Exposure to obstetric complications and subsequent development of bipolar disorder

Systematic review

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Background Research has suggested an association between obstetric complications and bipolar disorder. However, no quantitative evaluation has been made of the pooled data from existing studies.

Aims To systematically review studies comparing exposure to obstetric complications in cases of bipolar disorder vs. non-psychiatric controls, and in cases of bipolar disorder vs. cases of other mental disorders.

Method Publications were identified by computer searches of seven databases, by hand searches of reference lists and from raw data received from researchers.

Results Forty-six studies were identified, of which 22 met the inclusion criteria. The pooled odds ratio for exposure to obstetric complications and subsequent development of bipolar disorder was 1.01 (95% CI 0.76–1.35) compared with healthy controls, 1.13 (95% CI 0.64–1.99) compared with cases of unipolar disorder and 0.61 (95% CI 0.39–0.95) compared with those who developed schizophrenia.

Conclusions There is no robust evidence that exposure to obstetric complications increases the risk of developing bipolar disorder. However, the range of events regarded as obstetric complications and methodological inadequacies make definitive conclusions difficult.

Declaration of interest None.

Extensive research has shown that genetic factors have a role in the development of bipolar disorder. However, concordance rates of less than 100% in monozygotic twins (e.g. Bertelsen et al., 1977) imply that environmental factors may also be important in the aetiology of the disorder. Some researchers suggest that, rather like the neurodevelopmental hypothesis of schizophrenia (Murray & Lewis, 1986), exposure to obstetric complications increases vulnerability to bipolar disorder and that such exposure may account for some of the brain abnormalities reported in neuro-imaging studies of this disorder (Dalen, 1965; Pearlson et al., 1985; Nasrallah, 1991). Although earlier review articles provide tentative support for such conclusions (e.g. Buka & Fan, 1999), many of the purported studies of obstetric complications in bipolar disorder included samples of poorly defined affective disorders, selected populations with affective psychoses, or mixed samples of cases combined with varying proportions of cases of psychotic and/or non-psychotic unipolar disorders. Therefore, the empirical evidence for and against the hypothesis that exposure to obstetric complications increases the risk of bipolar disorder has not been fully elucidated.

We aimed, first, to systematically review studies comparing the obstetric histories of people with bipolar disorder and non-psychiatric control groups, and second, to systematically review studies comparing the obstetric histories of people with bipolar disorder and groups of people with other mental disorders. This quantitative review allowed the calculation of the pooled odds ratios for exposure to obstetric complications on the subsequent development of bipolar disorder.

METHOD

Search method

Definition of obstetric complications

Obstetric complications were defined according to McNeil (1987) as:

Inclusion criteria

All studies that stated the method used for measuring obstetric complications and for diagnosis of bipolar disorder (or other mental disorders) were eligible for inclusion in the review.

Exclusion criteria

The three exclusion criteria were:

(a) insufficient information to allow identification of a distinct subgroup of cases of bipolar disorder with obstetric complications that met the operational criteria defined;

(b) insufficient information to allow obstetric complications to be distinguished from other early developmental abnormalities or adverse events;

(c) review papers with no new empirical data.

Search strategy

The computerised databases searched were: Medline (1966 to January 2004), PreMedline (to January 2004), PsychINFO (1967 to January 2004), Cochrane Library (up to October 2003), Best Evidence (1991 to September 2003) and EMBASE (1980 to January 2004). The key words searched were [BIPOLAR AFFECTIVE DISORDER] or [MANIC-DEPRESSION] and [OBSTETRIC COMPLICATIONS]. The Thesaurus for Psychological Index Terms identified all terms mapping onto the key words, and an additional search was carried out using each of these terms (see Appendix 1 to the online version of this paper). All online abstracts were reviewed and relevant reports were obtained. Citations in relevant publications were also checked.

A total of 46 studies were identified, of which 45 were published papers or abstracts. Thirty-five were identified from electronic searches (Dalen, 1965; Waters et al., 1982, 1983; Pearlson et al., 1985; Wilcox, 1986; Done et al., 1991; Kinney et al., 1993, 1998; Takei et al., 1993; Verdoux & Bourgeois, 1993a,b; Cornelius et al., 1994; Gureje et al., 1994; Rifkin et al., 1994; Brown et al., 1995, 2000; Sacker et al., 1995; Cannon et al., 1996, 1997, 2002a; Vocius et al., 1996; Machon et al., 1997; Morgan et al., 1997; Stober et al., 1997; Marcelis et al., 1998; Buka & Fan, 1999; Gunduz et al., 2003).

A further 10 studies were identified following a manual search of reference lists and conference abstracts (Taylor & Abrams, 1981; Lewis & Murray, 1987; Schwarzkopf et al, 1989; Buka et al, 1993; Guth et al, 1993; Byrne et al, 1996; Sigurdsson et al, 1999; Zornberg et al, 2000; Ogendahl et al, 2002; Wals et al, 2003).

Five data-sets that met our inclusion criteria for ascertainment of obstetric complications and caseness were received from researchers in the field. Dr S. El-Badri of Hamilton, New Zealand, provided data and a draft of a paper ‘Family history, obstetric complications and age of onset in bipolar patients’ based on findings reported in his MD thesis ‘Neurobiological changes in bipolar affective disorder’ (University of Newcastle upon Tyne, UK) (El-Badri, personal communication, 1999). Dr H. Gunduz of Hillside Hospital, New York, USA, provided data that supplemented the research published as Gunduz et al (1999); this is referenced throughout the review as ‘Gunduz et al, updated’. Dr R. Murray and Dr M. Cannon of the Institute of Psychiatry, London, UK, provided an updated version of the database from the Camberwell Collaborative Psychosis Study (CCPS). Three publications report earlier findings from that project (Cannon et al, 1997; Marcelis et al, 1998; Rifkin et al, 1994), so the new data file is referred to as ‘CCPS, updated’ throughout this paper. Dr Cannon also provided additional data for the Dunedin cohort (Cannon et al, 2002a), and Dr M. Wals of the Department of Child/Adolescent Psychiatry, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands, provided additional data to supplement that published from the Dutch study of 140 offspring of parents with bipolar disorder (Wals et al, 2003); these studies are referred to in this review as ‘Cannon et al, updated’ and ‘Wals et al, updated’ respectively.

Twenty-four publications were excluded from the systematic review. Seventeen papers were excluded because distinct groups of participants with bipolar disorder and obstetric complications could not be identified (in 11 papers bipolar disorder was included in a category termed ‘broad affective disorders’). Three papers (Rifkin et al, 1994; Cannon et al, 1997; Marcelis et al, 1998) from the CCPS were excluded because the findings were superseded by new data from the researchers, as noted above. Two papers (Buka & Fan, 1999; Torrey, 1999) were excluded because they were review articles. The paper of Mortensen et al (2003) was excluded, as information on obstetric complications in this sample was available from the published abstract and poster reported by Ogendahl et al (2002). One paper (Verdoux & Bourgeois, 1993b) was excluded because it was written in French and the data about the sample were available in an English language publication (Verdoux & Bourgeois, 1993a).

A list of the included and excluded studies appears in Appendix 2 to the online version of this paper.

### Data extraction

Reports were initially assessed independently by Y.M. and J.C. The findings were cross-checked and analysed by J.S., and further reviewed by M.C. and R.M. The following methodological factors were recorded in a structured pro forma: reported clinical diagnosis; method of assigning diagnosis (structured clinical questionnaire, interview with psychiatrist, information obtained from medical records); demography (age, gender and ethnicity); family history of bipolar disorder or other mental disorders (and method of ascertainment); source of data about obstetric history (maternal recall, birth records, birth registers); and the assessment scale or tool used to identify and quantify obstetric complications. The scales were categorised as ‘no scale used’; ‘Lewis scale’ (Lewis et al, 1989); ‘Parnas scale’ (Parnas et al, 1982); ‘McNeil–Sjostrom scale’ (McNeil et al, 1994); and Mirdal scale (Mirdal et al, 1974). The reviewers also recorded whether healthy controls had been screened to exclude individuals with a possible or definite DSM–IV diagnosis and whether or not family history of mental disorders was assessed. Differences were noted between cases and controls with respect to gender distribution, age and socio-economic status. Study methodologies were classified as being of high quality (e.g. structured interview for assigning diagnosis and prospective measurement of obstetric complications), of medium quality or of lower quality (case-note information only, or no information on how diagnosis or complications were defined).

For the purposes of the review, studies were grouped into four categories in which the frequency and severity of exposure to obstetric complications were compared in:

- (a) individuals with bipolar disorder and non-psychiatric healthy controls;
- (b) individuals with bipolar disorder and individuals with another mental disorder;
- (c) early-onset as compared with late-onset bipolar disorder; and among cases of bipolar disorder with and without a family history of the disorder;
- (d) birth cohort or prospective longitudinal studies that examined the relative risk of developing bipolar disorder in individuals who did or did not experience prenatal exposure to a specified adverse event (the Dutch ‘hunger winter’, the Greater Helsinki influenza epidemic, and a prospective study of foetal and neonatal complications related to hypoxic ischaemia).

### Statistical analysis

Chi-squared tests of exposure to obstetric complications, in the bipolar disorder group and the comparison group (or, in one study, differences between mean number of complications per individual) were recorded from the papers or calculated from data provided. Where possible, estimates of the odds ratio (OR) or relative risk (RR) and the 95% confidence interval were also recorded or calculated. As information on pairing in matched case–control studies was not available, these data were analysed as unmatched (a more conservative approach). Estimates of effect sizes in individual studies were calculated for exposure to obstetric complications and, when possible, for exposure to complications of different levels of severity. Pooled data were analysed using the Comprehensive Meta-Analysis programme (Biostat, 2000). For the purposes of the meta-analysis, exposure to obstetric complications was dichotomised into ‘exposed’ (definite complications) or ‘unexposed’ (equivocal or no complication reported). Pooled estimates for specific complications (e.g. low birth weight) were calculated if more than two studies reported on that individual complication in a comparable way. The analyses were then repeated using studies providing data that allowed adjustment for potential confounders (e.g. gender of baby, maternal age, socio-economic status) and again after investigating any interaction with study quality; a separate analysis of only those studies regarded as high-quality was also undertaken. Estimates of effect sizes and their variance did
not change significantly in these repeated analyses so they are not reported here, although it should be noted that the analyses of confounders were hampered because relevant data were not reported in many studies.

Given the variability in sample sizes and in quality and quantity of the available data, we calculated random effects estimates for each association. A Mantel-Haenszel random effects model leads to wider 95% confidence intervals than a fixed model as it assumes a different underlying effect for each study. A homogeneity statistic \( Q \) was calculated for each pooled analysis. Funnel plots of study-specific estimates against sample size suggested some gaps in the region of large-scale negative studies (bipolar disorder vs. healthy controls) or positive studies (bipolar disorder vs. unipolar disorders).

### RESULTS

#### Bipolar disorder cases vs. healthy controls


The sample sizes were small and the majority of studies found no difference in rates of complications in cases or controls (Table 1). Only Kinney et al (1993, 1998) reported statistically significant differences between cases and healthy controls (who were the unaffected siblings of the cases), with odds ratios above 10 in each study. In their first study (Kinney et al, 1993), patients with bipolar disorder were significantly \( P=0.003 \) more likely than their healthy siblings to be exposed to a wide range of non-specific obstetric complications, such as maternal anaemia, rubella, prematurity, prolonged duration of labour and neonatal respiratory problems; the complications were also significantly more severe in the patient group (Wilcoxon test, \( P=0.034 \)). In their later study (Kinney et al, 1998), patients with bipolar disorder had significantly greater exposure to prenatal \( P=0.02 \) and perinatal obstetric complications \( P=0.04 \) compared with their healthy siblings. However, the CCPS study (CCPS, updated) reported similar rates of definite obstetric complications in patients with bipolar disorder \( n=49; 24 \) and controls \( n=100; 28 \). Stober et al (1997) found an OR of 0.8 for exposure to obstetric complications in those developing bipolar disorder vs. healthy controls. Likewise, Verdoux & Bourgeois (1993a), El-Badri (1999, personal communication), Gunduz et al (updated) and Brown et al (2000) did not report any significant between-group differences in number of individuals exposed to obstetric complications. As shown in Fig. 1, the pooled OR for the exposure to obstetric complications on subsequent development of bipolar disorder was 1.15 (95% CI 0.62–2.14). The \( Q \) statistic reflected the heterogeneity of the studies as it just failed to reach statistical significance \( (p^2=13.9, \ d.f.=7, P=0.053) \).

Data on exposure to obstetric complications of different levels of severity produced conflicting trends: Verdoux & Bourgeois (1993a) found that the mean number and severity of the complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis and assessment of complications</th>
<th>Obstetric complications</th>
<th>Estimated OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Biological sex</td>
<td>95%</td>
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<tr>
<td></td>
<td></td>
<td>Pregnancy</td>
<td>423 (17%)</td>
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<td></td>
<td></td>
<td>Pregnancy</td>
<td>423 (17%)</td>
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<td></td>
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<td>1.0 (0.22–4.59)</td>
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<tr>
<td>Verdox &amp; Bourgeois (1993a)</td>
<td>Cases: psychiatric assessment;</td>
<td>18/40 (45%)</td>
<td>0.82</td>
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<tr>
<td></td>
<td>OC: Parnas scale</td>
<td>20/40 (50%)</td>
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<td></td>
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<td>0.3–1.97</td>
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<tr>
<td>Stober et al (1997)</td>
<td>Cases: interview with psychiatrist</td>
<td>9/49 (18%)</td>
<td>0.57</td>
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<td></td>
<td>OC: Lewis scale</td>
<td>28/100 (28%)</td>
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<td></td>
<td></td>
<td>0.25–1.3</td>
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<tr>
<td>CCPS (updated)</td>
<td>Cases: interview with psychiatrist</td>
<td>15/30 (50%)</td>
<td>1.28</td>
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<tr>
<td></td>
<td>OC: Lewis scale</td>
<td>12/27 (44%)</td>
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<td>0.44–3.54</td>
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<tr>
<td>El-Badri (1999, p.c.)</td>
<td>Cases: DSM–IV</td>
<td>Potentially great</td>
<td>2/3 (15%)</td>
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<tr>
<td></td>
<td>OC: rating scale</td>
<td>harmful</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>OC: McNeil–Spitstorm</td>
<td>3.6 (0.3–44.8)</td>
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<td></td>
<td></td>
<td>pregnancy: 2 (15%)</td>
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<td></td>
<td>labour and delivery: 0 (0%)</td>
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<td></td>
<td></td>
<td>neonatal period: 1 (8%)</td>
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<td>total: 3/13 (23%)</td>
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<tr>
<td>Gunduz et al (updated)</td>
<td>Cases: SCID</td>
<td>Potentially great</td>
<td>9/76 (12%)</td>
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<td></td>
<td>Controls: SCID</td>
<td>harmful</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>OC: McNeil–Spitstrom scale</td>
<td>OC:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>pregnancy: 1 (5%)</td>
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<td></td>
<td></td>
<td>labour and delivery: 1 (5%)</td>
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<td></td>
<td></td>
<td>neonatal period: 2 (9.5%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>total: 4/21 (20%)</td>
<td></td>
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<tr>
<td>Browne et al (2000)</td>
<td>Cases: interview with psychiatrist</td>
<td>Perinatal OC: 15/16 (94%)</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>OC: Parnas and Lewis scales</td>
<td>Perinatal OC: 12/20 (60%)</td>
<td>15.33 (1.78–132.44)</td>
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<td></td>
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<tr>
<td></td>
<td>Controls (unaffected siblings): SCID+</td>
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<tr>
<td></td>
<td>interview with reliable informants</td>
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</table>

CCPS, Camberwell Collaborative Psychosis Study; OC, obstetric complications; OR, odds ratio; p.c., personal communication; SCID, Structured Clinical Interview for DSM–IV.
Study-specific odds ratios (log scale) and pooled random effects models for obstetric complications and bipolar disorder (BP), healthy controls, schizophrenia and unipolar disorders.

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis and assessment of complications</th>
<th>Obstetric complications</th>
<th>Estimated OR (95% CI)</th>
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<tr>
<td></td>
<td></td>
<td>BP</td>
<td>Healthy controls</td>
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<td></td>
<td></td>
<td>s.e.</td>
<td>Effect</td>
</tr>
<tr>
<td>Lewis &amp; Murray (1987)</td>
<td>Discharge diagnosis OC: Lewis scale</td>
<td>12/110 (11%)</td>
<td>30/207 (15%)</td>
</tr>
<tr>
<td>Schwarzkopf et al (1989)</td>
<td>SCID and medical records OC: Parnas scale</td>
<td>n=10</td>
<td>n=15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean OC per person 0.8</td>
<td>Mean OC per person 2.2</td>
</tr>
<tr>
<td>Verdoux &amp; Bourgeois (1993a)</td>
<td>Psychiatric assessment OC: Parnas scale</td>
<td>4/23 (17%)</td>
<td>11/23 (48%)</td>
</tr>
<tr>
<td>Vociasano et al (1996)</td>
<td>SCID</td>
<td>6/23 (26%)</td>
<td>7/29 (24%)</td>
</tr>
<tr>
<td>Gunduz et al (updated)</td>
<td>SCID</td>
<td>Potentially greatly harmful OC: pregnancy: 2 (15%)</td>
<td>Potentially greatly harmful OC: pregnancy: 13 (21%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>labour and delivery: 0 (0%)</td>
<td>labour and delivery: 5 (8%)</td>
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<tr>
<td></td>
<td></td>
<td>neonatal period: 1 (8%)</td>
<td>Neonatal: 0.5 (0.1–4.2)</td>
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<tr>
<td></td>
<td></td>
<td>total 3/13 (23%)</td>
<td>Total: 0.33 (0.8–1.31)</td>
</tr>
<tr>
<td>CCPS (updated)</td>
<td>Interview with psychiatrist OC: Lewis scale</td>
<td>9/49 (18%)</td>
<td>30/100 (30%)</td>
</tr>
</tbody>
</table>

Table 2  Studies comparing exposure to obstetric complications in individuals with bipolar disorder and schizophrenia

CCPS, Camberwell Collaborative Psychosis Study; OC, obstetric complications; OR, odds ratio; SCID, Structured Clinical Interview for DSM-IV.
were similar for both groups. Gunduz et al. (updated) reported that exposure to potentially harmful complications during pregnancy was lower (OR = 0.6, 95% CI 0.1–2.9), but exposure to potentially great harm during pregnancy was higher in those who developed bipolar disorder (OR = 3.6, 95% CI 0.3–44.8). Browne et al. (2000) found the opposite pattern.

It was possible to explore the odds ratios for only three specific complications: four studies reported on low birth weight (<2.5 kg) or being small for gestational age (Ogendahl et al., 2002; CCPS, updated; Cannon et al., updated; Wals et al., updated) and three studies on parity (Ogendahl et al., 2002; CCPS, updated; Cannon et al., updated). Wals et al. (updated) demonstrated that low birth weight is independently associated with increased risk of developing a mood disorder (bipolar disorder, 16%) in the offspring of parents with bipolar disorder (hazard ratio 0.7, 95% CI 0.5–0.9). However, the pooled OR for low birth weight and later development of bipolar disorder was 0.91 (95% CI 0.51–1.6) and for babies who were small for gestational age it was 1.79 (95% CI 0.83–3.86). Only the pooled OR (1.39, 95% CI 1.08–1.95; P = 0.04) for three or more previous pregnancies in the mothers of those in the bipolar disorder case groups was statistically significant and remained so when results were adjusted for baby gender and maternal age.

### Bipolar disorder cases v. other mental disorders

#### Schizophrenia

Giedde et al. (1999) highlighted that associations of labour and pregnancy are among the most extensively studied putative risk factors for schizophrenia. However, only eight studies allow comparison of exposure to any obstetric complications (Lewis & Murray, 1987; Schwarzkopf et al., 1989; Verdoux & Bourgeois, 1993a; Byrne et al., 1996; Vociosano et al., 1996; CCPS, updated; Gunduz et al., updated) or exposure to a specific complication (Schwarzkopf et al., 1989; Cannon et al., updated; CCPS, updated) in individuals who develop schizophrenia or bipolar disorder. Table 2 presents data that can be summarised from six studies.

Verdoux & Bourgeois (1993a) reported that 48% (n = 11) of participants who developed schizophrenia were exposed to obstetric complications and/or more severe complications during pregnancy compared with 17% (n = 4; Fisher’s exact test, P = 0.03) of those who developed bipolar disorder (OR = 0.2, 95% CI 0.1–0.9); Byrne et al. (1996) reported similar statistically significant differences for men. Schwarzkopf et al. (1989) reported a significantly higher mean rate of exposure to obstetric complications in individuals who developed schizophrenia compared with bipolar disorder (difference between means −1.4, 95% CI −2.48 to −0.32). The OR for two other studies demonstrated a non-significant trend for more frequent exposure to obstetric complications in individuals who developed schizophrenia rather than bipolar disorder (Lewis & Murray, 1987; CCPS, updated), although Vociosano et al. (1996) found no difference and no clear pattern emerged in the study by Gunduz et al. (updated). As shown in Fig. 1, the pooled OR for exposure to obstetric complications on subsequent development of bipolar disorder v. schizophrenia was 0.61 (95% CI 0.39–0.95; P = 0.035).

Data on exposure to individual obstetric complications were extracted from three studies (Schwarzkopf et al., 1989; Cannon et al., 1996, updated; CCPS,
updated). Although Schwarzkopf et al (1989) reported that individuals who developed bipolar disorder were significantly less likely to have experienced a prolonged labour compared with those who developed schizophrenia (bipolar disorder 1/10; schizophrenia 7/15; Fisher’s exact test, P = 0.02), the pooled OR for prolonged or difficult labour was not significant (OR = 0.99, 95% CI 0.46–2.41). The CCPS (updated) study demonstrated that significantly more individuals who developed schizophrenia (n = 9, 11%) had been exposed to maternal infections such as rubella during pregnancy compared with individuals who developed bipolar disorder (0%; Fisher’s exact test, P = 0.03). However, the pooled OR for exposure to infections during pregnancy was again not statistically significant (OR = 0.69, 95% CI 0.19–2.37).

**Major depressive disorder**

Data on exposure to obstetric complications in individuals who developed bipolar or unipolar disorders was available from five studies (Lewis & Murray, 1987; Vocisano et al, 1996; Sigurdsson et al, 1999; CCPS, updated; Gunduz et al, updated). As shown in Table 3, the majority of studies reported trends for either more frequent exposure to obstetric complications (Lewis & Murray, 1987; Vocisano et al, 1996; CCPS, updated) or exposure to more severe complications in those who developed bipolar compared with unipolar disorders (Gunduz et al, updated). However, there was a ten-fold variation in odds ratios (0.2 to 2.5) and no study found any statistically significant difference. Figure 1 shows that the pooled OR for exposure to obstetric complications on subsequent development of bipolar disorder v. unipolar disorder was 1.34 (95% CI 0.64–1.99).

**Other psychoses or other disorders**

Three studies reported non-significant trends for more individuals who developed schizoaffective disorder (Schwarzkopf et al, 1989; Gunduz et al, updated) or cycloid psychosis (Stobert et al, 1997) to have been exposed to obstetric complications than those who developed bipolar disorder. Lewis & Murray (1987) noted that exposure to definite obstetric complications was significantly more common in individuals with bipolar disorder (11%) compared with individuals who developed drug or alcohol dependence (3%; Fisher’s exact test, P = 0.04); marginally more individuals with anorexia nervosa (16%) had been exposed to such complications compared with individuals with bipolar disorder (11%). The data from these studies were not pooled, as few inferences can be drawn because of the mixture of diagnoses in the comparison groups, small sample sizes and inadequate statistical power.

**Studies of subgroups of bipolar disorder cases**

A small number of studies reported exposure to obstetric complications in individuals with early-onset (age <29 years) v. late-onset or familial v. non-familial bipolar disorder. Guth et al (1993) found that individuals with early-onset disorder were significantly (McNemar χ² = 7.7; P = 0.006) more likely to have been exposed to definite complications compared with individuals with late-onset disorder (OR = 12.0, 95% CI 2.1–69.5). Taylor & Abrams (1981) reported a similar trend, with exposure to gestational or neonatal obstetric complications in 13% (10/78) of patients with early-onset disorder compared with only 4% (2/54) in patients with late-onset disorder. However, El-Badri (1999, personal communication) found no difference in exposure to definite complications in those with early-onset (8/16; 50%) or late-onset (5/14; 36%) disorder. Pooled data failed to find differences in age at first presentation to psychiatric services (Brown et al, 2000; CCPS, updated) or age at first psychiatric admission in individuals with bipolar disorder who were or were not exposed to obstetric complications (Stobert et al, 1997; CCPS, updated). Dalen (1965), Browne et al (2000) and El-Badri (1999, personal communication) noted that patients with family history of bipolar disorder were equally likely to have been exposed to obstetric complications as those without such a family history (exposure rate 18% v. 14.5%).

The relationship between exposure to obstetric complications and the course of bipolar disorder is unclear. One study (Vocisano et al, 1996) reported a non-significant increase in exposure to complications among individuals with functionally deteriorated bipolar disorder (n = 6; 40%) compared with individuals with non-functionally deteriorated disorder (n = 2; 18%). (Functionally deteriorated disorder was defined as disorder in which patients were continually hospitalised or were out-patients dependent on others for necessities such as food or clothing, had no useful work or employment, and did not have full symptom remission over the previous 5 years.) No directly comparable data were available, but the CCPS (updated) study noted that individuals with bipolar disorder and a history of exposure to obstetric complications had significantly fewer psychiatric admissions (n = 9; mean 2.3, s.d. = 1.3) than those without exposure (n = 40; mean 4.3, s.d. = 3.1; 95% CI for difference in means –4.3 to –0.07). However, lengths of admission and out-patient attendances were not recorded, so it was not possible to apply the classification of Vocisano et al (1996).

**Incidence studies**

Brown et al (2000) reported the incidence of bipolar disorder among the offspring of mothers who were or were not exposed to famine during the Dutch ‘hunger winter’ of 1944–5. Relative to unexposed individuals (those born in the same region before the German invasion), the risk of developing an ICD–9 affective disorder requiring hospitalisation was significantly increased for people whose mothers were exposed during the second trimester (RR = 1.5, 95% CI 1.2–1.9) and third trimester (RR = 1.4, 95% CI 1.2–1.8) of pregnancy. Separate evaluations of the RR for unipolar disorders (including ICD–9 manic-depressive psychosis, depressed type) and bipolar disorders revealed similar trends in both disorders, but the risks were statistically significant for unipolar disorders but not for bipolar disorder (second trimester RR for bipolar disorder = 1.4, 95% CI 0.9–2.1, P = 0.08; third trimester RR = 1.3, 95% CI 0.9–1.9, P = 0.1).

Machon et al (1997) found a statistically significant increase in the risk of developing an affective disorder in the offspring of women who were pregnant during the 1957 Greater Helsinki influenza epidemic compared with the offspring of unexposed mothers (10/56 v. 36/442; RR = 2.19, 95% CI 1.15–4.17; P = 0.033). The association was strongest for exposure during the second trimester of pregnancy. The risk (RR = 2.89, 95% CI 1.03–8.09) was statistically significant for the development of an ICD–8 unipolar disorder requiring hospitalisation (exposed 7% v. unexposed 0.5%; Fisher’s exact test, P = 0.002), with a similar but non-significant increase in the risk of bipolar disorder (exposed 5% v. unexposed 1.6%;
Diseases (ICD–8 and ICD–9), the diagnosis of important ve-

The principal limitation of the available re-

The findings

The meta-analyses undertaken found that

in an individual, but was not statistically significant,

When studies that failed to provide these
data were excluded, the meta-analyses still
failed to produce additional significant results. Eagles et al. (1990) previously
detailed other methodological issues, such as failure to control for intra-uterine
environment, that can be surmounted by
comparing cases and controls that are bi-
ologically related. It is noteworthy that the
only research group that recruited un-
affected siblings as a comparison group
(Kinney et al., 1993, 1998) reported highly
significant ORs and that these findings con-
trasted markedly with the other studies of bipolar disorder cases and healthy controls.

There are particular issues that need to
be considered when attempting to distin-
guish whether exposure to obstetric compli-
cations or to an individual complication are
differentially associated with the develop-
ment of bipolar or unipolar disorders. First,
a significant proportion of cases of recur-
rent unipolar disorder may experience a
manic or hypomanic episode and be reclas-
sified as bipolar disorder cases at a later
date. Thus studies that reported significant
RR for affective disorders and for unipolar
disorders but not for bipolar disorder (e.g.
Machon et al., 1997; Brown et al., 2000;
Wals et al., updated) might have underesti-
mate the magnitude of risk for bipolar dis-
order because many individuals had not
been through the peak period of risk of its
development. Second, the diagnostic
criteria for affective disorders have changed
over time. For example, in earlier revisions
of the International Classification of Diseases (ICD–8 and ICD–9), the diagnosis of
‘manic-depressive psychosis’ included cases of severe unipolar disorder as well
as bipolar disorder. Also, mood disorders
with vegetative symptoms could be classified
as ‘affective psychosis’ even in the absence
of typical psychotic symptoms. These anomalies in diagnostic criteria may
contribute to the wide variations in the
magnitude of any association between exposure to obstetric complications and
unipolar disorders, bipolar disorder or
broadly defined affective disorders.

As highlighted in many earlier publica-
tions concerning obstetric complications in
schizophrenia, information gathered retro-
spectively through interviews with the
mothers of those with the disorder may be
subject to biased recall. Furthermore, there
are significant problems relating to the
quality and accuracy of scales specifically
designed to record obstetric complications
(McNeil et al., 1994). Exposure to any

in the risk of unipolar disorder in
those exposed to the epidemic in utero
(RR = 1.59, 95% CI 1.15–2.19), but a
non-significant increase in the risk of
bipolar disorder (RR = 1.15, 95% CI
0.4–2.95).

In a prospective study of over 1000
individuals from a 1959–66 birth cohort,
Zornberg et al. (2000) found a non-signifi-
cant increase in the risk (RR = 2.0, 95% CI
0.4–8.6) of developing bipolar disorder in
individuals who had experienced hy-
poxic ischaemia-related foetal or neonatal
complications (4/174) compared with those
who had not experienced such complica-
tions (6/519).

Discussion

This systematic review did not find any ro-
 bust evidence that overall exposure to ob-
stetric complications is associated with the
subsequent development of bipolar disor-
der. However, unlike the extensive research
on obstetric complications in schizo-
phrenia, relatively few studies have been
undertaken that are large-scale, methodol-
ogically sound and report on well-defined
complications in precisely ascertained po-
pulations of patients. Although the findings
of the pooled analyses must be interpreted
cautiously, we noted that meta-analyses
based only on studies of the highest quality
(e.g. employing prospective ascertainment
of obstetric complications using a robust
assessment tool and careful descriptions
of family history of mood disorders and of bi-
polar disorder cases) still did not yield
statistically significant results. Therefore,
we will briefly review the findings but then
highlight important limitations of the cur-
rently available literature and the implica-
tions for future research.

Limitations

The principal limitation of the available re-
search concerns small sample sizes (median
n = 44) and a lack of statistical power with
consequent risk of type II error. There are
also a number of problems with the design
of many of the studies. The basic principle
of a case–control study is that the cases
have the disorder of interest and that the
controls do not. It is also important to
know whether cases have a familial or
 genetic liability to the disorder in question.
Three studies failed to rule out a diagnosis
of bipolar disorder in the control group
(Stober et al., 1997; Brown et al., 2000;
CCPS, updated) and few studies reported
on whether cases or controls were screened
for any family history of bipolar or other
affective disorders, particularly in the
mother, nor whether the mothers had any
prenatal mood disorder, which might be
associated with problems such as preterm
delivery or low birth weight (O’Keane &
Scott, 2005). Four studies failed to control
for factors such as socio-economic status
and prenatal care (Verdoux & Bourgeois,
1993a; El-Badri, 1999, personal communi-
cation; CCPS, updated; Gunduz et al.,
updated) and few explored other demo-
graphic, illness history or lifestyle factors
(e.g. maternal cigarette and alcohol con-
sumption) that may increase the risk of
obstetric complications or moderate the
estimated effect size for different complica-
tions. The absence of such details represents
a significant problem when using meta-
analysis because the OR cannot be adjus-
ted adequately for confounders. However,

individual complications demonstrated some
interesting trends, but only parity – specifi-
cally being born to a mother with a history
of three or more previous pregnancies – in-
creased the risk of subsequent development
of bipolar disorder compared with healthy
controls. The studies do not differentiate
between live and still births, but other re-
search suggests the latter may be associated
with affective disorders (e.g. Done et al.,
1991). Although exposure to famine or
infection in utero, particularly during the
second trimester, increased the risk of
developing an adult mood disorder relative
to unexposed individuals, the RR was sig-
nificant for unipolar disorders, not bipolar
disorder. No association was found be-
tween exposure to obstetric complications
and age at onset or indicators of course
and prognosis of bipolar disorder.
obstetric complication in the studies reviewed varied from 12% to 95% in bipolar disorder cases; 4% to 60% in healthy controls; 10% to 28% in unipolar disorder cases; and 15% to 48% in schizophrenia cases. The high rate of complications in healthy controls (median 28%) and the considerable variability in rates of exposure to complications within diagnostic groups (an eight-fold difference across the 11 bipolar disorder samples) clearly calls into question the reliability and validity of the scales and the phenomena being measured. This finding reflects problems previously encountered in schizophrenia research, but as suggested by Cannon et al (2002b), the concept of 'obstetric complications' will be rendered meaningless unless there is agreement on more concise definitions of the nature, timing, duration or intensity of the exposures to be scrutinised.

The longitudinal studies we reviewed displayed fewer methodological flaws than the case-control studies. However, the potential weakness of this approach is the assumption that all the participants with bipolar disorder were exposed in foetal life to the complication or event being investigated. Although this – the so-called 'ecological fallacy' – is not relevant to most of the complications we studied, it is to variables such as exposure to influenza or the Dutch 'hunger winter'.

Implications for future research
This review suggests that increased methodological rigour in future studies will need to be accompanied by detailed proposals regarding the individual complication that might potentially have a causal role in affective disorders and a priori hypotheses outlining the mechanisms by which pregnancy, labour or perinatal complications affect individual risk of developing bipolar disorder (O'Keane & Scott, 2005). The traditional view of obstetric complications as a broad array of discrete, non-specific and largely unrelated events that may lead to structural brain abnormalities does not match the empirical evidence from contemporary studies (Cannon et al, 2002b; Mortensen et al, 2003). Maternal psychiatric disorders, genetic factors and perinatal events may all affect the likelihood of experiencing an obstetric complication, as well as affecting the timing of its occurrence. Furthermore, early abnormalities in foetal development may be associated with the occurrence of complications at a later stage in pregnancy that initially appear unrelated. This is illustrated by the meta-analysis by Geddes et al (1999), which suggests that the complications consistently associated with the development of schizophrenia, although apparently unrelated, may share a common pathophysiology, namely foetal hypoxia. In mood disorders, we would propose a greater focus on research on in utero exposures to adversity that have functional consequences for foetal brain development rather than on perinatal complications that are a direct source of cerebral insult. For example, longitudinal studies demonstrate that impaired foetal growth and low birth weight are associated with increased risk of mood disorder (Brown et al, 2000; Thompson et al, 2000; Wals et al, 2003). It has been suggested that this relationship is mediated by hormonal reprogramming in which plasma levels of hormones or the set points of the foetal hypothalamic–pituitary–adrenal axis are altered permanently, with diminished ability to inhibit stress-induced glucocorticoid secretion (Barker, 1997). Furthermore, prenatal mood disorder in the mother may be implicated in impaired foetal growth and low birth weight. The exploration of maternal and foetal stressors during critical periods of development will be more complex than a simple count of the number of exposures to obstetric complications, but may lead to the identification of causal factors and the greater understanding of non-genetic risk factors for bipolar disorders.

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OBSTETRIC COMPLICATIONS AND BIPOLAR DISORDER

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Affective Disorders


**APPENDIX 1**

Search terms used

Terms used for obstetric complications

Obstetrical complications
Prenatal care
Birth injury
Child birth
Labour complications
Labor complications
Prenatal exposure
Prenatal exposure delayed effects
Obstetric surgical procedures
Prenatal development stages
Prenatal exposure
Postnatal period
Obstetrics gynaecology
Neonatal
Neonates
Newborn infants
Neonatal development
Birth trauma
Fetal complications

Terms used for gestational infection

Delivery complications
Prenatal risk factors
Perinatal risk factors
Maternal infection
Pregnancy complications
Maternal influenza
Maternal exposure
Fetal hypoxia
Low birth weight
Premature birth

Terms used for bipolar affective disorder

Bipolar disorder
Bipolar depression
Affective psychosis
Bipolar manic disorder
Mania
Manic-depressive psychosis
Manic-depressive mania
Manic state
Manic depression
Mood disorders
Psychotic mania

**APPENDIX 2**

Included studies


Excluded studies

Exposure to obstetric complications and subsequent development of bipolar disorder: Systematic review
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