Postpartum psychosis and its relationship with bipolar disorder: a polygenic risk score analysis in the UK

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Abstract

Background: For more than 150 years, controversy over the status of postpartum psychosis has hindered research and caused considerable confusion for clinicians and women, with potentially negative consequences. We aimed to explore the hypothesis that genetic liability differs between women with first onset postpartum psychosis and those with bipolar disorder more generally.

Methods: Participants were 203 women with first onset postpartum psychosis (defined as a manic, mixed or psychotic depression episode within 6 weeks of delivery without previous psychiatric history) and 1,225 parous women with history of bipolar disorder. All were assessed using a semi-structured psychiatric interview and psychiatric case note review. 2,809 women from the general population were included as controls. All self-reported their ethnicity as White and were recruited across the UK.

Outcomes: In this case-control study, women with first onset postpartum psychosis (median age at interview: 46; range: 21-79) and women with bipolar disorder (49; 19-83) were ascertained between September 1991 and May 2013. Women with first onset postpartum psychosis had similar bipolar disorder and schizophrenia polygenic risk scores (PRS) to women with bipolar disorder, significantly higher than controls. When compared to controls, women with first onset postpartum psychosis had an adjusted relative risk ratio (adjRR) for bipolar disorder PRS of 1·71 (95% Confidence Intervals: 1·56-1·86, p<0.0001) and for schizophrenia PRS of 1·81 (1·66-1·97, p<0.0001). The effect sizes were similar when comparing women with bipolar disorder to controls (adjRR 1·77 (1·69, 1·84), p<0·0001 for bipolar disorder PRS; adjRR 2·00 (1·92, 2·08), p<0·0001 for schizophrenia PRS). While women with bipolar disorder also had higher major depression PRS than controls (adjRR 1·24 (1·17, 1·31), p<0·0001), women with first onset postpartum psychosis did not differ from controls in their polygenic liability to major depression (adjRR 0·97 (0·82-1·11),p=0·63).

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Interpretation: Our study supports the recognition of first onset postpartum psychosis as a separate nosological entity within the bipolar disorder spectrum both in research and clinical settings.

Introduction

Postpartum psychosis is one of the most severe psychiatric illnesses. It is characterized by the abrupt onset of affective and psychotic symptoms, typically in the first 2 weeks after childbirth.[1] It occurs in approximately 1 in 1000 women, with over half of these cases having no previous history of psychiatric disorders.[2]

Over 150 years of controversy on the status of postpartum psychosis has hindered research and caused considerable confusion for clinicians and women, with potentially negative consequences for their management.[2] This is particularly detrimental since, if not promptly and correctly diagnosed and treated, postpartum psychosis may have severe consequences, including suicide and, in very rare, tragic cases, infanticide.[3]

Postpartum psychosis is not adequately dealt with by the current diagnostic systems. The DSM of the American Psychiatric Association[4] and the World Health Organization ICD[5] do not consider postpartum psychosis as a separate nosological entity. Instead, severe postpartum episodes are diagnosed in the general mania or psychotic depression categories of the mood disorder or psychosis rubrics. The relationship to childbirth can be flagged by the use of a perinatal onset specifier, covering pregnancy and 4 weeks postpartum in DSM and 6 weeks postpartum in ICD. The concept of postpartum psychosis, however, remains in widespread use and is considered useful, both by clinicians and by women themselves.[6] Although a close link between postpartum psychosis and bipolar disorder is suggested by epidemiological,[7] clinical,[8-10] and family studies,[11-13] the exact nature of this relationship is not clear. The distinction between women with a liability to a puerperal trigger of illness and those without has important implications for prognosis and treatment. For example, one study has suggested that women with a history of illness limited to the postpartum do not need prophylaxis during subsequent pregnancies, in contrast to those with prior episodes outside

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the postpartum period, who are at significant risk of relapse during pregnancy as well as in the postpartum period.[14] Despite the clinical importance, these differences have rarely been considered and in particular, there is a lack of data on their biological underpinnings or correlates.

Advances in genomics have changed the conceptualization of many medical conditions. Genome-wide association studies have provided robust evidence that a significant proportion of the variance in susceptibility to psychiatric disorders is driven by many common genetic risk variants of small effect.[15] Methods aggregating these variants have been used to identify and quantify substantial overlaps between genetic risk of schizophrenia, bipolar disorder and major depression[16] as well as differences in the patterns of cross-disorder genetic liability in subtypes of bipolar disorder.[17,18]

Here we report the first polygenic risk score study of postpartum psychosis. We employ polygenic risk score methods to inform our understanding of the nosology of postpartum psychosis and its relationship to bipolar disorder. Based on previous findings from clinical, epidemiological and family studies (see appendix page 2 for a more detailed review of the evidence), we hypothesized that first onset postpartum psychosis identifies a group of women with a genetic liability that differs from that of women with bipolar disorder more generally (see appendix page 2 for further explanation of hypotheses).

Methods

Study design and participants

We compared the genetic liabitilies of three groups: cases with history of first onset postpartum psychosis, cases with history of bipolar disorder and female controls from the general population. We hypothesised that genetic liability differs between women with first onset postpartum psychosis and those with bipolar disorder more generally.

Cases

Information on women with bipolar disorder was obtained from the Bipolar Disorder Research Network (BDRN) database, an ongoing programme of research into the genetic and non-genetic determinants of bipolar disorder and related mood disorders. The research programme has UK National Health Service (NHS) Health Research Authority (HRA) approval – Research Ethics Committee (REC) reference (MREC/97/7/01) and local approvals in all participating NHS Trusts/Health Boards.

Participants were recruited through screening community mental health teams across the United Kingdom and via the media and patient support organizations and provided written informed consent. All team members involved in the consent procedure, assessment and diagnosis were research psychologists or psychiatrists.

Clinical assessment included a face-to-face interview using the Schedules for Clinical Assessment in Neuropsychiatry[19] and psychiatric case notes were reviewed where available. Best-estimate lifetime diagnoses were made according to DSM-IV diagnostic criteria. Postpartum psychosis was defined as a manic or mixed episode, with or without psychotic features, or psychotic depression that had an onset within 6 weeks of delivery. Psychosis was defined as the presence of positive, negative, or disorganised psychotic symptoms. Our definition therefore included women under the postpartum onset specifiers of both DSM and ICD (4 and 6 weeks respectively). Women with severe melancholia without psychosis were

excluded from the analyses, consistent with the literature.[1,20] It is important to note the use of "postpartum psychosis" in this paper refers to episodes occurring in the postpartum period whether or not there are any preceding episodes of bipolar disorder. To distinguish the two contexts in which postpartum psychosis presents, we define "first onset postpartum psychosis" as an episode of postpartum psychosis occurring as first lifetime ever psychiatric episode in women without previous psychiatric history and "postpartum bipolar relapse" as an episode of postpartum psychosis in the context of a pre-existing bipolar illness. Interrater reliability was assessed in a formal exercise using 20 randomly selected cases. The exercise involved 14 raters and 10 parous women, including 3 with postpartum psychosis, 3 with postpartum depression and 4 without perinatal mental illness. The mean kappa for postpartum psychosis diagnosis was 0·92, for psychosis 0·99, and for congruence 0·89; mean intraclass correlation coefficients were 0·94 for age of onset, 0·93 for number of episodes of depression and 0·98 for number of episodes of mania.

Control women were recruited via the British Blood service and the 1958 Birth Cohort (UK National Child Development Study); they were not screened for mental disorders and were matched for genetic ancestry to cases. Characteristics and recruitment of these samples has been described previously.[21]

Genotyping, Quality Control, and Imputation

A detailed description of genotype data and polygenic scores calculation is provided in Lewis et al.[18] Genotyping was conducted on Affymetrix GeneChip 500K Mapping Array Set, Illumina Omni Express Array, and Illumina PsychChip.

Quality control was performed separately on batches from each platform before merging using PLINK version 1.9 software.[22] After quality control, data for each platform were phased using SHAPEIT version 3·4·0·10233[23] and imputed using IMPUTE[24] with the 1000 Genomes Project reference panel (phase 3).[25] Imputed data were converted to the most

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probable genotypes (probability $\geq 0\cdot9$) with additional SNPs excluded if the imputation INFO score was $<0\cdot8$, MAF$<0\cdot01$ or HWE P $<1\text{x}10^6$. Imputed data were merged on shared SNPs. SNPs which showed large differences in frequency between samples on different genotyping platforms were removed, so were 1,036,851 variants showing frequency differences between platforms principal component analysis in the post-imputation dataset. PCA performed after this step showed no effect of platform.[18]

PLINK version $1\cdot9$ software[22] was used to conduct principal component analysis on the clumped dataset. Eigenvectors for the first 10 principal components were included in all association analyses in order to control for potential confounding from population structure.

Polygenic risk score generation

Polygenic risk scores were generated in PLINK version $1\cdot9$ from discovery genome-wide association studies of schizophrenia,[26] bipolar disorder,[27] and major depression[28] (Appendix page 5). Participants included in both discovery and testing datasets were excluded from the discovery datasets. Imputed genotypes were clumped for linkage disequilibrium using p-value informed clumping at $r^2<0\cdot2$ and 1MB windows. After clumping, polygenic risk scores were generated at standard p-value thresholds by summing the number of susceptibility alleles of each single nucleotide polymorphism weighted by the logarithm of its effect (odds ratio) in the discovery dataset. Scores were then standardized. Results are reported at a p-value threshold of $p \leq 0\cdot05$ for schizophrenia and depression and $p \leq 0\cdot01$ for bipolar disorder, as these are the thresholds that maximized the signal to noise ratio in the discovery datasets.[26-28]

Genotyping platform did not affect the effect and statistical significance of the results (Appendix page 5).

Statistical analyses

Data analyses were conducted in R versions 3·3 to 4·0.

Multinomial logistic regression (computed using the *multinom* function in the *nnet* R package[29]) was used to model the effect of each polygenic risk scores on diagnosis (first onset postpartum psychosis, bipolar disorder or control). Risk ratios were defined as the ratio of the probability of being in the first onset postpartum psychosis or, separately, bipolar disorder categories over the probability of being a control (reference category). Head to head comparisons between diagnostic groups were conducted using binomial logistic regression (*glm* fuction in the *stats* base R package) to model the effect of each polygenic risk scores on diagnosis.

The risk and odds ratios presented were adjusted for 10 principal components of genetic variation to account for population stratification. Sensitivity analyses were conducted to take into account the association of number of episodes of mania and depression and age at first impairing illness with both diagnosis and depression polygenic risk scores.

We compared the goodness-of-fit of the main full logistic regression models (dependent variable: first onset postpartum psychosis v bipolar disorder, independent variables: polygenic risk scores, 10 genetic principal components) against the likelihood of the data under a model with only the 10 principal components using the likelihood ratio test (anova function).

The discriminatory power was then assessed by separating the sample in a training (60% of the observations) and in a testing set and calculating the area under the curve.

Role of the funding source

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Results

Participant ascertainment occurred between September 1991 through to May 2013.
We identified for analyses 1) 203 women with history of postpartum psychosis as first lifetime ever psychiatric episode (thereafter "first onset postpartum psychosis"), and 2) 1,225 parous women with bipolar disorder, including a) 227 with postpartum psychosis in the context of a pre-existing bipolar illness (thereafter "postpartum bipolar relapse", bipolar I disorder (N=210); bipolar II disorder (N=8); schizo-affective bipolar disorder (N=8); bipolar disoder not otherwise specified (N=1)) and b) 998 parous women (DSM-IV bipolar I disorder (N=958), schizo-affective bipolar disorder (N=40)) without history of postpartum bipolar relapse, i.e. parous women with bipolar disorder without history of postpartum psychosis (Figure 1).

All self-reported their ethnicity as White. Women with bipolar II disorder without history of postpartum psychosis were excluded, as it has been previously shown that they have a different clinical[30] and genetic[27] risk profile to bipolar I and schizo-affective bipolar disorder. A total of 2,809 control women who reported their ethnicity as White British were also included. Demographic and clinical characteristics of participants with first onset postpartum psychosis and bipolar disorder are shown in Table 1.

Women with first onset postpartum psychosis were more likely to experience incongruent psychotic symptoms when ill (Chi-square = 11·45, df = 1, p=0·0007), but had a more favourable clinical course of illness, with a later illness onset (Wilcoxon rank sum test (W) = 83483, p<0·0001) and fewer episodes of depression (W = 137062, p<0·0001) and mania (W = 139399, p<0·0001) than women with bipolar disorder.

Polygenic risk scores for bipolar disorder and for schizophrenia were significantly higher in both women with first onset postpartum psychosis and in those with bipolar disorder compared to controls (adjusted relative risk ratios adjRR (95% Confidence Intervals): bipolar disorder polygenic risk scores: 1·71 (1·56, 1·86), p<0·0001 and 1·77 (1·69, 1·84), p<0·0001 respectively, Figure 2; schizophrenia polygenic risk scores: adjRR 1·82 (1·66, 1·97), p<0·0001, and adjRR 2·00 (1·92, 2·08, p<0·0001), respectively, Figure 2).

However, women with first onset postpartum psychosis and women with bipolar disorder did differ in their genetic liability to major depression (Figure 2). While women with bipolar disorder had a greater genetic liability to major depression compared to controls (adjRR 1·24 (1·17, 1·31), p<0·0001), those with first onset postpartum psychosis had similar major depression polygenic risk scores to controls (adjRR 0·97 (0·82, 1·11), p=0·63). When we directly compared polygenic risk scores within cases, women with first onset postpartum psychosis had significantly lower polygenic risk scores for major depression than women with bipolar disorder (post-hoc binomial logistic regression adjOR 0·79 (0·68, 0·91), p=0·0018; Figure 2). The full model, i.e., the model including depression polygenic risk scores provided better fit to the data (chi-square (1, n = 1428), 9·86, p=0·0017) than the model with only genetic principal components.

Episodes of postpartum psychosis can also occur in women with previous history of bipolar disorder outside the perinatal period (postpartum bipolar relapse, appendix page 3). In the main analysis, we combined them with parous women with bipolar disorder but without a history of postpartum relapse. Our secondary analyses supported this approach. We found that the course of illness (i.e. age at impairment, number of episodes of depression and mania) of women with postpartum bipolar relapse was similar to that of women with bipolar disorder without

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postpartum bipolar relapse and different from that of women with first onset postpartum psychosis (Appendix page 6). The presence or absence of postpartum bipolar relapse in the context of a previously established bipolar illness did not affect polygenic risk score profiles. Parous women with bipolar disorder had overlapping polygenic scores for bipolar disorder (adjOR 1·03 (0·89–1·19), p=0·72), schizophrenia (adjOR 1·03 (0·89–1·21), p=0·67) and major depression (adjOR 0·98 (0·85–1·14), p=0·80), regardless of their history of subsequent postpartum psychosis. In line with our hypothesis, women with postpartum bipolar relapse also had significantly higher polygenic scores for major depression than women with first onset postpartum psychosis (adjOR 0·80 (0·66–0·97), p=0·022).

According to our analyses, women with first onset postpartum psychosis experience significantly fewer recurrences of illness after the onset compared to women with bipolar disorder, even after adjusting the analyses for differences in age at first impairment and age at interview (Table 1). Age at first impairment and number of depressive and manic recurrences also correlated with polygenic scores for major depression (-0·43, p=0·0089; 0·85, p<·0001; 0·47, p=0·0018). We therefore introduced them as covariates when modelling the association between diagnosis and polygenic scores for major depression. The introduction of these covariates in the model did not significantly change the significance or effect size of the association (adjOR for first onset postpartum psychosis versus bipolar disorder, 0·79 (0·66, 0·93), p=0·0055; AUC = 0·72, 95% CI: 0·66-0·79).

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Discussion

In this case-control study, we used genomic approaches to inform the nosology of postpartum psychosis and its relationship with bipolar disorder.

When genetic liability to bipolar disorder and schizophrenia were considered, we found that first onset postpartum psychosis and bipolar disorder overlapped. This finding taken alone supports the inclusion of postpartum psychosis in the bipolar disorder spectrum (Figure 2). However, when genetic vulnerability to major depression was considered, differences emerged. Women with first onset postpartum psychosis had significantly lower genetic vulnerability to major depression than women with bipolar disorder, similar to that of controls (Figure 2).

Clinical and family studies have suggested differences in the presentation and risk profile between first onset postpartum psychosis and bipolar disorder.

To the best of our knowledge this is the first study using molecular genetic markers to address the nosological controversies surrounding postpartum psychosis. Our results do not support simplistic models of a unidimentional association between postpartum psychosis and bipolar disorder. Instead, we postulate a model (Figure 2) in which postpartum psychosis overlaps with bipolar disorder when genetic vulnerabilities to bipolar disorder and schizophrenia are considered, but significantly differs when vulnerability to major depression is considered.

Currently, "postpartum psychosis" is an umbrella term for a number of clinical manifestations and includes both women with a pre-existing bipolar illness that have a recurrence after childbirth and those with new onset postpartum psychosis.[31] Previous research has suggested differences in the clinical presentation[31,32] and more favorable long-term outcomes (such as fewer number of episodes) in women with first onset postpartum

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compared to bipolar disorder with onset at other times[33]. Our results provide biological

corroboration to clinical studies that have reported different risk profiles in the perinatal

period in women with first onset postpartum psychosis and in those with pre-existing bipolar

disorder.[13] Here we substantiate these findings and suggest partially different biological

mechanisms in the two groups. We found that, compared to women with first onset

postpartum psychosis, women with a postpartum bipolar relapse have a more recurrent

disease course and a higher genetic liability to depression, similar to that of women with

bipolar disorder without history of a psychotic or manic postpartum relapse.

Taken together, our findings support the hypothesis that women with first onset postpartum

psychosis have a better prognosis compared to women with bipolar disorder, in line with a

recent meta-analyses on the long-term outcomes after first onset postpartum psychosis.[33] Our

finding of a lower genetic vulnerability to depression may also explain why women only

have their first episode after delivery. If they had a high genetic loading for depression, they

may have had affective episodes ealier in life.

Etiological and intervention studies of bipolar disorder have long confronted the challenges

of heterogeneity. Recent genome wide association studies have suggested that bipolar

disorder is a complex, heterogenous nosological entity, with strong genetic overlaps with

schizophrenia and major depression.[27] More broadly, genetic overlap across psychiatric

disorders is the norm. The lack of genetic association between first onset postpartum

psychosis and major depression may represent an exception. Major depression is in fact

genetically correlated with a plethora of disorders and traits, including disorders with a

similar presentation to first onset postpartum psychosis such as schizophrenia ($rg=0.34$,

$se=0.025$)[28], bipolar I ($rg = 0.30$, $se = 0.028$)[27] and bipolar II ($rg = 0.69$, $se = 0.093$)[27]

disorders. The association with genetic liability to bipolar disorder, but not depression,

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suggests that first onset postpartum psychosis may represent a promising phenotype for biological studies focusing on the manic-affective psychosis switch.

Our results need to be interpreted in light of the following methodological considerations. Our findings concern the onset of affective psychosis, in relation to childbirth or at other times, rather than the lifelong longitudinal course of illness.

Second, we considered only common genetic variants derived from genome wide association studies. These variants are only a reflection of the current progress in genomic discovery of risk alleles and do not capture all of the heritability of phenotypes.[34] Current evidence, however, suggests that rare genetic variants play a minor role in the heritability to bipolar disorder.[35]

The effect common genetic variants have on discriminating individual psychiatric diagnoses is small. Their applicability outside European populations is also limited.[36] Larger and more diverse samples are required to improve the precision and generalisability of our estimates. Moreover, the strong genetic overlap between bipolar disorder and schizophrenia suggests that larger samples and new statistical methods are especially necessary to disentangle the genetic relationship between schizophrenia, bipolar disorder and postpartum psychosis. Finally, controls were not screened for mental disorders. For disorders with population prevalence below 20% (such as bipolar disorder and postpartum psychosis), however, the use of unscreened controls has a negligible effect on the statistical power.[37] Moreover, the composition of the control group does not affect the difference in major depression polygenic risk score in the direct comparison between first onset postpartum psychosis and bipolar disorder.

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Our study focused on the onset of bipolar/affective psychosis rather than the longitudinal course of illness. Only 54 (27%) of women with first onset postpartum psychosis in our study did not experience any subsequent manic episode outside the postpartum period. Interestingly, we found that the timing of onset of illness (within or outside the postpartum period) rather than the presence of absence of a postpartum episode is associated with the genetic liability to major depression.

To conclude, our study provides, for the first time, genomic evidence to inform the definition and classification of postpartum psychosis. Our results have important implications for future research suggesting first onset postpartum psychosis should be differentiated from postpartum episodes occurring in the context of pre-existing bipolar illness. They also provide biological corroboration of previous clinical evidence, pointing to the importance of individualized management that will lead to improved outcomes for women and their families.

Contributors statement

ADF: Conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, visualisation, writing - original draft, writing - review and editing

JMKY: Data curation, formal analysis, investigation, project administration, validation, visualisation, writing - review and editing

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Declaration of interest

We declare no competing interests.

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Figures, legends and tables

[provided in a separate file as requested]

Research in context

Evidence before this study: Postpartum psychosis is currently not recognized by diagnostic systems, but diagnosed in the general mania or psychotic depression categories of the mood or psychotic disorders. The validity of this approach has been widely discussed for years. Ovid MEDLINE (January 1946-March 2020), Embase (January 1947- March 2020), APA PsycINFO (January 1806-March 2020), and the Cochrane Library were searched on April 3rd 2020 for all postpartum psychosis related studies published in English. Original searches were done for systematic reviews, epidemiological, clinical, family, adoption, twin or molecular genetic studies with the following search terms: ("postnatal" or "postpartum" or "perinatal" or "puerperal" or "childbirth" or "trimester" or "peripartum" or "post-natal" or "post-partum") and ("psychosis" or "mood disorder" or "mania" or "manic" or "bipolar"). Some research supports the inclusion of postpartum psychosis as part of the bipolar disorder spectrum due to similarities in clinical presentation; however, a significant number of women with postpartum psychosis do not exhibit any episodes outside the postpartum period. Further evidence supports the finding that women with a history of bipolar disorder are at high risk of developing postpartum psychosis and vice versa. First–degree relatives of women with postpartum psychosis and bipolar disorder are also at similar risk for bipolar disorder. Nonetheless, the literature suggests differences in risk for family members for other affective disorders when comparing bipolar disorder and postpartum psychosis. There are also differences in clinical presentation and outcomes which suggests an incomplete picture of the relationship between the two disorders.

Added value of this study: To our knowledge, this study is the first to provide biological evidence to inform the definition and classification of postpartum psychosis and corroborates

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previous clinical findings pointing to the importance of individualized management. It suggests a multi-axial relationship between bipolar disorder and postpartum psychosis. First onset postpartum psychosis has a distinctive genetic risk profile, that only partially overlaps with that of bipolar disorder.

Implications of all the available evidence: Future research and clinical practice should move towards considering first onset postpartum psychosis as a separate entity to postpartum bipolar recurrences. This distinction will have important ramifications for disease classification as well as for appropriate treatment and management of these conditions.

Data sharing

Anonymised individual genotype data has been shared with the Psychiatric Genomics Consortium. Detailed information here https://www.med.unc.edu/pgc/shared-methods/.

Figure 1: Sample selection

Boxes content:

- BDRN database participants with genotype and phenotype information available N=5,461

- Non parous N=1,064
Males N=1,861
Information not available N=535

- Postpartum psychosis, but no information on first onset postpartum available, N= 44
Bipolar II disorder (N=481) or bipolar disorder not otherwise specified (N=31) or major depression (N=8) or diagnosis on available (N=9) without history of postpartum psychosis

- Parous women N= 2,001

- Bipolar disorder N= 1,225
First onset postpartum psychosis N= 203

- Controls from the general population with genotype information available N= 5,714
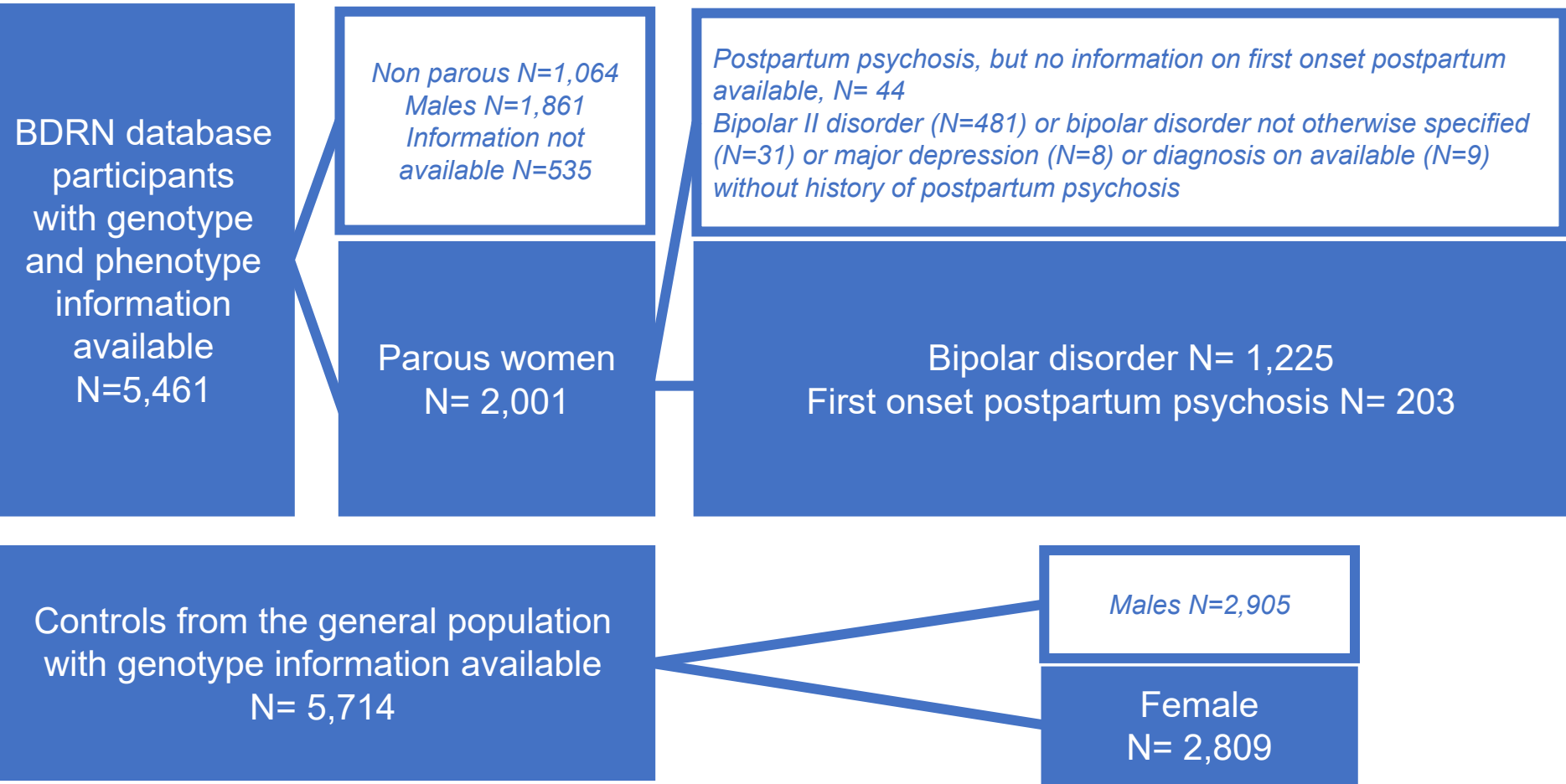
- Males N=2,905

- Female N= 2,809

Table 1: Demographic and lifetime clinical characteristics of participants.

	First onset postpartum psychosis (n=203)	Bipolar disorder (n=1225)
Age at interview (years: median; min-max)[a]	46 (21-79)	49 (19-83)
Number of pregnancies (median; min-max) [no stat?]	2 (1-7)	2 (1-11)
Number of deliveries (median; min-max)	2 (1-5)	2 (1-10)
Age at impairment (years: median; min-max)[b]	26 (13-39)	21 (4-68)
Number of episodes of depression (present: N; %)[c]		
Up to 2	103 (54)	236 (20)
3 to 5	33 (17)	255 (22)
6 to 10	25 (13)	254 (22)
11 to 20	12 (6)	208 (18)
More than 20[d]	19 (10)	212 (18)
Number of episodes of mania (present: N; %)[c]		
Up to 2	80 (40)	220 (19)
3 to 5	35 (18)	246 (21)
6 to 7	44 (22)	288 (25)
8 to 15	28 (14)	203 (17)
More than 15[d]	12 (6)	214 (18)
Psychosis (present: N; %)[b]	157 (84)	708 (66)
Mood-incongruent psychotic features (present: N; %)[e,f]	103 (67)	390 (52)

[a] p = 0·0004
[b] p < 0·0001
[c] p < 0·0001 after correcting for age and length of illness using ordinal logistic regression
[d] including too many to count or chronic depression statistically
[e] p = 0·0007
[f] Determined using Schedules for Clinical Assessment in Neuropsychiatry as in Allardyce and colleagues[17]
Note: Percentages based on individuals with available data.

Supplementary Content

Figure1. Heuristic models.
Figure 2: Lifetime relationship between bipolar disorder and postpartum psychosis.

Table 1: Potential validators of the inclusion or exclusion of postpartum psychosis in the bipolar disorder spectrum.

Methods
Table 2: Genome-wide association studies used as training sets to generate polygenic risk scores.
Table 3: Odds ratios of history of first onset postpartum psychosis compared to history of bipolar disorder for a unit change in standardised polygenic risk scores. Analyses corrected for 10 principal component and genotyping platform.
Table 4: Clinical characteristics of affected participants with first onset bipolar disorder outside the perinatal period and history of postpartum relapse and comparisons with women with first onset postpartum psychosis and women with bipolar disorder without history of postpartum relapse.

Development of testable hypotheses

In order to develop testable hypotheses, here we considered two extreme heuristic models of the relationship between episodes of postpartum psychosis and bipolar disorder, based on genetic risk (Figure 1):

1) Bipolar disorder and postpartum psychosis are a single disease entity (Figure 1, panel A). This model would be in line with the current classification of postpartum psychosis in DSM(1) and ICD(2), but not with clinical evidence showing differences between the two disorders (Table 1).

2) Bipolar disorder and postpartum psychosis are two separate disease entities (Figure 1, panel B), despite similarities in the clinical presentation. This model implies genetic "zones of rarity"(3) separating them. Molecular genetic studies have however falsified this hypothetical model for other psychiatric traits, by providing robust evidence of overlapping genetic liability between psychiatric disorders.(4)
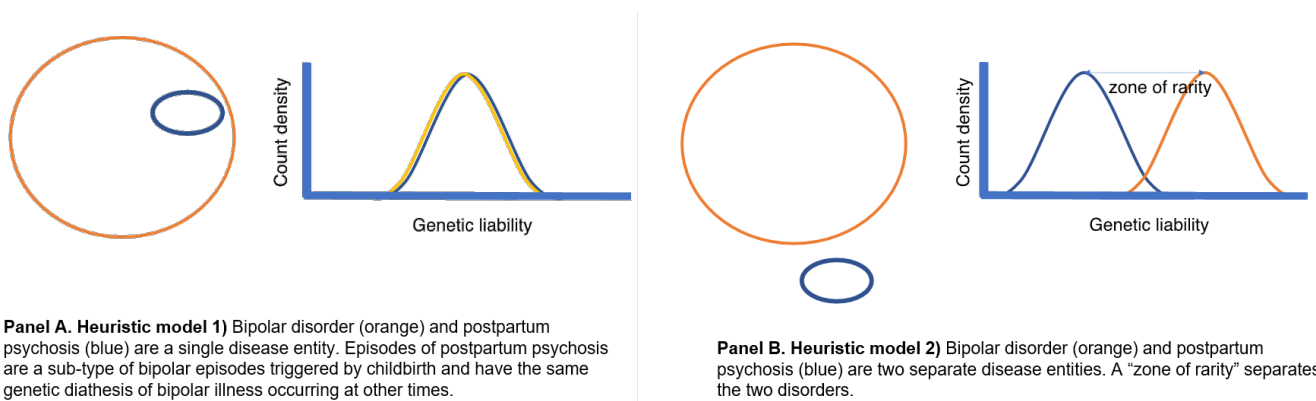

Panel A. Heuristic model 1) Bipolar disorder (orange) and postpartum psychosis (blue) are a single disease entity. Episodes of postpartum psychosis are a sub-type of bipolar episodes triggered by childbirth and have the same genetic diathesis of bipolar illness occurring at other times.

Panel B. Heuristic model 2) Bipolar disorder (orange) and postpartum psychosis (blue) are two separate disease entities. A "zone of rarity" separates the two disorders.

Figure 1: Heuristic models. In order to develop testable hypotheses, here we considered two extreme heuristic models of the relationship between episodes of postpartum psychosis and bipolar disorder, based on genetic risk.

Table 1: Potential validators of the inclusion or exclusion of postpartum psychosis in the bipolar disorder spectrum(5)

VALIDATOR	SUPPORTING INCLUSION IN THE BIPOLAR SPECTRUM	REJECTING THE INCLUSION IN THE BIPOLAR SPECTRUM
ANTECEDENT	First-degree relatives of women with postpartum psychosis have a risk of bipolar disorder similar to that of first-degree relatives of patients with bipolar disorder(6-9)	A lower risk for affective illness and other psychiatric disorders among family members of women with puerperal psychosis than that among non-puerperal bipolar controls(10, 11); a higher risk of severe mental illness in women with postpartum psychosis compared to bipolar disorder.(12)
CURRENT	The clinical presentation of postpartum psychosis overlaps that of severe mania, psychotic depression or mixed episodes.	Between subject design: Disturbance of consciousness, disorientation mood incongruence more common in postpartum psychosis than mania.(13-15) Within subject design: classic manic symptoms, specifically pressured speech and increased sociability significantly less frequent in postpartum manic episodes.(16)
PREDICTIVE	Women with history of bipolar disorder are at high risk of postpartum psychosis(17) and women who suffered from postpartum psychosis have a high risk of subsequent bipolar illness outside the postpartum period (over 50%).	About 40% of women with postpartum psychosis do not experience any recurrence outside the postpartum period. Clinical outcomes and response to prophylactic treatment during pregnancy and after childbirth differ between women with history of postpartum psychosis only and those with bipolar disorder.(18)

Indirect evidence from genetic studies of other psychiatric traits therefore supports some degree of overlap between bipolar disorder and postpartum psychosis and intermediate models with quantitative or qualitative differences in genetic liability between the two.

For example, childbirth may act as a powerful trigger on a genetic predisposition that would otherwise not manifest itself. Women with first onset postpartum psychosis may therefore have a genetic vulnerability to bipolar disorder higher than the general population, but lower than women who develop bipolar disorder independently from childbirth. If data support this hypothesis, differences would be quantitative.

The differences in genetic liability between bipolar disorder and postpartum psychosis could however be *qualitative* rather than quantitative. There is for example robust evidence that the link between childbirth and psychiatric illness is specific for episodes of mania or affective psychosis and does not extend to schizophrenia or major depression.(17, 19, 20) Family studies have also suggested a specific familial vulnerability to the postpartum trigger and that postpartum psychosis may represents a marker for a more familial subtype of bipolar disorder.(21, 22) Moreover, in our previous research, we have found two distinct clinical risk profiles for postpartum psychosis and postpartum non-psychotic bipolar depression, suggesting that the two illnesses may not share causative mechanisms.(16, 19, 23-28) In particular, we did not find any association between postpartum psychosis and factors associated with mental disorders in general, such as childhood trauma,(26) smoking(19) and personality traits, cognitive styles or temperaments.(26)

Taken together, these streams of research suggest that the causative mechanisms underpinning postpartum psychosis may be quantitatively and qualitatively different from those of bipolar disorder as a whole.

Based on the previous evidence of a distinct clinical and familial risk profile, here we hypothesized that first onset postpartum psychosis identifies a group of women with specific genetic liability to bipolar disorder, that does not extend to the liability to schizophrenia and major depression. We also hypothesized that women with postpartum psychosis in the context of an established bipolar illness (thereafter "postpartum bipolar relapse") have similar genetic risk profile to those with bipolar disorder without history of postpartum relapse.

There are a number of women with history of bipolar disorder not associated with childbirth who subsequently suffer from postpartum relapse (Figure 2).

Figure 2: Lifetime relationship between bipolar disorder and postpartum psychosis. A lifetime diagnosis of bipolar I disorder in DSM-5 and ICD-11 includes three groups of women: 1) those with bipolar episodes outside of the postpartum only (orange), 2) those with both postpartum psychosis and manic episodes outside the postnatal period (intersection) and 3) women with postpartum psychosis only (blue). A small proportion of women with mania or psychotic depression after childbirth may be diagnosed with lifetime schizoaffective disorder or unipolar psychotic depression or bipolar II disorder. It has been estimated that about 1 in 3 parous women with DSM bipolar I disorder experience at least one episode of postpartum psychosis. On the other hand, while only 1 in 3 women with postpartum psychosis has an antecedent psychiatric history, mostly of major depression, over 40% will suffer from subsequent bipolar episodes outside the postpartum period.(29)

For these women, postpartum bipolar relapse may index an illness with frequent recurrences, without a specific link with childbirth. Women with a history of frequent recurrences or a chronic course of illness are in fact more likely to be unwell at any point in time. These women would become unwell whether or not childbirth occurs. We therefore also hypothesized that women with a history of postpartum bipolar relapse do not have any specific biological vulnerability associated with childbirth, rather they have a disorder with many recurrences, some of which happen in relation to childbirth. In other words, we tested the hypothesis that women with a history of postpartum bipolar relapse have similar genetic risk profiles to those with bipolar disorder without postpartum relapse.

Methods
Genotyping
Genotyping was conducted on Affymetrix GeneChip 500K Mapping Array Set, Illumina Omni Express Array, and Illumina PsychChip.

Quality control
Quality control was performed separately on batches from each platform before merging using PLINK version 1.9 software. (30)

Single nucleotide polymorphisms (SNPs) were excluded if the minor allele frequency was less than 0.01, and if they deviated from Hardy-Weinberg Equilibrium at $P \leq 10\text{-}6$ or call rate < 98%.

Individuals were excluded from the sample if they had increased or decreased heterozygosity of $|F| > 0.1$, a discrepancy between their genotypic and reported sex, genotype call rate < 98%, high pairwise relatedness (pi-hat > 0.2) or did not cluster with European population samples in principal component analysis of 2000 participants from 19 populations of the 1000 Genomes Project.

Variants showing frequency differences between platforms principal component analysis (PCA) in the post-imputation dataset (n=1,036,851) were excluded by performing pairwise association analyses between 1) the case batches, and 2) control batches and excluding variants with association p<0.01. PCA performed after this step showed no effect of platform.(31)

Imputation
After quality control, data for each platform were phased using SHAPEIT version 3.4.0.10233(32) and imputed using IMPUTE(33) with the 1000 Genomes Project reference panel (phase 3).(34) Imputed data were converted to the most probable genotypes (probability ≥ 0.9) with additional SNPs excluded if the imputation INFO score was <0.8, MAF<0.01 or HWE P <1x10-6). Imputed data were merged on shared SNPs. SNPs which showed large differences in frequency between samples on different genotyping platforms were removed.

Principal Component Analysis
PLINK version 1.9 software(30) was used to conduct principal component analysis on the clumped dataset. Eigenvectors for the first 10 principal components were included in all association analyses in order to control for potential confounding from population structure.

Polygenic risk score generation
Polygenic risk scores were generated in PLINK version 1.9 from discovery genome-wide association studies (discovery datasets) of bipolar disorder, major depression and schizophrenia (Table 2). Participants included in both discovery and testing datasets were excluded from the discovery datasets. Imputed genotypes were clumped for linkage disequilibrium using p-value informed clumping at $r^2<0.2$ and 1MB windows. Single nucleotide polymorphisms most significantly associated with the phenotype of the discovery datasets were retained. After clumping, polygenic risk scores were generated at standard p-value thresholds by summing the number of susceptibility alleles of each single nucleotide polymorphism weighted by the logarithm of its effect (odds ratio) in the discovery dataset. Scores were then standardized. Results are reported at a p-value threshold of $p \leq 0.05$ for schizophrenia and depression and $p \leq 0.01$ for bipolar disorder, as these are the thresholds that maximized the signal to noise ratio in the discovery datasets.(35-37)

All analyses were adjusted for 10 population principal components.

Genotyping platform did not affect the effect and statistical significance of the results (Table 3).

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Table 2: Genome-wide association studies used as training sets to generate polygenic risk scores. The majority of cohorts included in the genome wide association study of major depression used to generate polygenic risk scores of major depression were screened for major depression

	Publication	Cases	Controls	Total	p threshold reported	Notes
BIPOLAR DISORDER	Stahl et al.(36)	16192	25620	41812	0.01	excludes BDRN samples
SCHIZOPHRENIA	Pardiñas et al.(35)	11199	19940	31139	0.05	excludes control duplicates and cases related to BDRN cases
MAJOR DEPRESSION	Wray et al.(37)	51865	112200	164065	0.05	excludes 23andme samples

Table 3: Odds ratios of history of first onset postpartum psychosis compared to history of bipolar disorder for a unit change in standardised polygenic risk scores. Analyses corrected for 10 principal component and genotyping platform.

Polygenic risk scores	OR	95% CI	P value
Bipolar disorder	0.97	0.83, 1.13	0.71
Schizophrenia	0.90	0.76, 1.06	0.19
Major depression	0.79	0.68, 0.91	0.0018

Table 4: Clinical characteristics of affected participants with first onset bipolar disorder outside the perinatal period and history of postpartum psychosis and comparisons with women with first onset postpartum psychosis and women with bipolar disorder without history of postpartum psychosis.

	First onset outside the perinatal period and history of postpartum relapse (N=227)	First onset postpartum psychosis (N=203)	Bipolar disorder without postpartum psychosis (N=998)
Age at impairment (years: median; min-max)	19 (4-39)[a, b]	26 (13-39)[b]	22 (4-68)[a]
Number of episodes of depression (present: N; %)[c]			
Up to 2	62 (28)	103 (54)	174 (18)
3 to 5	42 (19)	33 (17)	213 (23)
6 to 10	46 (21)	25 (13)	208 (22)
11 to 20	31 (14)	12 (6)	177 (19)
More than 20[d]	40 (18)	19 (9)	172 (18)
Number of episodes of mania (present: N; %)[e]			
Up to 2	40 (18)	80 (40)	180 (19)
3 to 5	43 (19)	35 (18)	203 (21)
6 to 7	67 (30)	44 (22)	221 (23)
8 to 15	45 (20)	28 (14)	158 (17)
More than 15[d]	31 (14)	12 (6)	183 (19)
Eysenck Personality Questionnaire(38)			
Neuroticism (median; min-max)	16 (0-23)[f]	14 (2-23)	17 (0-23)[a]
Psychoticism (median; min-max)	2 (0-14)[g]	2 (0-11)	3 (0-15)[a]
Extraversion (median; min-max)	12 (1-21)	10 (0-21)	11 (0-21)
Psychosis (present: N; %)[h]	177 (85)[b]	157 (84)	531 (62)[a]
Mood-incongruent psychotic features (present: N; %)[h]	98 (54)[b]	103 (67)	292 (51)[a]

[a] statistically significant difference with first onset postpartum psychosis (P <0.0001)
[b] statistically significant difference with bipolar disorder without postpartum relapse (P <0.0001)
[c] statistically significant difference between bipolar disorder without postpartum relapse and first onset postpartum psychosis (P <0.0001) and between bipolar disorder with and without postpartum relapse (P=0.0006) after correcting for age and length of illness using ordinal logistic regression
[d] including too many to count or chronic depression statistically
[e] significant difference between bipolar disorder without postpartum psychosis and first onset postpartum psychosis (P <0.0001) after correcting for age and length of illness using ordinal logistic regression
[f] statistically significant difference with first onset postpartum psychosis (P=0.0005)
[g] statistically significant difference with bipolar disorder without postpartum relapse (P=0.005)
[h] Defined as in Lewis et al.(31)
Note: Percentages based on individuals with available data.

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