# Mood episodes in pregnancy and risk of postpartum recurrence in bipolar disorder: The Bipolar Disorder Research Network Pregnancy Study

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**Highlights**

- Episodes of bipolar disorder in pregnancy and postpartum examined prospectively
- Mania/psychosis in pregnancy significantly elevated risk of postpartum psychosis
- Depression in pregnancy did not increase risk of postpartum psychosis
- No relationship between any mood episodes in pregnancy and postpartum depression
- Limitations include predominantly White sample and modest sample size

## Abstract

### Background

Women with bipolar disorder (BD) are at high risk of mania/psychosis following childbirth. The risk factors for these episodes remain poorly understood and prospective studies are rare. Here, we examine whether mood episodes occurring within pregnancy predict postpartum recurrence in women with BD using a prospective design.

### Method

128 women with DSM-5 BD were followed from week 12 of pregnancy (baseline) to 12-weeks postpartum. Semi-structured interviews, supplemented by clinician questionnaires and case-note review, assessed lifetime psychiatric history at baseline, and perinatal psychopathology at two follow-up assessments: third-trimester of pregnancy and 12-weeks postpartum.

### Results

Postpartum follow-up data were obtained for 124/128 (97%) women [98 bipolar I disorder/schizoaffective-BD (BD-I/SA-BD group) and 26 bipolar II disorder/other specified BD and related disorder (BD-II/BD-OS group)]. Perinatal recurrence was high in both diagnostic groups (57% and 62% respectively). Women with BD-I/SA-BD were significantly more likely to experience mania/psychosis within 6 weeks postpartum (23%, n=22/96) compared to those with BD-II/BD-NOS (4%, n=1/25; p=0.042). In BD-I/SA-BD, mania/psychosis in pregnancy significantly elevated risk of mania/psychosis postpartum compared to remaining well (RR 7.0, p<0.001) and experiencing non-psychotic depression in pregnancy (RR 3.18, p=0.023)

### Limitations

Predominantly United Kingdom White sample and limited BD-II/BD-OS sample size.

### Conclusions

Women with BD are at high risk of recurrence during pregnancy and the postpartum. Over and above risk conferred by a history of BD-I/SA-BD, mania/psychosis during pregnancy further increased risk of postpartum mania/psychosis in this high-risk group. These data may have important implications for prediction and management of severe postpartum recurrence of BD.

## 1. Introduction

Childbirth is a potent trigger of episodes of bipolar disorder (BD) (Langan Martin et al., 2016; Munk-Olsen et al., 2009). Findings from large retrospective cohorts suggest risk of at least one episode of BD (of any polarity) is high in the postpartum period, with between 40-55% of women with BD having a lifetime history of recurrence within the first six months following delivery (Di Florio et al., 2013; Viguera et al., 2011). Quantifying precisely the level of risk of postpartum recurrence of BD is challenging, given that there is considerable heterogeneity between studies in their design (retrospective/prospective), definitions of the postpartum period, selected outcomes and inclusion criteria (Wesseloo et al., 2016). Nevertheless, an estimate from a recent meta-analysis of predominantly retrospective data indicates that around 37% of women with BD are affected in the postpartum period (Wesseloo et al., 2016).

The risk of mania and/or psychosis (consistent with the concept of postpartum psychosis; Jones et al., 2014) is especially high soon after childbirth in women with BD (Munk-Olsen et al., 2006), with psychiatric admissions for such episodes being 37 times more likely within the first three months of delivery compared to any other time in their lives (Munk-Olsen et al., 2009). Overall, as many as one in five (17-19%) women with BD experience postpartum psychosis (Munk-Olsen et al., 2006; Wesseloo et al., 2016), with further evidence suggesting those with bipolar I disorder (BD-I) and schizoaffective disorder – bipolar type (SA-BD) are particularly vulnerable (Di Florio et al., 2018, 2013; Maina et al., 2014; Sit et al., 2006). Risk of postpartum psychosis is strikingly elevated among women with BD, compared to the general population (1-2 in every 1000 deliveries) (VanderKruik et al., 2017) but also to other psychiatric disorders (Munk-Olsen et al., 2009). Together, these

data strongly indicate specificity of the childbirth trigger to BD. In contrast, though episodes of non-psychotic depression occur frequently in the first six months following childbirth (affecting between 19-60% of women with BD) (Di Florio et al., 2015; Mandelli et al., 2016; Viguera et al., 2011), evidence to suggest that the postpartum period may be a time of particularly high risk for the onset of depressive episodes is comparatively lacking (Heron et al., 2009; Le Strat et al., 2011).

Postpartum psychosis is a psychiatric emergency that can have devastating consequences for the mother, her baby and wider family (Brockington, 2017; Holford et al., 2018). Affected mothers are at increased risk of suicide (Gressier et al., 2017), with suicide being identified as a leading cause of maternal deaths in the United Kingdom (Knight, 2019). During acute phases of illness, safety of the infant may be an immediate concern (Brockington, 2017), while in the long-term, developmental outcomes may also be negatively impacted (Hoffman et al., 2017). For these reasons, identifying factors which place women with BD at greatest risk of postpartum psychosis is crucially important for the prevention and management of these episodes. In particular, women who have BD who are pregnant or planning pregnancy face difficult decisions regarding the management of their illness, specifically those relating to psychotropic medication use during the perinatal period (Dolman et al., 2016). Risk prediction models informed by high-quality data in this area would aid women and their clinicians in this decision-making process. Furthermore, this data would also facilitate the development of clinical services that could be more specifically targeted to women who are identified as being at greatest risk of postpartum psychosis.

Thus far, genetic, hormonal and immunological factors have all been implicated in the pathogenesis of postpartum psychosis (Perry et al. 2021). Nonetheless, the specific

mechanisms and potential role of other triggering factors in the onset of these episodes remain poorly understood. Previous literature has shown antenatal depression to be an important risk factor for non-psychotic postpartum depression in samples of women with unipolar major depression (Howard et al., 2014). Yet, despite indication that almost one in five women (19%) experience an antenatal recurrence of BD (Stevens et al., 2019), studies examining the potential relationship between the occurrence of mood episodes during pregnancy and the postpartum period within this high-risk group are limited (Akdeniz et al., 2003; Bergink et al., 2012; Doyle et al., 2012; Freeman, 2002; Viguera et al., 2011). In one such study of 30 women with BD assessed retrospectively, an increase of depressive symptoms in pregnancy was found to be significantly associated with postpartum recurrence (Freeman, 2002). However, nearly all postpartum recurrences in this sample were of depression and it was not clear whether women experienced the onset of a new episode following childbirth or if episodes were a continuation of those that had onset during pregnancy. Moreover, neither this study nor others have examined the potential relationship between antenatal and postpartum recurrences of BD according to diagnostic subtype or importantly, assessed whether an antenatal recurrence of BD is predictive of episodes of postpartum psychosis independently of postpartum depression.

To our knowledge, only one study in this area has used a prospective methodology and the sample size was modest (n=41) (Bergink et al., 2012). Additional prospective studies are important to overcome limitations of retrospective methods that are more prone to recall errors and bias. Specifically, use of a prospective methodology enables the collection of rich data that more accurately characterises the presence, timing of onset and type of mood episodes occurring within the perinatal period in women with BD. Also, the relationship between distinct episodes occurring with onset in pregnancy and the

postpartum period can be examined according to diagnostic subtype of BD at the time of pregnancy, as opposed to on a lifetime basis which may be influenced by perinatal psychiatric outcome.

Accordingly, the current study examined a sample of pregnant women with BD (n=128) who were recruited to a United Kingdom (UK) prospective study and followed from week 12 of pregnancy to 12 weeks following childbirth. The aims of the study were to (1) characterise and compare the occurrence of mood episodes (mania/psychosis, non-psychotic depression, hypomania) with onset during the perinatal period (pregnancy and/or within 12 weeks postpartum) according to diagnostic subtype of BD (BD-I/SA-BD and bipolar II disorder [BD-II]/other specified bipolar and related disorder [BD-OS]); (2) examine whether the occurrence of a mood episode with onset during pregnancy (including the type of episode; mania/psychosis and non-psychotic depression) predicts postpartum psychosis independently from episodes of postpartum depression. These data may have important clinical implications for individualising risk prediction and management of women with BD during the perinatal period.

## 2. Methods

### 2.1 Participants

Participants were 128 women with a lifetime history of BD recruited to the Bipolar Disorder Research Network Pregnancy Study (BDRN.org) between April 2011 and January 2019. Participants were recruited systematically via UK National Health Service (NHS) psychiatric services (including specialist perinatal services) or non-systematically through advertisements on the BDRN website and via the national patient support charities, Bipolar

UK and Action on Postpartum Psychosis. Participants were eligible to participate if they were aged 18 years or over and currently pregnant (≥12 week's gestation). Participants were excluded if they had only ever experienced mood episodes secondary to substance use or medical illness, or if they were unable to provide written informed consent.

## 2.2 Procedure

The research programme has UK NHS Health Research Authority approval, Research Ethics Committee approval (reference MREC/97/7/01) and Research and Development approval in all participating NHS Trusts/Health Boards. This study utilised a prospective follow-up design in which participants were followed from 12 weeks of pregnancy (baseline) to three months postpartum.

### 2.2.1 Measures

*Baseline assessments*

A baseline semi-structured interview (Schedules for Clinical Assessment in Neuropsychiatry; SCAN (Wing et al., 1990)) was conducted in person or via telephone by a trained research psychologist or psychiatrist to assess demographic factors, parity (number of deliveries at time of current pregnancy) and lifetime psychopathology before pregnancy.

*Follow-up assessments*

Modified versions of the SCAN were administered by telephone in the third trimester of pregnancy and at three months postpartum to assess the presence or absence of psychopathology with onset within the current perinatal period. Data were also gathered on psychotropic medication use within the perinatal period. Participants who were recruited to

the study from 24 weeks of pregnancy completed baseline and third trimester assessments simultaneously. For participants who provided written consent for clinician contact, a postal questionnaire was completed by their psychiatrist and/or general practitioner at two months postpartum. This was to ensure we were aware of the outcome of the pregnancy prior to contacting women at three months postpartum and to obtain clinical details of psychotropic medication use and episodes that had occurred with onset within the perinatal period. Where consent was provided, assessment data were supplemented by information obtained from psychiatric case-notes.

A summary of the data collected at each assessment timepoint is shown in **Figure 1.** Of 128 women who completed the semi-structured interview at baseline, 83% (106/128) completed the third trimester pregnancy interview and 83% (106/128) the postpartum follow-up interview. Of those who provided consent for clinician contact and/or access to psychiatric case-notes, clinician questionnaires were completed in 78% (98/126) of cases and case-notes were available in 61% (76/125) of cases. Postpartum psychiatric outcome data was obtained from at least one follow-up method for 97% (124/128) of participants assessed at baseline.

### 2.2.2. Ratings of demographics, key clinical characteristics and mood episodes occurring within the current perinatal period

Interview, clinician and case-note data were combined to create a detailed written vignette for each participant. Ratings were made from vignettes for demographics and key clinical history variables at the time of pregnancy which included best-estimate main lifetime diagnosis according to Diagnostic and Statistical Manual of Mental Disorders-5 criteria

(DSM-5; American Psychiatric Association, 2013) (defined as DSM-5 lifetime diagnosis from the onset of first impairing episode of BD to time of conception of the current pregnancy). Among parous women (i.e., women who had given birth prior to the current pregnancy), history of perinatal mood episodes was rated. Use of prophylactic mood stabilising medication in the postpartum period was assessed and defined as use of lithium, anticonvulsants or antipsychotics (atypical or typical) commenced or continued within the postpartum period for reasons other than treatment. Ratings were made for psychiatric outcomes with onset within the current perinatal period (including the presence/absence, type, timing of onset and duration of any DSM-5 mood episodes). The two most impairing DSM-5 mood episodes with onset during pregnancy and with onset within 12 weeks postpartum were rated for each woman where relevant. Time of onset for each episode was determined as the day and/or week (during pregnancy or the postpartum period) that symptoms first caused impairment. All ratings were made independently by at least two members of the study team and consensus agreed by discussion.

### 2.2.3 Definitions of perinatal psychiatric outcomes

The occurrence of at least one of each of the following DSM-5 mood episodes with onset during pregnancy, within 6 weeks postpartum (to be consistent with both International Classification of Diseases -10 [ICD-10, World Health Organization, 1993] and DSM-5 definitions of the postpartum period) and within 12 weeks postpartum were used to define the main study outcomes: i) *mania/psychosis*; including mania with or without mixed features or psychosis, major depression with psychotic features or non-affective psychosis; ii) *non-psychotic depression*; an episode of major depression without psychotic features (with or without mixed features); and, iii) *hypomania*. Where a participant experienced the

onset of two rated mood episodes of different types within the same perinatal time period (for example, an episode of non-psychotic depression and an episode of mania/psychosis with onset during pregnancy), both episodes were included.

2.2.4 Statistical analysis

The final sample comprised the 124 women for whom postpartum psychiatric outcome data were obtained, stratified to the following two groups according to lifetime DSM-5 diagnosis at baseline: 1) BD-I/SA-BD (n=98: 95 BD-I; 3 SA-BD); and, 2) BD-II/BD-OS (n=26: 24 BD-II; 2 BD-OS).

All analysis was conducted using SPSS version 27. The two diagnostic groups (BD-I/SA-BD and BD-II/BD-OS) were compared for demographics, parity, previous perinatal psychiatric history (parous women only) and key clinical variables using Mann-Whitney U, Chi-squared and Fisher's exact tests. Perinatal psychiatric outcomes were described within each group according to phase of the perinatal period and type of episode as outlined above, and proportions compared between diagnostic groups using Chi-squared and Fisher's exact tests. Relative risk ratios (RR) were calculated to examine whether mood episodes with onset during pregnancy predicted the occurrence of postpartum mood episodes. Where relevant, post-hoc analyses were conducted examining the relationship between episodes in pregnancy and the postpartum period after adjusting for use of prophylactic mood stabilising medication in the postpartum period. Due to the exploratory nature of the current study, corrections were not made for multiple testing and a p value of $<0.05$ was considered statistically significant.

## 3. Results

3.1 Demographics, parity and clinical characteristics at the time of pregnancy

Demographics, parity and clinical characteristics of the two diagnostic groups are shown in **Table 1**. Age ranged between 18 and 44 years. Most participants were of UK White ethnicity, educated to at least degree level, had worked in a professional occupation and had a partner present in the current pregnancy. Just over half of the sample was recruited non-systematically. Most participants were primiparous (i.e., had never given birth). Of parous participants (n=56), approximately 90% had a lifetime history of at least one perinatal mood episode. In both groups, approximately 60% of women (60-66.7%) were using a prophylactic mood stabilising medication in the current postpartum period. Median age at onset of impairing BD was significantly younger in the BD-II/BD-OS group (16 years) compared to the BD-I/SA-BD group (20 years; p=0.002). Women in the BD-II/BD-OS group also experienced a greater number of episodes of depression per illness year (on average; 0.85) compared to women in the BD-I/SA-BD group (0.45; p=0.039). No significant differences were found between the two groups with respect to duration of BD (13-15 years), average number of episodes of (hypo)mania per illness year (0.35-0.37) or any other demographic or clinical variable.

*3.2 Perinatal recurrence of bipolar disorder according to diagnostic subtype of bipolar disorder*

Perinatal psychiatric outcomes within diagnostic groups are shown in **Table 2**. 56.7% (55/97) of women in the BD-I/SA-BD group and 61.5% (16/26) in the BD-II/BD-OS group experienced at least one episode of mood disorder (of any type) with onset during the perinatal period (pregnancy and/or within 12 weeks postpartum, p=0.657).

*3.2.1 Recurrence of bipolar disorder during pregnancy*

40.6% (39/96) women in the BD-I/SA-BD group experienced at least one mood episode with onset during pregnancy, compared to 38.5% (10/26) of those in the BD-II/BD-OS group (p=0.842). There were no significant differences between diagnostic groups in the types of episodes experienced during pregnancy, although mania/psychosis was close to statistical significance (p=0.068). None of the BD-II/BD-OS participants experienced an episode of mania/psychosis during pregnancy, compared to 13.5% (13/96) of those with BD-I/SA-BD (including only one episode of non-affective psychosis).

*3.2.2 Recurrence of bipolar disorder in the postpartum period*

Three women experienced the onset of a mood episode during pregnancy that continued through the postpartum period (two with BD-I/SA-BD and one with BD-II/BD-OS). These women were therefore excluded from subsequent analyses because it was not possible to determine whether a postpartum recurrence would have occurred had they not been experiencing a mood episode at the time of delivery. Postpartum mood episodes occurred in similar frequency between those with BD-I/SA-BD and BD-II/BD-OS when examining onset of at least one mood episode (of any type) within six weeks (37.5% and 32.0% respectively; p=0.611) and 12 weeks postpartum (40.6% and 44.0% respectively; p=0.760). However, women in the BD-I/SA-BD group were significantly more likely to experience at least one episode of mania/psychosis (postpartum psychosis) compared to those in the BD-II/BD-OS group (22.9%, 22/96 and 4%, 1/25; 0.042). All postpartum episodes of mania/psychosis occurred within 6 weeks of delivery in both diagnostic groups and no women experienced an episode of non-affective psychosis. There was not a significant difference between

diagnostic groups in the frequency of women experiencing postpartum depression (p=0.116), despite the proportion in the BD-II/BD-OS group being almost double that of the BD-I/SA-BD group (32.0% and 17.7% within 12 weeks postpartum). The pattern of postpartum hypomanic episodes was similar (16% BD-II/BD-OS; 5.2% BD-I/SA-BD) and close to significance (p=0.087).

**Figure 2** shows the distribution of times of onset of all DSM-5 mood episodes occurring within the postpartum period**.** Using a temporal definition of the postpartum period consistent with DSM-5 criteria, 91% (21/23) episodes of mania/psychosis had onset within 4 weeks of childbirth, compared to 56% (5/9) episodes of hypomania and 68% (17/25) of episodes of non-psychotic depression. In line with expanded onset criteria specified by the ICD-10, all episodes of mania/psychosis, 66% (6/9) episodes of hypomania and 76% (19/25) of episodes of non-psychotic depression occurred within six weeks postpartum. No episodes had onset during delivery.

*3.3 Association between antenatal and postpartum recurrence according to diagnostic subtype of bipolar disorder*

In a combined group analysis of all women for whom we were able to ascertain if they had or had not experienced an episode with onset in both time periods respectively (n=119), women who experienced at least one mood episode of any type during pregnancy were at 2.12 times significantly greater risk of postpartum recurrence of BD within 12 weeks of delivery than women who remained well during pregnancy (RR 2.12, 95% CI 1.38-3.25, p=0.001). When stratified by diagnostic subgroup, this association remained significant among women with BD-I/SA-BD (RR 2.36, 95% CI 1.43-3.90, p=0.001), but not in those with BD-II/BD-OS (RR 1.48, 95% CI 0.63-3.51, p=0.434).

Post-hoc analyses were conducted in the BD-I/SA-BD group to examine the association between antenatal recurrence of BD during pregnancy and the type of episode occurring with onset in the postpartum period. Postpartum psychiatric outcomes in the BD-I/SA-BD group according to the presence or absence of mood episodes in pregnancy are described in **Figure 3**. Four women were excluded from subsequent analyses as they experienced a combination of episodes of mania/psychosis and non-psychotic depression with onset in the 12-week postpartum period. 90.9% (10/11) women with BD-I/SA-BD who experienced an episode of mania or psychosis with onset during pregnancy experienced at least one postpartum recurrence of BD (of any polarity). Of women who experienced an episode of non-psychotic depression only during pregnancy, 45% (9/20) subsequently experienced at least one postpartum recurrence of BD.

*3.3.1 Mood episodes in pregnancy and risk of postpartum mania/psychosis*

Compared to women who remained well during pregnancy, risk of postpartum mania/psychosis was significantly greater among women who experienced an episode of mania/psychosis during pregnancy (9.1%, 5/55 and 63.6%, 7/11 respectively; RR 7.00, 95% CI 2.71-18.06, $p<0.001$) and this relationship remained significant after adjusting for use of prophylactic mood stabilising medication in the postpartum period ($p<0.01$). In contrast, those who experienced non-psychotic depression antenatally were not more likely to experience postpartum mania/psychosis compared to women who remained well in pregnancy (20.0%, 4/20 and 9.1%, 5/55 respectively; RR 2.20, 95% CI 0.66-7.39, $p=0.236$). Risk of postpartum mania/psychosis was more than three times greater among women who experienced mania or psychosis in pregnancy (63.6%, 7/11) compared to those who

experienced non-psychotic depression in pregnancy (20%, 4/20; RR 3.18, 95% CI 1.19-8.51, p=0.023).

*3.3.2 Mood episodes in pregnancy and risk of postpartum depression*

Compared to women who remained well during pregnancy, episodes of postpartum non-psychotic depression were not significantly more likely to occur in women who experienced episodes of mania/psychosis (9.1%, 5/55 and 27.3%, 3/11 respectively; RR 3.00, 95% CI 0.84-10.75, p=0.122) or non-psychotic depression during pregnancy (9.1%, 5/55 and 25%, 5/20 respectively; RR 2.75, 95% CI 0.89-8.50, p=0.119). Risk of postpartum non-psychotic depression did not significantly differ between those with a pregnancy onset of mania/affective psychosis and those of non-psychotic depression (25%, 5/20 and 27.3%, 3/11 respectively; RR 1.09, 95% CI 0.32-3.72, p=1.000).

## 4. Discussion

To our knowledge, this prospective study is one of the largest such studies to date to describe and compare perinatal psychiatric outcomes between women with BD-I/SA-BD and BD-II/BD-OS. Moreover, this is the first study to examine the polarity of well-defined mood episodes (using DSM-5 criteria) with onset in pregnancy and subsequent risk of postpartum psychosis independently of postpartum depression in women with BD.

Direct comparisons of risk estimates for perinatal recurrence of BD between studies is difficult due to methodological heterogeneity. However, our findings are generally consistent with previous reports (Stevens et al., 2019; Wesseloo et al., 2016), showing perinatal recurrence of BD to be high, with approximately six out of every ten women with

BD-I/SA-BD (57%) and BD-II/BD-OS (62%) experiencing the onset of at least one mood episode during pregnancy and/or the postpartum period. Within pregnancy, 40.6% women in the BD-I/SA-BD group and 38.5% of those in the BD-II/BD-OS group experienced a new onset recurrence of BD, which is higher than an overall estimate reported in a recent systematic review of 16 studies (19%; Stevens et al., 2019). Nevertheless, in their review, estimates of recurrence during pregnancy varied widely between studies, ranging from 0-73%, and our estimate falls within this range. Importantly, incidence of recurrence may have been higher in our study than others due to our use of a prospective methodology, which reduces potential risk of recall error and bias over retrospective methods. Furthermore, in nearly all previous studies (which are predominantly retrospective), assessment of antenatal recurrence of BD was based on data obtained from routine clinical assessments, potentially resulting in episodes that had onset during pregnancy being undetected or underreported. In comparison, we assessed recurrence during the perinatal period (including specifically during pregnancy) systematically according to DSM-5 criteria using a semi-structured psychiatric assessment tool (SCAN) during pregnancy and again at postpartum follow-up. To our knowledge, only one other previous study has utilised a psychiatric assessment tool to assess antenatal recurrence of BD according to clinical diagnostic criteria (Blehar et al., 1998) and the rate observed within their study (37%) was comparable to our findings. Notably, we also supplemented data obtained at interview with information from questionnaires completed by participants' general practitioner and/or psychiatrist (that asked specifically about episodes during pregnancy) and psychiatric case-notes, providing further opportunity to identify episodes that had onset during pregnancy.

In the current study, the rate of recurrence during pregnancy in both diagnostic groups (41% and 39%) was comparable to that within the postpartum period (41% and

44%), however, the onset of mood episodes in the postpartum period all occurred within close temporal proximity to childbirth. Namely, over 90% of episodes of mania and psychosis had onset within 4 weeks of childbirth, with 56% of episodes of hypomania and 68% of non-psychotic depressions having onset within the same time-frame. In line with retrospective cohorts (Di Florio et al., 2013) and large epidemiological studies (Langan Martin et al., 2016; Munk-Olsen et al., 2009) our findings further support evidence indicating childbirth to be a potent trigger of mood episodes and in particular, of mania and psychosis.

Similar to previous studies (Di Florio et al., 2013; Viguera et al., 2011), we found no significant difference in the occurrence of broadly-defined mood episodes with onset during the perinatal period between diagnostic subtypes of BD. Episodes of non-psychotic depression occurred frequently in both diagnostic groups during pregnancy (25-35%) and the postpartum period (18-32%), while episodes of hypomania were less common (6-15% and 5-16% respectively). Women with BD-I or SA-BD were however significantly more likely to experience mania or psychosis in the postpartum period compared to those with BD-II/BD-OS. Specifically, we found that nearly one in four (23%) women with BD-I/SA-BD experienced a postpartum psychosis following childbirth, compared to only one woman of 25 (4%) with BD-II/BD-OS. This single episode was the only episode of mania/psychosis that occurred within the BD-II/BD-OS group during the perinatal period, subsequently resulting in a lifetime switch in DSM-5 diagnosis from BD-II to BD-I. Our findings therefore support those of retrospective research (Di Florio et al., 2013; Maina et al., 2014), further highlighting women with BD-I/SA-BD (according to diagnosis) at the time of pregnancy to be at greatest risk of postpartum psychosis.

In this study, we demonstrated that over and above risk conferred by a history of BD-I or SA-BD, the occurrence of mania or psychosis during pregnancy further increased risk of severe postpartum recurrence within this high-risk group, despite use of prophylactic mood stabilising medication in the postpartum period. Strikingly, we found 90% women with BD-I or SA-BD who experienced mania or psychosis in pregnancy to experience at least one postpartum recurrence of BD. Specifically, mania or psychosis in pregnancy was associated with a seven times increased risk of postpartum mania/psychosis compared to women who remained well antenatally and a three times greater risk of postpartum mania/psychosis than those who experienced non-psychotic depression in pregnancy. In contrast, no significant association was found between antenatal non-psychotic depression and subsequent mania/psychosis or non-psychotic depression occurring within the postpartum period. Our findings support those of previous literature which has shown postpartum recurrence of BD to occur more frequently among women who experience episodes of mood illness during pregnancy, compared to those remain well antenatally (Akdeniz et al., 2003; Bergink et al., 2012; Doyle et al., 2012; Freeman, 2002; Viguera et al., 2011). While one study has shown a significant relationship between symptoms of depression during pregnancy and subsequent postpartum depression in women with BD (Freeman et al., 2002), to our knowledge, we are the first to report a specific association between the onset of mania or psychosis during pregnancy and subsequent risk of mania or psychosis in the postpartum period. Overall, our results may inform clinicians and patients about potential risk of severe postpartum recurrence of BD, highlighting not only diagnostic subtypes of BD-I/SA-BD but also the occurrence of mania/psychosis in pregnancy to be important risk factors for onset of postpartum psychosis.

### 4.1 Limitations

Our study is subject to several limitations. First, despite effort to recruit a representative sample of women with BD to this research, our study was predominantly comprised of well-educated UK White women, nearly all of whom reported having a partner present in the current pregnancy. Additionally, half of all women were under the care of perinatal psychiatric services. Despite our study being naturalistic by design, it is therefore possible that risk of recurrence was underestimated in our sample and findings may therefore be less generalisable to the wider BD population. Conversely, as 90% of parous women had a history of at least one perinatal recurrence of BD in a previous pregnancy, it could be argued that our estimations of risk are potentially inflated. However, more than half of the sample was primiparous and so did not have a previous history of perinatal psychiatric illness. In addition, to minimise the potential for bias, we adopted a range of systematic and non-systematic approaches to recruitment. Moreover, comparisons between parous and non-parous women revealed no significant differences between overall postpartum psychiatric outcomes or in the frequency of women who experienced postpartum psychosis (data not shown).

A second limitation is that due to the modest size of this sample, it was not possible to examine further the influence of psychotropic medication use on risk of perinatal recurrence within BD subtypes. Previous research has shown psychotropic medication to be effective for prophylaxis of BD both during pregnancy (Salim et al., 2018) and the postpartum period (Wesseloo et al., 2016). Psychotropic medication use and specifically, associated factors such as the type, timing and dosage of medications used may therefore have influenced outcomes within the current sample and requires further investigation. As recruitment to the BDRN Pregnancy Study is ongoing, we aim to investigate these

relationships in larger, more powerful samples in the future. Third, potentially due to less severe cases of BD-II or BD-OS being under detected and untreated by clinical services, our sample size of women with BD-II/BD-OS was small, giving us less confidence in the risk estimates among this group. Finally, we did not correct for the number of statistical tests we conducted, therefore the potential for type I errors is increased. However, due to the exploratory nature of this study, use of a p-value of less than 0.05 was deemed too conservative and corrections not applied to conversely, mitigate risk of type II errors.

**4.2 Conclusions**

Using prospective methodology, we have shown morbidity of BD to be high during both pregnancy and the postpartum period, with around 60% women with BD, independent of diagnostic subtype, experiencing a perinatal illness episode. Our findings suggest that all women with BD should be monitored carefully during pregnancy as well as after birth. However, our data indicate women with BD-I and SA-BD, and particularly those who experience mania or psychosis during pregnancy, are at especially high risk of postpartum psychosis, despite use of prophylactic mood stabilising medication in the postpartum period. These women may therefore comprise a group that require additional targeted and specialist clinical intervention aimed at reducing risk of postpartum psychosis. Additional prospective studies with larger sample sizes are required to further examine within-pregnancy factors that may influence risk of perinatal recurrence in women with BD, including characteristics of psychotropic medication use. Future studies should take into consideration the bipolar diagnostic subtypes of women given the different patterns of risk we have demonstrated in this study.

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**Table 1. Lifetime demographics, parity and key psychiatric history characteristics at the time of current pregnancy and prophylactic mood stabilising medication in the current postpartum period within each diagnostic subgroup of BD**

| | BD-I/SA-BD (n=98) | BD-II/BD-OS (n=26) | p-value |
|---|---|---|---|
| ***Demographics*** | | | |
| **Age at current pregnancy (years)** | | | |
| Median (IQR) | 34 (6) | 32 (7) | .106 |
| Range | 23-44 | 18-41 | |
| **Ethnicity (%, n)** | | | |
| White | 91.8 (90) | 96.2 (25) | .683 |
| Other | 8.2 (8) | 3.8 (1) | |
| **Education (%, n)** | | | |
| Degree level | 64.3 (63) | 61.5 (16) | .796 |
| No degree level | 35.7 (35) | 38.5 (10) | |
| **Highest occupation level (%, n)** | | | |
| Professional | 55.1 (54) | 53.8 (14) | .909 |
| Non-professional | 44.9 (44) | 46.2 (12) | |
| **Method of recruitment (%, n)** | | | |
| Systematic | 46.9 (46) | 46.2 (12) | .943 |
| Non-systematic | 53.1 (52) | 53.8 (14) | |
| **Partner in current pregnancy (%, n)** | | | |
| No | 1.0 (1) | - | 1.000 |
| Yes | 99.0 (96) | 100 (25) | |
| ***Parity (%, n)*** | | | |
| Primiparous | 53.1 (52) | 61.5 (16) | .440 |
| Parous | 46.9 (46) | 38.5 (10) | |
| ***Use of prophylactic mood stabilising medication in the postpartum period*** | | | |
| No | 40% (38) | 33.3% (8) | 0.549 |
| Yes | 60% (57) | 66.7% (16) | |
| ***Key psychiatric history characteristics*** | | | |
| **History of perinatal mood episode[†] (%, n)** | 9.3 (4) | 10.0 (1) | 1.000 |
| No | 90.7 (39) | 90.0 (9) | |
| Yes | | | |
| **Age at onset of impairing BD (years)** | | | |
| Median (IQR) | 20 (8) | 16 (20) | 0.002** |
| Range | 11-36 | 12-32 | |
| **Duration of BD (years)** | | | |
| Median (IQR) | 13 (9) | 15 (8) | 0.095 |
| Range | 1-28 | 3-23 | |
| **Average number of episodes of (hypo)mania per illness year** | 0.35 (0.45) | 0.37 (0.44) | 0.761 |
| Median (IQR) | 0.05-7.37 | 0.06-5.00 | |
| Range | | | |
| **Average number of episodes of depression per illness year** | | | |
| Median (IQR) | 0.45 (0.61) | 0.86 (0.96) | 0.039* |
| Range | 0.00-4.34 | 0.00-9.81 | |

Ns differ due to unknown data. BD: bipolar disorder. BD-I: bipolar I disorder. BD-II: bipolar II disorder, BD-OS: other specified bipolar and related disorder, SA-BD: schizoaffective bipolar disorder. [†] Lifetime history prior to current pregnancy of at least one perinatal mood episode with onset during pregnancy or within six months postpartum (parous women only for whom data were known). *p<0.05 **p<0.01

**Table. 2. Occurrence of DSM-5 mood episodes with onset during pregnancy and the postpartum period according to diagnostic subgroup of bipolar disorder (BD)**

| | **BD-I/SA-BD** (n=98) | **BD-II/BD-OS** (n=26) | **p-value** |
|---|---|---|---|
| **Onset of at least one DSM-5 mood episode of any type in perinatal period** % (95% CI, n) | 56.7 (46.3-66.7, 55/97) [†] | 61.5 (40.6-79.8, 16/26) | .657 |
| **Onset of at least one DSM-5 mood episode of any type in pregnancy** % (95% CI, n) | 40.6 (30.7-51.1, 39/96)[‡] | 38.5 (20.2-59.4, 10/26) | .842 |
| At least one episode of mania/psychosis | 13.5 (7.4-22.0, 13/96) | 0 (0/26) | .068[§] |
| At least one episode of non-psychotic depression | 25.0 (16.7-34.9, 24/96) | 34.6 (17.2-55.7, 9/26) | .328 |
| At least one episode of hypomania | 6.3 (2.3-13.1, 6/96) | 15.4 (4.4-34.9, 4/26) | .218[§] |
| **Onset of at least one DSM-5 mood episode of any type <6 weeks postpartum**[¶] % (95% CI, n) | 37.5 (27.8-48.0, 36/96) | 32.0 (15.0-53.5, 8/25) | .611 |
| At least one episode of mania/psychosis | 22.9 (15-32.6, 22/96) | 4.0 (0.1-20.4, 1/25) | .042[§]* |
| At least one episode of non-psychotic depression | 13.5 (7.4-22.0, 13/96) | 24.0 (9.4-45.1, 6/25) | .222[§] |
| At least one episode of hypomania | 3.1 (0.6-8.9, 3/96) | 12.0 (2.6-31.2, 3/25) | .102[§] |
| **Onset of at least one DSM-5 mood episode of any type <12 weeks postpartum**[¶] % (95% CI, n) | 40.6 (30.7-51.1, 39/96) | 44.0 (24.4-65.1, 11/25) | .760 |
| At least one episode of mania/psychosis | 22.9 (15.0-32.6, 22/96) | 4.0 (0.1-20.4, 1/25) | .042[§]* |
| At least one episode of non-psychotic depression | 17.7 (10.7-27.0, 17/96) | 32.0 (15.0-53.5, 8/25) | .116 |
| At least one episode of hypomania | 5.2 (1.7-11.7, 5/96) | 16.0 (4.5-36.1, 4/25) | .087[§] |

95% CI: 95% confidence intervals. Mania/psychosis defined as an episode of mania (with or without mixed features or psychosis), depression with psychotic features or non-affective psychosis. Analyses of episodes by type include women who experienced the onset of two different types of mood episode within the same perinatal period (during pregnancy [4 BD-I/SA-BD; 3 BD-II/BD-OS] and/or the postpartum period [5 BD-I/SA-BD; 2 BD-II/BD-OS]. [†] One case excluded as the definite presence/absence of at least one perinatal episode could not be determined (episode in pregnancy undetermined and no episode postpartum). [‡] Two cases excluded as the definite presence/absence of at least one episode with onset during pregnancy could not be determined. [§] Fisher's exact test. [¶] Three cases excluded (2 BD-I/SA-BD; 1 BD-II/BD-OS) as episode had onset in pregnancy which continued postpartum. * p-value <0.05

**Figure 1. Summary of data collected at each stage of assessment of The Bipolar Disorder Research Network Pregnancy Study**

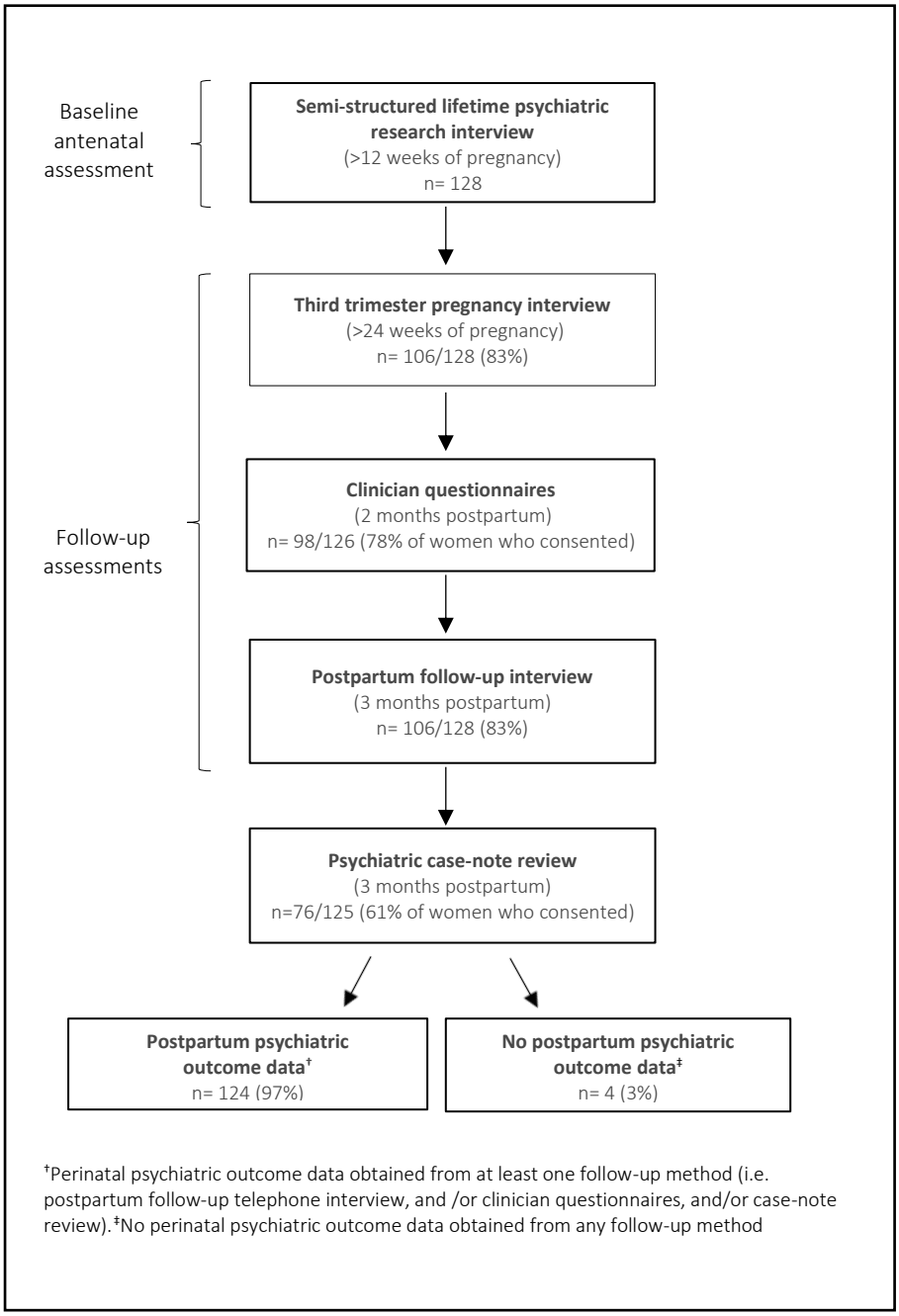
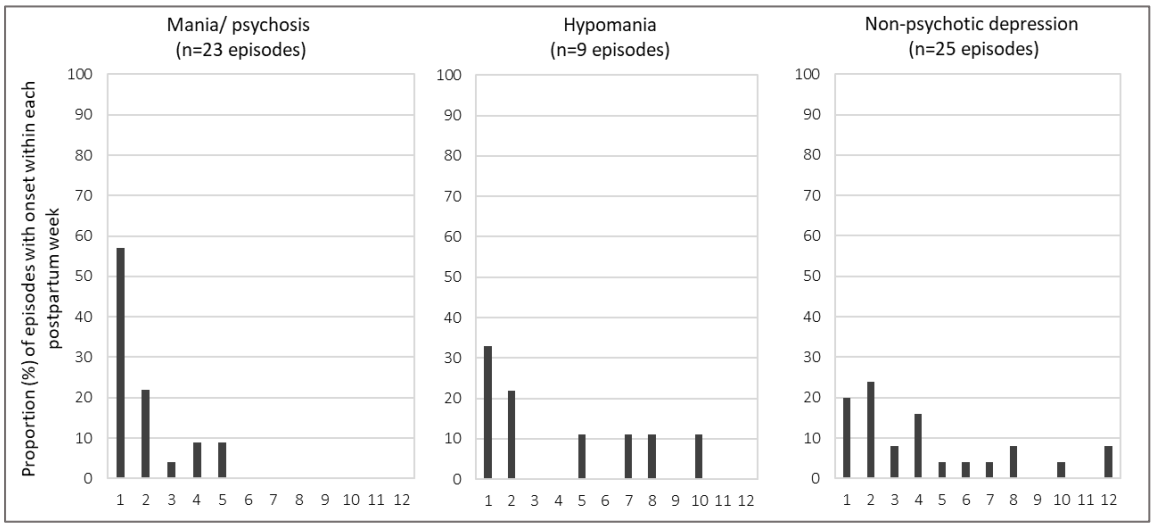
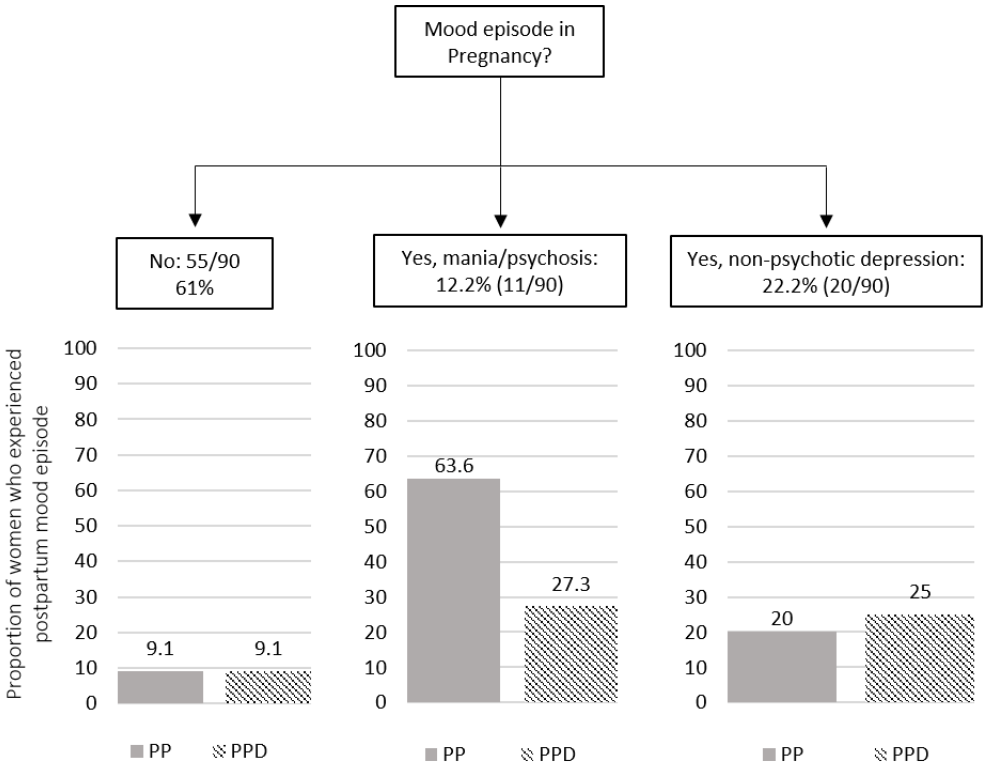


**Figure 2. Proportion of DSM-5 mood episodes that had onset within each week of the postpartum period (weeks 1-12)**




DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th Ed). Mania/psychosis: DSM-5 mania (with or without mixed features or psychosis), depression with psychotic features or non-affective psychosis.

**Figure 3**. **Proportion of women with BD-I/SA-BD who experienced a DSM-5 mood episode with onset within 12 weeks postpartum according to the presence/absence of a DSM-5 mood episode in pregnancy**




DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th Ed). Mania/psychosis: DSM-5 mania (with or without mixed features or psychotic features), major depression with psychotic features or non-affective psychosis with onset during pregnancy. PP: postpartum psychosis (DSM-5 mania with or without mixed features or psychosis, major depression with psychotic features or non-affective psychosis) with onset within 12 weeks of childbirth, PPD: DSM-5 postpartum non-psychotic depression with onset within 12 weeks of childbirth. Occurrences of hypomania not shown due to limited number of cases.

**Supplementary Table I:** Definitions of key terms used throughout manuscript

| Term | Definition |
|---|---|
| Antenatal | Time period from conception of pregnancy to childbirth |
| Postpartum | Time period following childbirth, defined by the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) as the first four weeks and the International Classification of Diseases-10 (ICD-10) as the first six weeks. |
| Perinatal | Time period encompassing pregnancy and the postpartum period, defined by the DSM-5 as the period from conception of pregnancy and including the first four weeks following childbirth and the ICD-10 as from conception of pregnancy and including the first six weeks following childbirth. |
| Bipolar I Disorder (BD-I) | This term is used within the current study to describe DSM-5 best-estimate main lifetime diagnosis at the time of the current pregnancy consistent with codes 296.41-296.44. |
| Bipolar II Disorder (BD-II) | This term is used within the current study to describe DSM-5 best-estimate main lifetime diagnosis at the time of the current pregnancy consistent with code 296.89. |
| Other specified bipolar and related disorder (BD-OS) | This term is used within the current study to describe DSM-5 best-estimate main lifetime diagnosis at the time of the current pregnancy consistent with codes 301.12 and 296.89. |
| Schizoaffective Bipolar Disorder (SA-BD) | This term is used within the current study to describe DSM-5 best-estimate main lifetime diagnosis at the time of the current pregnancy consistent with code 295.70. |
| Depression/depressive episode | Unless stated otherwise, this term is used within the current study to describe episodes of major non-psychotic depression that meet DSM-5 diagnostic criteria corresponding to codes 295.70, 296.51-296.53 and 296.89. |
| Mania/Manic episode | This term is used within the current study to describe episodes of mania, with or without mixed features and with or without psychotic features, that meet DSM-5 diagnostic criteria corresponding to codes 295.70 and 296.41-296.44. |
| Hypomania/hypomanic episode | This term is used within the current study to describe episodes of hypomania meeting DSM-5 diagnostic criteria corresponding to codes 295.70, 296.40 and 296.89. |
| Mixed features | Specifier used within the current study to denote the presence of mixed features occurring in the context of an episode of mania or depression consistent with DSM-5 diagnostic criteria. |