison of two conservative treatment approaches. *Med J Aust* 1982;**1**:160-4.
30 Kendall PH, Jenkins JM. Exercises for backache: a double-blind controlled trial. *Physiotherapy* 1968;**54**:154-7.
31 Davies JR, Gibson T, Tester L. The value of exercises in the treatment of low back pain. *Rheumatology and Rehabilitation* 1979;**18**:243-7.
32 Buswell J. Low back pain: a comparison of two treatment programmes. *New Zealand Journal of Physiotherapy* 1982;**10**:13-7.
33 Nwuga G, Nwuga V. Relative therapeutic efficacy of the Williams and McKenzie protocols in back pain management. *Physiotherapy Practice.* 1985;**1**:99-105.
34 White AWM. Low back pain in men receiving workmen's compensation. *Can Med Assoc J* 1966;**95**:50-6.
35 Chalmers TC, Smith H, Blackburn B, *et al.* A method for assessing the quality of a randomized control trial. *Controlled Clin Trials* 1981;**2**:31-49.
36 Tysen J, Furzan J, Reisch J, *et al.* An evaluation of the quality of therapeutic trials in perinatal medicine. *J Pediatr* 1983;**102**:10-3.
37 Kleijnen J, Knipschild P, Ter Riet G. Clinical trials of homoeopathy. *BMJ* 1991;**302**:316-23.

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# Complications of pregnancy and delivery in relation to psychosis in adult life: data from the British perinatal mortality survey sample

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## Abstract

***Objective*—To evaluate whether events occurring at or around the time of birth contribute to the onset of psychotic illness in adult life.**

***Design*—Pregnancy and birth complications as possible causes of adult mental illness were studied in the population sample of the British perinatal mortality survey. Subsequent psychiatric admissions were independently identified through the Mental Health Enquiry and records of regional and special health authorities. Logistic regression was used to compare data on perinatal deaths with those on survivors to determine factors independently associated with perinatal death, and this equation was then used to calculate the risk of perinatal death for each survivor.**

***Subjects*—16 980 people born in a single week in 1958 (the British perinatal mortality survey sample), including 252 patients admitted to psychiatric care; case notes of 235 patients were supplied.**

***Main outcome measures and results*—Patients with a schizophrenic illness (whether defined by "broad" (n=57) or "narrow" (n=35) diagnostic criteria) did not have a greater mean risk of perinatal death than the population in general, but there was some evidence of increased liability (relative risk 2·43; 95% confidence interval 1·17 to 5·05) for those with affective psychosis (n=32). Specific high risk variables for affective psychosis were decreased gestation time (273·9 *v* 281·2 days; mean difference 7·3 days, 95% confidence interval 3·1 to 11·5; p<0·002) and prescription of vitamin K to the child in the first week of life (19% of patients *v* 5% of controls, p=0·016).**

***Conclusions*—The findings give no support to theories that factors predicting perinatal mortality contribute significantly to causation of schizophrenic illness. Further investigation of decreased gestation length in relation to affective disorder is required.**

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## Introduction

Schizophrenia and manic-depressive psychosis (the "functional" psychoses), the major causes of severe psychiatric morbidity in adult life, have a worldwide distribution with lifetime prevalences, where these have been assessed, of 2-3%.[1-3] The role of genetic factors has been established by twin[4-6] and adoption studies.[7,8] It is often assumed there are also environmental contributions, but their nature is obscure.

One suggestion is that brain damage occurring at or around the time of birth in some way contributes to the later onset of psychosis.[9-11] The time interval (on average over 20 years) means that there are substantial practical difficulties in examining an association between perinatal trauma and the later development of psychosis. There have been two types of study: the first (retrospective) has identified a sample of schizophrenic patients and obtained information about their birth histories; the second (high risk) studied the confinements of mothers with schizophrenia, whose children are at high risk of going on to develop schizophrenia.

Retrospective studies (reviewed in table I)[9-20] may include carefully selected and documented schizophrenic patients, but it is often difficult to obtain birth histories of good quality. Table I shows that in seven of 13 studies data were collected in whole or in part by asking the mother to recollect quite specific details after the patient had become ill (that is, after the passage of 20 or more years). Clearly neither she nor the person recording the history would have been blind to the fact that the patient had become mentally ill, and it cannot be assumed that this knowledge did not affect the information given or recorded. A more appropriate method is to make use of birth histories recorded before the onset of illness—that is, obtained through reference to obstetric records. Such records are often unsystematic, and they have been shown to be prone to error.[21] The weakness of retrospective studies has been discussed by Lewis, who stated that the link between schizophrenia and a history of presumed obstetric complications "hides a wide discrepancy in methodology between studies. Paradoxically, the main similarity between the studies is their collective weakness: the use of retrospective assessment of obstetric histories even if assessed blindly."[22]

High risk studies[23-28] may acquire birth histories of a high quality, but accounts of the mental states of the offspring in the period of maximum risk for schizophrenia in adult life are usually not available.

The separate limitations of retrospective and high risk studies can be overcome only by a systematic collection of birth histories of a large cohort in which a

TABLE I—*Retrospective studies of perinatal and birth complications*

| Study | Sample | Source | Results |
|---|---|---|---|
| Dalen (1965)[12] | 27 With manic psychotics; no controls | Maternity records or reports from a relative | Complications increased in familial *v* non-familial cases ($p=0·25$) |
| Lane and Albee (1966)[13] | 52 Schizophrenics; 115 siblings | Birth certificate including birth weight | Schizophrenics weighed 7 lbs (3200 g), siblings 7·5 lbs (3400 g) ($p<0·01$) |
| Pollack *et al* (1966)[14] | 33 Schizophrenics *v* siblings | Questionnaire completed by mother | No difference between groups |
| Pollack *et al* (1968)[15] | 51 Schizophrenics; no controls | Maternal reports | Early onset schizophrenics had more complications ($p<0·01$) |
| Woerner *et al* (1973)[9] | 46 Schizophrenics *v* siblings; 67 personality disorders *v* siblings | Hospital records; mothers' reports | Only schizophrenics had more risk of complications ($p<0·02$) |
| McNeil and Kaij (1978)[10] | 56 Process schizophrenics; 46 with schizophrenia-like psychoses | Hospital records | Risk of complications increased in process schizophrenics but not in those with schizophrenia-like psychoses ($p=0·04$) |
| Jacobsen and Kinney (1980)[16] | 35 Adopted schizophrenics *v* with normals | Midwife records | Frequency, but not severity, of complications was raised in adopted schizophrenics ($p<0·10$) |
| | 31 Non-adopted schizophrenics *v* normals | | Severity increased only in non-adopted schizophrenics ($p<0·05$) |
| Parnas *et al* (1982)[19 23] | 13 Schizophrenics; 29 borderline schizophrenics; 55 with no mental illness | Midwife records | Schizophrenics had more complications than borderline ($p<0·009$) but not more than controls ($p>0·05$) |
| Lewis and Murray (1987)[11] | 207 Schizophrenics; 748 other psychiatric patients | Questionnaire completed by relative | Schizophrenics had more complications ($p<0·001$) |
| Owen *et al* (1988)[17] | 61 Schizophrenics | Reports in psychiatric case notes and computed tomography scan data | Some structural changes on scan commoner in patients with obstetric complications |
| Olsen *et al* (1989)[18] | Schizophrenics, patients with schizo-affective psychosis; bipolar depressives; controls | Parental reports | No difference between groups |
| Reddy *et al* (1989)[19] | Schizophrenics and patients with bipolar affective disorder | Not stated | More complications in schizophrenics |
| Eagles *et al* (1989)[20] | 36 DSM-III schizophrenics; 36 sibling controls | Maternity records | Frequency ($p<0·002$) and severity ($p<0·025$) of complications greater in schizophrenics |

proportion develops psychosis in adulthood. The study reported here used the well documented birth histories from the British perinatal mortality survey[28] and screened all psychiatric admissions to hospitals in England, Scotland, and Wales during 1974-86 for patients who were a part of this birth cohort.

## Method

### SOURCES OF DATA

The study population comprised about 16 980 births registered during the week 3-9 March 1958, representing 98% of all births in England, Scotland, and Wales in that week (the British perinatal mortality survey[28]). At that time the stillbirth and neonatal mortality rate was 35 per 1000 births; the main purpose of the perinatal mortality survey was to examine social and obstetric factors associated with such deaths. In 1974 the Mental Health Enquiry was set up, and it recorded data on all psychiatric admissions between 1974 and 1986. From this source the records of every patient with a date of birth between 3 March and 9 March 1958 (and thus every member of the study cohort) who had been admitted to psychiatric care between 1974 and 1986 could be identified.

### DATA COLLECTION

Approval was sought for the disclosure of Mental Health Enquiry or other records for all admissions born 3 to 9 March 1958 from each of the 15 regional health authorities, two special health authorities, and four special hospitals. With permission granted, the regional statistician screened the tapes of the Mental Health Enquiry and identified the patients. Consent was sought from consultants in charge to send the notes to the investigators. In all, 698 admissions were notified, but these included many readmissions and in total represented 252 patients. In four cases the consultant refused permission for inclusion in the study, and in 13 cases the notes were irretrievably lost. This meant that 235 sets of case notes were sent to Northwick Park. The syndrome checklist of the present state examination[29] was applied (by ECJ), and a survey form recording histories of previous admissions, medication, education, and employment as well as family history, social decline, and police contact was completed (by DJD). Table II shows the nature of the sample finally obtained in terms of schizophrenia and affective psychosis classifications derived from the present state examination (PSE) by application of the CATEGO program.

In fact the numbers reported here are surprisingly representative of a disease with a lifetime prevalence of 0·8% to 1%. Estimates for proportion of lifetime risk used up by age 27 (derived from data from England and Wales 1952-60[30]) are 0·40 for men and 0·32 for women, giving an average of 0·36. Data provided by the Social Statistics Unit for the national child development study shows that by age 23 the expected number in the cohort was 16 457 (if immigrants are included and emigrants and deaths excluded). Extrapolating this would reduce the cohort to approximately 16 000 by age 27. Therefore (assuming a lifetime prevalence of either 0·8% or 1%) the expected number of schizophrenic individuals is $(0·008 \text{ to } 0·01)\times 0·36\times 16000 = 46·1$ to 57·6. These values compare with the obtained values in table II of 49 for the "narrow" diagnosis of schizophrenia and 79 for the broad category of schizophrenia using PSE-CATEGO diagnosis. It should be noted that the figures of 0·45 for men and 0·27 for women for proportion of risk used by age 30 from data for England and Wales between 1970 and 1981 reported by Der *et al*[31] would give closely similar expectations.

### METHOD OF ANALYSIS

We assumed (as did retrospective studies) that the nature of the prenatal and perinatal events relevant to the later development of schizophrenia was the same as those responsible for stillbirth and neonatal death. Logistic regression analysis was used to derive the probability of stillbirth or neonatal death for each

TABLE II—*Cases recorded by Mental Health Enquiry with dates of birth 3-9 March 1958*

| | Broad category of schizophrenia | | | Affective psychosis | | | | |
|---|---|---|---|---|---|---|---|---|
| | Narrow schizophrenia | Paranoid psychosis | Other psychosis | Mania | Depressive psychosis | Retarded depression | Neurosis | No abnormality |
| CATEGO diagnosis[32] | S+/S? | P+/P? | O+/O? | M+/M? | D+/D? | R+/R? | N+/N?/X | NO |
| Total | 49 | 10 | 20 | 15 | 9 | 20 | 93 | 20 |
| No born abroad | 8 | 3 | 4 | 3 | 2 | 3 | 3 | |
| Otherwise unusable | 6 | 0 | 1 | 2 | 0 | 2 | 14 | |
| No included | 35 | 7 | 15 | 10 | 7 | 15 | 76 | |

TABLE III—*Estimated probability of stillbirth or neonatal death in groups diagnosed as psychotic*

| | Average probability of stillbirth or neonatal death | Difference between means* (95% confidence interval) | p Value |
|---|---|---|---|
| Controls (n=12 946) | 0·0098 | | |
| Diagnostic category based on PSE-CATEGO:† | | | |
| Narrow schizophrenia (n=35) | 0·0111 | 0·0012 (−0·00142 to 0·005) | 0·40 |
| Broad schizophrenia (n=57) | 0·0112 | 0·0014 (−0·0008 to 0·004) | 0·24 |
| Affective psychosis (n=32) | 0·0125 | 0·0027 (−0·0005 to 0·007) | 0·105 |
| Neurosis (n=75) | 0·0103 | 0·0005 (−0·001 to 0·0027) | 0·60 |
| Diagnosis from case notes: | | | |
| Schizophrenia (n=37) | 0·0121 | 0·0022 (−0·0006 to 0·006) | 0·14 |
| Affective psychosis (n=31) | 0·0106 | 0·0008 (−0·0007 to 0·0026) | 0·60 |

Estimated average probability (p) was derived from the dependent variable (log odds) according to the formula log odds $=\ln\frac{p}{1-p}$.

*$\bar{X}_{Patient}-\bar{X}_{Control}$.

†Present state examination.

cohort member. This will be referred to as "the risk." The method of logistic regression establishes those variables that uniquely explain some of the risk and appropriate weights for these variables.

All subjects from the perinatal mortality survey were recorded as being either alive or dead after the first week of life. Given these data the logistic regression program was used to formulate the optimal equation for predicting whether a subject is dead or alive. The equation is given in the appendix. Certain variables were rejected, either because they are variables of insignificant risk or because their contribution to risk has been covered by others already included in the equation. The advantages of this method over summing the occurrence of selected high risk variables are that only those variables that increased the risk within the cohort itself were used; high risk variables that covary with other risk variables could be excluded (see table A2 of the appendix); and those variables that carry a greater degree of risk were given due weighting.

The equation that results can then be used to calculate the risk to each cohort member. In this way an average risk can be obtained for a particular group within the cohort (for example, schizophrenics), which can then be compared with the control group (that is, the well members of the cohort) with a *t* test.

## Results

Table III shows that the risk is not significantly greater for any of the diagnostic groups. This form of analysis treats all cases within the patient group equally. In this way an extreme subgroup may be missed; the small increase in relative risk in psychiatric groups previously reported might result from the presence of a subgroup with an exceptionally high risk. To assess this possibility the 30% of patients at the greatest risk in each patient group were selected and the risk value (the probability of stillbirth or neonatal death) that distinguished this subgroup from the rest of their group was used as a cut off point. This value could then be used to find the proportion of the well control group that was at similarly high risk. From this a 2×2 table could be made of high *v* low risk against patient *v* control and a $\chi^2$ test used to test for an increased risk in the patient group (odds ratio). Table IV presents the data for this analysis.

TABLE IV—*Odds ratio of stillbirth or neonatal death in different diagnostic groups*

| Diagnostic group | Odds ratio (95% confidence interval) | $\chi^2$ | p Value |
|---|---|---|---|
| *Present state examination with CATEGO program* | | | |
| Narrow schizophrenia | 1·41 (0·66 to 3·02) | 0·445 | 0·505 |
| Broad category of schizophrenia | 1·50 (0·86 to 2·63) | 1·61 | 0·2 |
| Affective psychosis | 2·43 (1·17 to 5·05) | 4·93 | 0·03 |
| Neurosis | 1·00 (0·63 to 1·92) | 0 | 1·0 |
| *Case notes* | | | |
| Schizophrenia | 1·77 (0·9 to 3·5) | 2·18 | 0·14 |
| Affective psychosis | 1·55 (0·73 to 3·3) | 0·89 | 0·35 |

TABLE V—*Family histories of psychiatric illness in relatives of patients with narrowly defined schizophrenia and affective psychosis (diagnosis according to present state examination categories)*

| | Narrowly defined schizophrenia (n=49) | | Affective psychosis (n=44) | |
|---|---|---|---|---|
| Information from case notes | No of patients with first degree relatives affected | No of patients with any relatives affected | No of patients with first degree relatives affected | No of patients with any relatives affected |
| No family history available | 16 | 13 | 24 | 20 |
| Inadequate information given | 10 | 10 | 9 | 9 |
| Unspecified mental illness | 14 | 14 | 5 | 8 |
| Affective illness | 3 | 3 | 6 | 7 |
| Schizophrenia | 5 | 6 | | |
| Mental handicap | 1 | 3 | | |

The results in table IV indicate that there is no significant increase in risk for schizophrenic patients, regardless of the diagnostic scheme adopted. It may be argued that because the odds ratio for the schizophrenic group is consistently above unity (although the groups are of course overlapping) a larger sample size might have revealed a significant effect. Even if this were the case, the association might still be a consequence of something about the mother (for example, she has a diagnosis of schizophrenia) rather than obstetric complications.

In the PSE-CATEGO affective psychotic group the odds ratio was 2·43 (p=0·03). This increased risk remained significant (p=0·04) with a cut off set at 40% but was less clear (p=0·10) if the cut off point was set at 25%.

The analysis of the data so far utilised an equation that optimally predicts stillbirth or neonatal death. However, the relation between the high risk variables and adult psychosis might well be different. For example, an equation that would predict intracranial haemorrhage or some other cerebral insult might be preferable. No such model at present is available, but in the absence of a model an exploratory analysis was conducted in an attempt to devise an equation that would predict each of the diagnoses from the list of variables significantly and independently associated with stillbirth or infant mortality. The list includes maternal variables—parity, all bleeding in pregnancy or before delivery, maternal weight before pregnancy, duration of gestation, toxaemia, duration of second stage of labour, time between rupture of membranes and delivery, induction of labour, method of delivery, inhalation analgesia, influenza, gastrointestinal disorder, hydramnios, and falls and accidents; and infant variables—birth weight and administration of Coramine (nikethamide), sedatives, antagonists, Synkavit (menadiol sodium diphosphate), penicillin, or other drugs.

Each individual in the cohort was designated as either a well control or a patient in terms of the PSE-CATEGO classification (table II). Using logistic regression, the variables significantly associated with membership of each diagnosis group separately were determined. "Narrow" schizophrenia was significantly associated with maternal weight (8·6 stones (54·6 kg) (SD 2·86 stones (18·2 kg)) *v* 9·0 stones (57·2 kg) (SD 2·94 stones (18·7 kg)) in cohort; $\chi^2=7·7$, df=4, p=0·10) and "other" drugs (non-routine drugs were given to two patients in the first week of life: $\chi^2=3·3$, df=1, p=0·07 in comparison with cohort). The broad category of schizophrenia was significantly associated with maternal weight (8·6 stones (54·6 kg) *v* 9·0 stones (57·2 kg) in cohort, $\chi^2=13·5$, df=4, p=0·01). Affective psychosis was significantly associated with length of gestation (mean 273·9 (17·8) days *v* 281·2 (12·1) days in cohort, $\chi^2=9·2$, df=1, p<0·002) and prescription of Synkavit, a fat soluble form of vitamin K which was given to the baby when there was a risk of haemorrhage at the time of birth; it was given to six (19%) patients with affective psychosis and 816 (5%) controls ($\chi^2=5·8$,

df=1, p=0·016). Bleeding during the pregnancy was commoner in subjects with neurotic disorder than in controls ($\chi^2$=4·9, df=2, p=0·09).

## Discussion

The findings presented here offer little support for the suggestion that some schizophrenic illnesses are a result of birth trauma or a high risk pregnancy. When either a narrow or a broad diagnosis based on the present state examination is adopted there is no significant difference between schizophrenic patients and normal controls in risk of early death from exposure to high risk variables. There was also no support for the notion that there was a small group of schizophrenic patients who had an exceptionally risky gestation or birth. However, an increased prevalence of cases with a high risk was found (in the subgroup analysis) in the group of patients with affective psychoses. The large group of neurotic subjects did not differ from the control groups.

The strength of these findings should be considered in the light of what is known about these data sets. Reliability can be assessed from the quality of the perinatal mortality survey and of the psychiatric diagnoses obtained from histories in the case notes. The high quality of the survey data is well supported by other studies with replicated findings that have used this source of data over the last 20 or so years.[32 33] The quality of the PSE-CATEGO diagnosis is less certain because it depends on case notes of variable styles. Examination of family histories obtained from case notes before the syndrome checklist was applied offers some support for the classification. Table V shows family histories of the patients narrowly defined as schizophrenic and of those with affective illness (n=44). Of the schizophrenic patients, five of 39 (12·8%) for whom adequate information was available had a first degree relative with schizophrenia and three (7·7%) a first degree relative with affective illness. The patients with affective psychosis had no relatives with schizophrenia but six out of 35 with documentation (17·1%) had first degree relatives with affective illness.

The exploratory analysis isolated specific risk variables associated with each diagnostic category. Two variables were associated with narrowly defined schizophrenia. These were maternal weight (mothers of schizophrenic patients tended to weigh less than mothers of normal subjects) and "other drugs" given to the baby. The drugs concerned were antibiotics given to two babies (who were in fact the children of schizophrenic mothers) for skin sepsis and septic ear. The maternal weight effect does not seem to be a spurious association; the significance holds up for a narrow (p=0·052) and a broad definition (p=0·01) of schizophrenia. In the group of neurotic patients the only variable that approached significance was bleeding during pregnancy.

The only group in which a significant relation in the main analysis was found was that of affective psychosis. The variables of most significance were duration of gestation (shorter by some 7·3 days in subjects with affective disorder) and prescription of Synkavit to the baby. The reasons for giving Synkavit were forceps delivery, premature delivery, moulding of the head, and routine (one case each), and there was no reason given in two cases. None of these babies were recorded as preterm (<259 days' gestation).

TABLE A1—*Independent variables included in the model and their weights*

| Variable | Reference category | Contrast categories | Coefficient | SE | Coefficient SE |
|---|---|---|---|---|---|
| Constant | | | 34·24 | 2·427 | 14·11 |
| Parity | First | Second | −0·225 | 0·123 | −1·83 |
| | | Third | −0·013 | 0·125 | −0·10 |
| | | ≥Fourth | 0·050 | 0·174 | 0·29 |
| All bleeding | None | >28 | 0·912 | 0·207 | 4·416 |
| | | <28 | −0·606 | 0·292 | −2·07 |
| Birth weight (grams) | <2500 | 2501-3000 | −0·291 | 0·15 | −1·94 |
| | | 3001-4000 | −0·147 | 0·108 | −1·37 |
| | | ≥4001 | 0·158 | 0·151 | 1·05 |
| Maternal weight (stones) | <8 | 8 to <9 | −0·255 | 0·122 | −2·1 |
| | | 9 to <10 | −0·120 | 0·121 | −0·998 |
| | | 10 to <11 | −0·087 | 0·148 | −0·589 |
| | | ≥11 | 0·296 | 0·142 | 2·08 |
| Gestation (months) | Continuous | | −0·135 | 0·009 | −14·16 |
| Toxaemia | Normal | Abnormal | 0·402 | 0·091 | 4·43 |
| Duration of second stage of labour (minutes) | None | <60 | 0·892 | 0·169 | 5·29 |
| | | 60-120 | 0·177 | 0·203 | 0·873 |
| | | >120 | 0·058 | 0·238 | 0·244 |
| Duration membranes ruptured (hours) | None | <24 | −0·201 | 0·199 | −1·01 |
| | | >24 | 0·182 | 0·204 | 0·89 |
| Labour induced | No | Yes | 0·164 | 0·084 | 1·96 |
| Method of delivery | Normal | Complex | 0·731 | 0·089 | 8·24 |
| Inhalation analgesia | Yes | No | 0·25 | 0·076 | 3·29 |
| Influenza during pregnancy | No | Yes | 0·25 | 0·084 | 2·94 |
| Gastrointestinal disorders during pregnancy | No | Yes | 0·71 | 0·175 | 4·07 |
| Hydramnios | No | Yes | 1·29 | 0·17 | 7·56 |
| Falls and accidents | No | Yes | 0·653 | 0·30 | 2·175 |
| Prescription of drugs to baby: | | | | | |
| Coramine | No | Yes | 0·83 | 0·17 | 4·99 |
| Sedatives | No | Yes | 0·447 | 0·22 | 2·03 |
| Antagonists | No | Yes | −1·306 | 0·65 | −2·02 |
| Synkavit | No | Yes | −0·241 | 0·122 | −1·97 |
| Penicillin | No | Yes | 0·723 | 0·142 | 5·1 |
| Other drugs | No | Yes | 0·517 | 0·154 | 3·35 |

## Conclusions

The intention of this study was to take advantage of the perinatal mortality survey sample so that technical difficulties could be overcome. These difficulties had led Mednick to state that a prospective birth cohort study of perhaps 10 000 consecutive deliveries in a well defined area and time was clearly the only satisfactory approach to comparing high risk and low risk.[34] Although our sample exceeded these requirements, our result is not as definitive as we had hoped. On their own the findings in the schizophrenic patients can be taken as providing evidence against a role for early brain injury as an aetiological factor in schizophrenia. The findings on affective patients raise a number of questions. We cannot know what a standardised interview (rather than case note review) might have revealed or what diagnostic picture these cases of affective illness of early onset may finally show. Perhaps affective illness is truly associated with reduced mean gestation time or other perinatal anomaly; possibly some of the affective patients will turn out to have schizophrenia later. The results do, however, show that if there is an effect of perinatal trauma on the later development of psychotic illness it is weak, difficult to define, and apparently absent in typical schizophrenia of early onset.

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## Appendix

In the logistic regression model of the form:

$$y=\delta+\beta_1X_1+\beta_2X_2\ldots$$

y is the log odds of stillbirth and neonatal mortality; $\delta$ is the constant; $\beta_{1\ldots n}$ the coefficients of the independent variables $X_{1\ldots n}$. $X_1$ and $X_2$ are unrelated and hence separate variables such as the interval variable "gestation" (days) or the categorical variable "toxaemia" (present or absent); or $X_1$ and $X_2$ can be "design variables" for a categorical variable with three categories. For such categorical variables with k categories, k-1 design variables are generated by using the BMDP logistic regression program.

Table A1 gives a complete list of the independent variables

TABLE A2—*Independent variables significantly associated with still-birth or neonatal death excluded from model because of covariance*

| |
|---|
| Height of mother |
| Number of previous premature births |
| Haemoglobin concentration |
| Duration of first stage of labour |
| Maternal age |
| Fetal distress (cord/prolapse/ meconium/fetal heart) |
| Social and economic status |
| Fever/tonsillitis/laryngitis |
| Urinary tract infection |
| Type of resuscitation |
| Prescription of drugs to baby |
| Lobelline |
| Streptomycin |

included in the model that optimally estimates the log odds of stillbirth or neonatal death in the whole British perinatal mortality survey (1958) cohort. This list of variables includes the names of categorical variables together with the design variables that are generated (for example, "parity" is a categorical variable with four categories and hence three design variables labelled as "1", "2", "3"), as well as their coefficients. Categorical variables with two categories have been listed in table A2 as having only a single entry in the model. No interactions were included in the model owing to the computational problems that these would have generated for little improvement of the model.


1 Hare EH. Epidemiology of schizophrenia and affective psychoses. *Br Med Bull* 1987;**43**:514-30.
2 Eaton WW. Epidemiology of schizophrenia. *Epidemiol Rev* 1985;**7**:105-26.
3 Weissman MM, Boyd JH. The epidemiology of affective disorders. In: Post RM, Ballenger JC, eds. *Neurobiology of mood disorders*. Baltimore: Williams and Wilkins, 1984:60-75.
4 Gottesman II, Shields J. Schizophrenia and genetics: a twin vantage point. New York: Academic, 1972.
5 Kendler KS, Robinette CD. Schizophrenia in the NAS-NRC twin registry: a 16 year update. *Am J Psychiatry* 1983;**140**:1551-63.
6 Bertelsen A, Harvald B, Hauge M. A Danish twin study of manic-depressive disorders. *Br J Psychiatry* 1977;**130**:330-51.
7 Kety SS. Mental illness in the biological and adoptive relatives of schizophrenic adoptees: findings relevant to genetic and environmental factors in etiology. *Am J Psychiatry* 1983;**140**:720-7.
8 Mendelwicz J, Rainer JD. Adoption study supporting genetic transmission in manic-depressive illness. *Nature* 1977;**268**:327-9.
9 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.
10 McNeil TF, Kaij L. Obstetric factors in the development of schizophrenia: complications in the births of preschizophrenics and in reproduction by schizophrenic patients. In: Wynne LC, Cromwell RL, Matthysse S, eds. *The nature of schizophrenia*. New York: Wiley, 1978:401-29.
11 Lewis SW, Murray RM. Obstetric complications, neurodevelopmental deviance and risk of schizophrenia. *J Psychiat Research* 1987;**21**:413-22.
12 Dalen P. Family history, the electroencephalogram, and perinatal factors in manic conditions. *Acta Psychiatr Scand* 1965;**41**:527-63.
13 Lane EA, Albee GW. Comparative birth weights of schizophrenics and their siblings. *J Psychology* 1966;**64**:227-31.
14 Pollack M, Woerner M, Goodman W, Greenberg I. Childhood development patterns of hospitalised adult schizophrenic and non-schizophrenic patients and their siblings. *Am J Orthopsychiatry* 1966;**36**:510-97.
15 Pollack M, Levenstein S, Klein DF. A three year post-hospital follow-up of adolescent and adult schizophrenics. *Am J Orthopsychiatry* 1968;**38**:94-109.
16 Jacobsen B, Kinney DK. Perinatal complications in adopted and non-adopted schizophrenics and their controls: preliminary results. *Acta Psychiatr Scand* 1980;**62**(suppl 285):337-46.
17 Owen MJ, Lewis SW, Murray RM. Obstetric complications and schizophrenia: a computer tomographic study. *Psychol Med* 1988;**18**:331-9.
18 Olson SC, Nasrallah HA, Coffman JA, Schwarzkopf SB. Perinatal complications and premorbid function in psychosis. *Biol Psychiatry* 1989;**25**: 93-106A.
19 Reddy R, Mukherjee S, Schnur D. Pregnancy and birth complications and premorbid functioning in schizophrenic and bipolar patients. *Biol Psychiatry* 1989;**25**:93A.
20 Eagles JM, Gibson I, Bremner MH, Clunie F, Ebmeier KP, Smith NC. Obstetric complications in DSM-III schizophrenics and their siblings. *Lancet* 1990;**336**:1139-41.
21 Joffe M, Grisso JA. Comparison of antenatal hospital records with retrospective interviewing. *J Biol Science* 1985;**17**:113-9.
22 Lewis SW. Congenital risk factors for schizophrenia. *Psychol Med* 1989;**19**: 5-13.
23 Parnas J, Schulsinger F, Teasdale TW, Schulsinger H, Feldman PM, Mednick SA. Perinatal complications and clinical outcome within the schizophrenia spectrum. *Br J Psychiatry* 1982;**140**:416-20.
24 Wrede G, Mednick SA, Huttunen MO, Nilsson CG. Pregnancy and delivery complications in the births of an unselected series of Finnish children with schizophrenic mothers. *Acta Psychiatr Scand* 1980;**62**:369-81.
25 Mednick SA, Mura E, Schulsinger F, Mednick B. Perinatal conditions and infant development in children with schizophrenic parents. *Soc Biol* 1971;**18**:103-13.
26 Mirdal GKM, Mednick SA, Schulsinger F, Fuchs F. Perinatal complications in the children of schizophrenic mothers. *Acta Psychiatr Scand* 1974;**50**: 553-68.
27 McNeil TF, Kaij L. Obstetric complications and physical size of offspring of schizophrenic, schizophrenic-like, and control mothers. *Br J Psychiatry* 1973;**123**:341-8.
28 Shepherd PM. *The national child development study. An introduction to the background to the study and methods of data collection*. London: Social Statistics Research Unit, City University, 1985. (Working paper No 1.)
29 Wing JK, Cooper JE, Sartorius N. *The measurement and classification of psychiatric symptoms: an instruction manual for the PSE and CATEGO program*. London: Cambridge University Press, 1974.
30 Gottesman II, Shields J. *Schizophrenia: the epigenetic puzzle*. Cambridge University Press, 1982.
31 Der G, Gupta S, Murray RM. Is schizophrenia disappearing? *Lancet* 1990;**335**:513-6.
32 Butler N, Alberman ED. *Perinatal problems*. Edinburgh: Livingston, 1969.
33 Butler N, Goldstein H, Ross EM. Cigarette smoking in pregnancy: influence on birth and perinatal mortality. *BMJ* 1971;i:127-30.
34 Mednick SA. Berkson's fallacy and high risk research. In: Wynne LC, Cromwell RC, Matthysse S, eds. *The nature of schizophrenia*. New York: Wiley, 1978:442-52.


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# Infant feeding practices and ulcerative colitis in childhood


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Accumulating evidence indicates that events early in life, including infant feeding practices, can have long term effects on health and disease.[1] We recently showed that the absence of breast feeding and early diarrhoea are independent risk factors associated with development of Crohn's disease later in childhood.[2] To determine if similar risk factors were linked to the development of ulcerative colitis we carried out an epidemiological case-control study.

## Patients, methods, and results

A questionnaire was sent to 118 families with at least one child with ulcerative colitis diagnosed by endoscopic and histological criteria. Data obtained included age, sex, premature delivery, diarrhoeal illnesses during the first six months of life, type of feeding used from birth, duration of exclusive breast feeding, total duration of breast feeding, and the age at which solids were introduced. As in our previous study breast feeding referred to any provision of human milk and exclusive breast feeding indicated the absence of formula milk and solids.[2] Unaffected siblings served as controls to reduce the variation of genetic factors and confounding variables. Potential risk factors were analysed within families by using the conditional logistic regression model.[2]

Of the 118 families, 108 (92%) completed the questionnaires. This included 17 children without unaffected siblings, leaving 93 affected children and 138 siblings available for analysis. The mean (14·2 (SD 4·1) years) and median (15·0 years) ages for children with ulcerative colitis were comparable with those of the group of unaffected siblings (15·7 (6·5); 15·8).

Multivariate analysis showed that children with ulcerative colitis were more likely to have had diarrhoeal diseases during infancy (relative risk 3·2 (95% confidence limits 1·15 to 8·75), p=0·03) compared with their unaffected siblings. Female sex was also an independent risk factor (2·3 (1·23 to 4·35), p=0·01). In contrast to our previous findings for childhood Crohn's disease,[2] absence of breast feeding was not significantly different among children with ulcerative colitis (1·7 (0·77 to 3·65), p=0·19). Duration of exclusive breast feeding, total length of breast feeding, and age at introduction of solid foods did not differ between children with ulcerative colitis and their siblings. Birth order and the incidence of premature delivery were comparable in the two groups.

## Comment

In this study the lack of breast feeding and presence of formula feeding were not identified as risk factors for the development of childhood ulcerative colitis. This finding agrees with the results of one study[3] but contrasts with two studies in adults with ulcerative colitis[4,5] and our previous observation of paediatric Crohn's disease.[2] Our study design reduces the possibility of recall bias because parents completed the questionnaires for both cases and controls. In addition,