Bipolar disorder in pregnancy and the postpartum

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Rather than love, than money, than fame, give me truth.
Henry David Thoreau

To my Grandfather

Abstract

In the first part of my PhD I explored the link between childbirth and mood disorders in a retrospective sample of over 1500 parous women with mood disorders, recruited as part of ongoing molecular generic studies.

Around two thirds of participants reported at least one episode of illness during pregnancy or the postpartum. Women with bipolar I disorder reported an approximately 50% risk of a perinatal major affective episode. Risks were lower in recurrent major depression and bipolar II disorder at around 40%. The majority of perinatal episodes occurred within 4 weeks of childbirth. Episodes of mania or psychosis had an earlier onset than those of depression. For bipolar II disorder, onsets of psychiatric episodes were more spread out over the perinatal period with more onsets in pregnancy and later in the postpartum. Moreover, childbirth did not seem to be a specific trigger for the majority of perinatal episodes of bipolar II disorder.

Primiparity was associated with postpartum mania/psychosis and unipolar postpartum depression in women who experienced their first lifetime episode within 6 weeks postpartum. My findings raise the possibility of a relationship between postpartum mood disorders and other disorders influenced by parity, such as pre-eclampsia.

In the second part of my PhD I designed and piloted a prospective study aimed i) to replicate and ii) to extend the findings on the retrospective sample, exploring the influence of a range of variables on the vulnerability to develop an episode of severe illness in pregnancy or the postpartum. Over 14 months of recruitment 19 women completed the follow-up assessment. To capture the clinical complexity of bipolar disorder in pregnancy and the postpartum period very large scale longitudinal studies are needed. These studies must be based on a strong collaboration with the NHS.

Acknowledgment

"e più d'onore ancora assai mi fenno,   "and even greater honor then was mine,
ch'è sì mi fecer de la loro schiera,"   for they invited me to join their ranks-"

Dante, Inferno, IV, 100-101   Dante, Hell, IV, 100-101

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List of abbreviations

APP:Action on Postpartum Psychosis

BD-I: Bipolar I disorder

BD-II: Bipolar II disorder

BDRN: Bipolar Disorder Research Network

BEP-C: Bipolar Education Program - Cymru

CUPS: Cardiff University Psychiatry Second Opinion Service

DSM: Diagnostic and Statistical Manual of Mental Disorders

EM algorithm: Expectation-Maximization algorithm

GP: General practitioner

ICD: International Classification of Diseases

NHS: National health system

OR: Odds ratio

PND: Postnatal depression

PNE: Perinatal mood episode

PNS: Perinatal psychiatric services

RMD: Recurrent major depression

SCAN:Schedules for Clinical Assessment in Neuropsychiatry

sd: Standard deviation

SE: Standard error

Glossary

$100(1-\alpha)\%$ **confidence interval estimate**:a random interval that include the parameter with probability $1 - \alpha$ for some $0 < \alpha < 1$.

Bipolar depression An episode of DSM-IV major depression in subjects who have previously experienced a manic/hypomanic/mixed episode

Postpartum or postnatal The period beginning immediately after childbirth. The length of the postnatal period varies. In the DSM-IV the postpartum onset specifier covered episodes occurring within 4 weeks, the ICD-10 has a category for episodes occurring within 6 weeks after childbirth, while in the clinical practice a 6 months interval is usually accepted. In general a manic or affective psychotic episode occurring after childbirth.

Postpartum or postnatal (non psychotic) depression DSM-IV major depressive episode without psychotic features occurring in the postpartum period.

Postpartum or postnatal or puerperal psychosis In my analyses DSM-IV mania, or DSM-IV psychotic depression or DSM-IV mixed episode or cycloid psychosis, defined as Brockington, with onset after delivery.

Primigravida A woman who is pregnant for the first time.

Primipara A woman who has given birth to only one child.

Probability or random sample: sample selected through probability sampling. The sample is selected from a frame, that contains all the units of the population under consideration (target population). Randomness does not imply haphazardness.

The work in this thesis is reproduced in whole or in part in the following publications:

Di Florio A, Forty L, Gordon-Smith K, Heron J, Jones L, Craddock N, Jones I. Perinatal episodes across the mood disorder spectrum. Archives of general Psychiatry, In press

Di Florio A, Jones I. Postnatal depression. BMJ Best Practice. http://bestpractice.bmj.com/best-practice/monograph/512/resources/credits.html

Di Florio A, Smith S, Jones I. Postpartum psychosis. The Obstetrician and Gynecologist, In press

DiFlorio A, Jones I. Is sex important? Gender differences in bipolar disorder. Int Rev Psychiatry. 2010;22(5):437-52.

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List of my contributions to the work described in this thesis

Work presented in section II: Perinatal mood episodes in a large dataset of women with mood disorders: I did not contribute to the design of the study nor to the recruitment or assessment of participants. I contributed to the design of the analytic plan, I cleaned the database, conducted the statistical analyses and contributed to the interpretation of the results.

Work presented in section III: A pilot prospective study on bipolar disorder in pregnancy and the postpartum: I did contribute to the design of the study, of the questionnaires and of the follow-up interview. I contributed to the procedures involved in obtaining ethical approval and my research passport. I contributed to the recruitment of participants by contacting the perinatal services, by providing information to possible participants and perinatal services, by writing the advertisements and articles for newsletters and magazines (BDRN newsletter, APP magazine, Pendulum magazine). I conducted the initial telephone screening with possible participants. I coordinated the project by maintaining the contacts with the research assistants who conducted the assessment interviews in pregnancy and with the women who took part. I sent and collected the questionnaires to GPs and psychiatrists. I conducted the follow-up interviews. I then implemented the dataset and designed the analytic plan. I conducted the analyses and interpreted the results.

Introduction

Bipolar disorder is a protean term that indicates a spectrum of psychiatric disorders characterised by periods of pathological mood elation, called mania. Bipolar disorder is often a recurrent illness consisting in episodes of mania and depression alternating with periods of well being. It has been estimated that about 2-7% of women of childbirth age suffers from some form of bipolar disorder [1]. The boundaries between bipolar disorder and unipolar depression are still controversial. If bipolar disorder and unipolar depression are conceptualised in a continuum model, called the mood disorder spectrum, mood disorders are the leading cause of disability worldwide, with unipolar depression ranking first and bipolar disorder 6th among causes of years lived with disability [2].

Among psychiatric illnesses, bipolar disorder is most robustly associated with childbirth [3]. However, the link between childbirth and mood spectrum disorders is still poorly understood. The gap in knowledge is wider for the less severe, but more prevalent, forms, such as postnatal bipolar depression and hypomania, that have been almost neglected by research and clinical practice [4], while more severe forms have intrigued scientists for centuries, with mixed results. Confusion in the clinical nosology of perinatal mood episodes has probably prevented firm and consistent conclusions on the nature of the postpartum trigger. Moreover, the research in this field relies mostly on arbitrary definitions of postpartum disorders, while more evidence-based criteria are needed.
My PhD project sought to address these deficiencies. The 3-year project was organised in 2 parts, that reflect the core structure of this thesis.

In the first part, I explored the link between childbirth and mood disorders in a large retrospective sample of women with mood disorders. The nosology of bipolar disorder is controversial and a lot of research efforts have

been spent in disentangling the relationship between unipolar and bipolar mood conditions. I therefore investigated the childbirth trigger across the entire mood disorder spectrum. I divided the sample with bipolar disorder in two groups, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [5] criteria of bipolar I disorder (BD-I) and bipolar II disorder (BD-II) and used a sample of women with recurrent major depression (RMD) as a comparison group. The large samples analysed were already collected and my input involved: i) formulation of the hypotheses, ii) selection of the samples, iii) data cleaning, iv) statistical analyses, v) interpretation of the results.

In the second part, I designed and piloted a prospective study. Prospective studies are the gold standard design of observational research. I sought to test the feasibility and the validity of a study aimed to recruit a large, well characterised sample of women with bipolar disorder preconception or in early pregnancy and to monitor them through pregnancy and the postpartum. The full-scale study was aimed i) to replicate and ii) to extend the findings on the retrospective sample, exploring the influence of a range of variables on the vulnerability to develop an episode of severe illness in pregnancy or in the postpartum.

Outline of the thesis

This thesis is divided in 4 parts:

1. *A background section in which I give an account of mood disorders and their relationship with childbirth.*

   - In **chapter 1** I attempt to elucidate the terminology used in the thesis by giving a brief overview of the history and the controversies in the definition and classification of mood disorders. The first chapter is dedicated to the broad subject of mood disorders and psychiatric nosology, because I think that the confusion in the terminology and nosology of postpartum mood disorders is rooted on a deeper level in the epistemic limitations of the study of mood disorders. Moreover, I argue that the distinction between unipolar and bipolar disorder is still not clear and that a sample of women with recurrent major depression was therefore needed in the analyses I have conducted. I

finally introduce the current definitions of perinatal mood disorders.

- In **chapter 2** I focus on the childbirth trigger. I critically review the literature on the link between bipolar disorders and childbirth. Many studies have investigated severe episodes of mania or psychotic depression in the perinatal period, while little attention has been devoted to hypomania and bipolar depression. With few exceptions [4, 6, 7], studies investigating postnatal depression have largely neglected bipolar depressioin and have mainly focused only on unipolar depression. Most of the literature on postnatal depression I present is therefore based on unipolar perinatal depression.

- In **chapter 3** I introduce mood disorders in pregnancy and the postpartum, with particular emphasis on postpartum depression and postpartum psychosis. These two conditions are the main topic of my research and are extensively discussed throughout the entire thesis. This chapter has a clinical focus on diagnosis, prognosis and treatment. An in-depth discussion of the clinical issues in identifying and treating perinatal mood disorders is beyond the scope of this thesis. Here I provide a schematic overview on the clinical aspects of perinatal mood disorders. I particularly stress the diagnostic features and the risk factors involved in the liability to postnatal episodes, because they are key factors in the design of the prospective study described in the third and last part of the thesis.

- I conclude the background section in **chapter 4**, where I summarise the gaps in knowledge that have emerged in the previous chapters and I formally state my research hypotheses.

2. *A core section on the research I conducted on the existing retrospective sample.*

- In **Chapter 5** I report the methodology of the research on the retrospective sample. I first describe the Mood Disorder Research Project, from which the data were obtained, then I focus on the statistical methodology I employed. The Mood Disorder Research Project database collects information on individuals who took part in different sub-projects over a 20-year period. Although the main structure of the dataset has remained unchanged, little variations in the inclusion criteria and in the variables assessed have occurred over the

years. In this chapter I provide an overview the methods of recruitment and assessment of the participants in relation to the research hypotheses. Different research hypotheses required sub-samples with different characteristics. Given the complexity of my analytic plan, I provide the reader with a flow-chart summarising the different inclusion criteria for each analysis that I conducted. My major research effort in the study of the retrospective sample was the statistical analyses. Analysing retrospective data on reproductive events is a complex task. Pregnancies from the same woman cannot be considered independent events and many covariates can bias the association between bipolar disorder and the childbirth trigger. Moreover, as in any clinical dataset, I had to deal with missing values. I therefore dedicate the second part of chapter 5 to a general discussion of the statistical methodology that I employed in the analyses of the retrospective dataset. In chapter 5 I do not provide a detailed account of the specific statistical methods that I have employed in different analyses, because I describe them in the pertinent chapters along with the results of the analyses.

- In chapters 6 to 9 I present the results of the analyses that I conducted on the retrospective sample. As I largely discuss in the background chapters, previous studies reported very heterogeneous estimates of the rates of perinatal mood episodes (PNEs) and only few of them reported on less severe episodes of hypomania and bipolar depression. In **chapter 6** I therefore estimate the rates of PNEs across the mood disorder spectrum and explore potential differences across lifetime diagnoses of BD-I, BD-II and RMD.

- One of the main current controversies in perinatal nosology is the duration of the onset criterion. In **chapter 7** I explore the time-to-onset of perinatal mania, psychotic depression and both unipolar and bipolar depression. I present the survival curves according to the phenomenology of the perinatal episodes (mania, psychotic depression, non psychotic depression) and according to the longitudinal course of illness (bipolar vs unipolar depression, first vs second episode, first vs second pregnancy). I also use the Cox proportional hazards model methodology to establish which explanatory variables influenced the latency between childbirth and onset of a postnatal episode.

- In **chapter 8** I follow up the results gathered in chapter 6 and 7

and investigate the specificity of the childbirth trigger. The rates
of PNEs, in fact, need to be interpreted in the light of the longi-
tudinal life-course of mood disorders. First I report the estimates
for first lifetime episode in relation to childbirth, then the propor-
tion of women who experienced only perinatal episodes, without any
episodes outsides the perinatal period. Then I compare the rates of
episodes occurring in relation to childbirth with the rates of episodes
occurring at other times. Finally I test whether the childbirth trig-
ger is specific for postpartum psychosis or women who experienced
postpartum psychosis are also vulnerable to postnatal depression.

- In **chapter 9** I introduce the intriguing hypothesis that a specific
childbirth trigger is related to first deliveries. The link to primipar-
ity may suggest relationships with other pregnancy related disorders
such as pre-eclampsia in which parity is known to play an important
role and lead to specific hypotheses about the nature of the postnatal
trigger. Here I use some of the results emerged in the previous chap-
ters and conduct separate analyses according to the time-to-onset of
the perinatal episodes and to the longitudinal lifetime course of the
disorders.

3. *A section on the design and feasibility of a prospective study on bipolar
disorder in pregnancy and the postpartum.*

- In **chapter 10** I describe the methodology of the research protocol of
the study. I provide only a brief background, because I have already
discussed the clinical relevance of the bipolar trigger in the general
background section. The study was conducted as part of the Mood
Disorder Research Project, so my major effort was to integrate the
current research protocol with the one of the mood disorder research
project. Because the recruitment methods overlapped between the 2
studies, the reader can refer to chapter 5 for a detailed account of the
general recruitment methods. In this chapter I outline in detail the
assessment tools that I included in the protocol. Finally, I describe
the process of obtaining ethical approval.

- In **chapter 11** I report the research outcomes of the pilot study.
Based on the findings of the pilot study, I report the estimates of the
sample size that should be needed to test the research hypotheses I
formulated in the research protocol. Finally I discuss the feasibility

of a large-scale study. The main focus of the chapter is the discussion of the problems that I have encountered and of the limitations that have emerged. Finally I propose some adjustment to the protocol in order to optimise the resources.

4. *The last section is dedicated to a general discussion.*
   Here I summarise the results of the analyses I conducted, discuss the limitations to my approach and the implication of my findings for the nosology and aetiology of the postpartum trigger. Finally, I propose some suggestions for further research.

Part I

Background

Chapter 1

Epistemic issues in the study of perinatal mood disorders

"Irrespective of whether it is a clinician or a scientist who eventually unlocks the secrets of schizophrenia and bipolar disorder, they are much more likely to succeed if the syndromes in question have been accurately identified to begin with. "

R. E. Kendell [8]

"The contradiction so puzzling to the ordinary way of thinking comes from the fact that we have to use language to communicate our inner experience, which in its very nature transcends linguistics."

D.T. Suzuki [9]

I start my 'journey' in understanding the childbirth trigger of mood episodes with a general introduction to mood disorders, because I think that the confusion in the study of postpartum mood disorders is rooted on a deeper level in the epistemic limitations of the study of mood disorders. A discussion on the epistemology of mood disorders is not academic sophistry. It is relevant for both research and clinical practice, as its limitations have probably prevented firm and consistent conclusions on the nature of the postpartum trigger. In

medicine, differently from other sciences such as physics, definitions need to be explicit [10] [1] In this chapter and in the next I identify and discuss three related problems - in order of complexity:

1. It is difficult to conceptualise emotions, because, as pointed out by Suzuki, inner experience transcends linguistics. Scientific research in the emotions has always been challenging and, in this field, the demarcation between science and pseudo-science has always been flimsy. [2]

2. Assuming that it is possible to define emotions and to explore them using the scientific method, the concept of mood disorder introduces a further level of complexity. The definition of disorder, in general, is not neat and consistent. Again, this is not an academic/philosophical conundrum. Scadding [10] emphasised the importance of this topic in a letter to the Lancet about 50 years ago. He claimed that "To apply precise methods to vague and ill-defined concepts is likely to perpetuate confusion, by lending it an air of respectability, and to provide an example of what I call, borrowing and adapting a phrase from A. N. Whitehead, the fallacy of misplaced precision.". In this chapter I first overview some of the current opinions on the definition and criteria of disorder. Then I give a brief historical account on the nosology of mood disorders. I particularly emphasise the debate on the distinction between unipolar and bipolar disorders across the mood disorders spectrum.

3. Assuming that there is an agreement on the logical construct of 'mood disorder' (or 'bipolar disorder'), the link between mood disorders (or bipolar disorder) and childbirth represents a further epistemic problem. In this chapter I concentrate on the current definitions and classifications of PNEs, while the next chapter is dedicated to a critical overview of the literature on the postpartum trigger.

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[1]Thomas Kuhn pointed out that "scientists don't need to define concepts. Empirical concepts, in fact, don't need explicit definitions. Einstein, for example, did not have to invent or even explicitly redefine *space* and *time* in order to give them new meaning within the context of his work." [11] Explicit definitions of empirical concepts are not only unnecessary, but they would often hinder scientific progress.

[2]Although Popper's critique of psychoanalysis is reductionistic and based on observations dated a century ago, I think it is thought-provoking, as it may easily be applied to current clinical research in psychiatry, especially to nosology. In "Science: Conjectures and Refutations "Popper claims that a theory is scientific only if it is falsifiable and that the "*clinical observations* which analysts naively believe confirm their theory cannot do this any more than the daily confirmations which astrologers find in their practice " [12]

1.1   What is an emotion?

In a book published in 1884 William James asked "What is an emotion? "
[13]. Today, more than a century later, the definitions of emotions and feelings
are still heterogeneous and problematic. Contrary to the almost unambiguous
meaning given to concrete objects, the description and objectivation of feelings
and emotions have always been influenced by cultural differences, that act both
on a lexical and on a phenomenical level. An extensive discussion of emotions
goes beyond the scope of this thesis, so only some terminology used in this text
is presented and summarised in table 1.1.

Emotion, affect, feeling and mood are protean terms [14] with different etymo-
logical and cultural roots. A common etymological denominator is the shift
from meaning a physical act to a psychological experience. For example, as re-
ported in table 1.1, the term *affect* initially meant "to do something to", "to act
on"and only later it gains a psychological meaning. Despite the longstanding
philosophical and scientific debate on the meaning and characteristics of these
terms, their characteristics are not unequivocally defined.

Table 1.1: Some general terminology used to describe inner experiences

TERM	ETYMOLOGY	CURRENT MEANING	CHARACTERISTICS
EMOTION	From Latin *emovere*, to move out, to remove. The term gained a social connotation in the mid-16th century French, where it was used to indicate a social agitation	The current meaning of strong feeling was first recorded in the 17th century	Short-lived, salient, related to a recognisable object, accompanied by physiological changes
FEELING	From Proto-Germanic *fōljan* to touch, perceive	The experience of something physical or emotional	Wide, abstract and controversial term. It describes both the active somatic experience and the passive and subjective experience of emotion
AFFECT	From Latin *affectus*, figuratively disposed, constituted, inclined; past participle of *afficere* (*ad+facere*), to do something to, to act on	The experience of specific feelings towards object. As mental state first recorded in the late 14th century	Controversial: Long lasting, objectless, dispositional while according to Jaspers, it is complex and short lived
MOOD	Disposition		Long lasting, objectless, dispositional

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1.2 Mood disorders

> "But although accurate identification of the clinical syndrome is not
> a necessary preliminary it undoubtedly increases the likelihood that
> attempts to elucidate aetiology will be successful. "

R. E. Kendell [8]

1.2.1 What is a disorder?

The definition of a disorder in epistemologically difficult and controversial and
the arguments range from metaphysics to science. A detailed debate over the
nature of psychiatric disorders is beyond the scope of my thesis. In table 1.2 I
summarise some of the most commonly used definitions and their consequences,
while I point the readers to Phillips at al 2012 [15] for a detailed discussion on
the epistemology of psychiatric disorders.

The definition of psychiatric disorder is crucial in the field of perinatal psy-
chiatry because there are several syndromic entities such as postpartum blues
and mother-infant relationship disorders that are not included in the current
diagnostic systems [20]. I return to the nosology of postpartum disorders in the
next section.

Psychiatric syndromes and disorders are currently systematised in discrete di-
agnostic categories, listed in the Diagnostic and Statistic Manual of Mental Dis-
orders (DSM) [5] and in the International Classification of Disorders (ICD) [21].
These diagnostic systems provide diagnostic criteria to establish the presence
of the psychiatric disorders listed. DSM, authored by the American Psychiatric
Association, and ICD, authored by the World Health Organisation, are widely
used in Western medicine. They provide both researchers and clinicians with
explicit diagnostic criteria, improving communication and enabling better diag-
nostic agreement [17]. However, the current discrete categorical approach is not
optimal, even according to the authors of DSM.[3]

For the work I present in this thesis I employed the DSM-IV definition of disor-

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[3]"There is no assumption that each category of mental disorder is a completely discrete
entity with absolute boundaries dividing it from other mental disorders or from no mental
disorder"([5], p. xxii)

Table 1.2: Definitions of disorder. Only positions pertinent with the subject of the thesis are displayed. The classification proposed is modified and adapted from [10,16,17]

VIEW	DEFINITION	CONSEQUENCES
Essentialism - realism	Causes of illness. Clinical features constitute a disease only if the causal mechanisms are clearly identified	The aim of doctors is to identifying the causal disease and then prescribing the appropriate treatment (but causation may be complex and often unknown)
Nominalism[a]	"sum of the abnormal events shown by a group of living organisms in association with a specified characteristic or set of characteristics by which they differ from the norm in such a way as to place them at a biological disadvantage"	Patient centered, holistic. Suits psychiatric disorders better than the essentialist's definition.
Cultural relativism	labels provided by profession or society to exercise power	according to the anti-psychiatric movement mental disorders are not medical disorders, but problems in living [19]

[a]Here nominalism includes the view of statistical normativism. The term 'nominalism' was used according to Scadding [10] and in a different acceptation from Albert et al [18] who linked nominalism to cultural-relativistic theories

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der, that embraces both nominalistic and essentialistic positions and defines a mental disorder as either A) a "clinically significant behavioural or psychological syndrome or pattern "associated with disability, distress, or "with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom "or as B) a manifestation of a behavioural, psychological, or biological dysfunction. This definition accounts for the socio-cultural context and does not include culturally sanctioned beliefs and behaviours or conflicts that are "primarily between the individual and society". [4]

In my research I use the concept of disease-entities as classified in DSM-IV, bearing in mind Jaspers's observations. Jaspers pointed out that the concept of mental disorders is a Kantian idea, i.e. an unending object that cannot be reached. However, it shows a fruitful research direction and is a true point of orientation for individual empiric research. [5]

The discussion on the validity and utility of the diagnosis of postpartum episodes is central for this thesis. Unfortunately, the concept of validity and utility are themselves controversial. In table 1.3 I provide several possible criteria that have been proposed to establish the validity of psychiatric diagnoses. The main limitation of these validators is that they consider psychiatric diagnoses as separate nosological entities. It has been pointed out by a number of authors [17] that the categorical approach in which categories do not overlap is not in agreement with the evidence from clinical and non clinical studies.

1.2.2 Conceptualisation of mood disorders

The conceptual heterogeneity that characterises *emotion, affect, feeling and mood* afflicts also the definition and conceptualisation of their pathological counterparts. In the past two centuries psychiatry has relatively neglected disorders of affectivity in comparison to disorders of thinking. According to Berrios 1985 [14], the lack of emphasis on feelings reflects "earlier views on the subordinate role played by the emotions in the definition of man".

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[4]The website of DSM-5 Task Force proposed a revised definition of a mental disorder, in which the symptoms reflect "a disturbance in the psychological, biological, or developmental processes underlying mental functioning "- see http://www.dsm5.org/proposedrevisions/pages/proposedrevision.aspx?rid=465

[5]"Die Idee der Krankheitseinheit ist [..] eine Idee im Kantischen Sinne: der Begriff einer Aufgabe, daren Ziel zu erreichen unmöglich ist, da sas Ziel in der Unendlichkeit liegt; die uns aber trotzdem die fruchtbare Forschungsrichtungen weist und due ein waherer Orientierungspunkt fur empirische Einzelforschung bedeutet" [22]

Table 1.3: Criteria for establishing the validity of psychiatric diagnoses

Robins and Guze [23]	Kendler [24]	Kendell [8]	Kendell&Jablensky [17]
1) clinical description (symptom, demographics, typical precipitants), 2) laboratory studies (psychological tests, radiology and postmortem findings), 3) delimitation from other disorders (exclusion criteria), 4) follow-up studies (diagnostic stability), 5) family studies	1) antecedent validators (familial aggregation, premorbid personality, precipitating factors),2) concurrent validators (including psychological tests), 3) predictive validators (diagnostic consistency over time, rates of relapse and recovery, response to treatment)	1) Identification and description of the syndrome (by 'clinical intuition' or by cluster analysis), 2) Demonstration of boundaries or 'points of rarity' between related syndromes (by discriminant function analysis, latent class analysis) 3) Follow-up studies establishing a distinctive course or outcome. 4) Therapeutic trials establishing a distinctive treatment response, 5) Family studies establishing that the syndrome' breeds 6) Association with some more fundamental abnormality - histological, psychological, biochemical or molecular.	Demonstration of boundaries or 'zones of rarity' between related syndromes OR physiological, anatomical, histological, chromosomal, or molecular abnormality

In the current Western psychiatric framework, an alteration of the mood can indicate:

- A *symptom*: a change from the normal experience noticed by the subject and usually caused by a disorder. Mood symptoms are pervasive mood states, extreme manifestations along an axis from happiness to sadness. A condition of extreme pathological low mood is called depression, while a condition of extreme elevated mood is called mania.

- An *episode* or a *syndrome*, characterised by different combinations of signs and symptoms. In the modern classification systems episodes of major mood disorders are usually labeled as major depression, (hypo)mania or mixed episodes. Mood episodes can present with or without psychotic features.

- A *disorder*. In this thesis I use the term mood disorder to label the longitudinal/lifetime diagnoses of recurrent major depression and bipolar disorder.

In this thesis I deal with a number of concepts such as melancholia, cycloid, bipolar spectrum. The vast majority of terms and concepts used to define and describe mood disorders are antecedent to and not always in agreement with the current diagnostic systems, so I provide here some historical notes and I briefly explore current controversies.

I have already mentioned that the terms 'depression' and 'mania' are currently used to describe both extreme mood states (symptoms) and complex mood disorders (syndromes). In the current categorical diagnostic systems, the overlap between a symptom and a syndrome is not necessary.

For example, in both DSM-IV [5] and ICD-10 [21] depressed mood is not a necessary criterion for a major depressive episode. However, this view is not unanimously accepted. Stefanis and Stefanis [25], for example, considered depressed mood as a necessary symptom for a depressive syndrome and criticised the concept of *depressio sine depressione.* On the other hand, depressed mood may be present outside a major depressive episode in the context of other syndromes or, less frequently, as an isolated symptom.

Similarly, mania describes a pathological elevation of mood, but in DSM-IV a manic episode is characterised not necessarily by elevated and expansive mood. The diagnostic criterion of mood in mania can be fulfilled also by irritable mood. Hypomania is a milder, but still clinically significant, elevation of mood. The presence of hypomania is sufficient to make a diagnosis of bipolar disorder ac-

cording to DSM-IV, but not according to ICD-10, which labels as bipolar only disorders characterised by a history of both full-blown mania and depression.

The concept of **melancholia** is etymologically rooted in the theory of the 'four humors' of Alcmaeon of Crotona and the pre-Hippocratic Greek physicians and literally means 'black bile' (μελανχολια). Until the 20th century the term *melancholia* defined a periodic mood disorder with both manic and depressive episodes. Melancholia was often described as a severe illness, characterised by psychosis, psychomotor disturbance and vegetative signs. Mood was often reported as manic or mixed (depressive and manic features together) or rapidly switching from mania to depression (Falret's *folie circulaire*). Later, melancholia has generally been considered the 'biological' type of depression. Since the introduction in the third edition of DSM (1980), melancholia has been a specifier for a major depressive episode (in the context of either a lifetime diagnosis of major depressive disorder or bipolar disorder). According to DSM-IV melancholic features are: ahnedonia, lack of mood reactivity, the low mood is subjectively different from grief or loss, severe weight loss or loss of appetite, psychomotor disturbance (agitation or bradykinesia), early morning awakening and worse mood in the morning and excessive guilt.

However, in the recent years many authors have argued that melancholia should be treated as a nosological entity separated from major depression. It is of interest that it has been proposed to include postpartum depression together with psychotic depression and manic depression in a new separate diagnostic category of melancholia [26].

The concept of **bipolar disorder** is rooted in the classic pre-Hippocratic period [27]. However, Hippocrates was the first who described systematically melancholia and mania as biologically determined diseases. Hippocratic descriptions of mania and melancholia included not only what we labeled as depression and mania, but also mixed states and psychotic states.

In the first century after Christ by Aretaeus of Cappadocia linked mania and melancholia for the first time[6]. However, at the beginning of the 19th century mania and melancholia were still conceptualised as two different syndromes.

The father of the modern concept of bipolar disorder is probably the French psychiatrist Jean-Pierre Falret, who, in the 19th century, described the *circulaire*,

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[6]"melancholia is the beginning and a part of mania . . . The development of a mania is really a worsening of ..[melancholia] rather than a change into another disease. . . In most of them (melancholics) the sadness became better after various lengths of time and changed into happiness; the patients then developed a mania" [27]

an illness characterised by periodical episodes of mania and melancholia alternated with periods of well-being [28]. The term *folie circulaire* was introduced to the German speaking psychiatry by Karl Kahlbaum in 1863 as *circuläres Irresein* [29]. At the end of the 19th century, Emil Kreapelin unified, not without a certain skepticism, the *circuläres Irresein* with depressive illness, labelling the unified syndrome as *manisch-depressives Irresein* (manic-depressive insanity) [30].

The current distinction between unipolar and bipolar disorders is rooted in the German psychiatry of the beginning of 20th century. Carl Wernicke differentiated unipolar mania or depression from manic-depressive insanity [31]. Karl Kleist was the first to use the term *bipolar*, labelling manic-depressive insanity and atypical cycloid psychoses as *zweipolig*(bipolar) in contraposition to *einpolig*(unipolar) mania and depression [27]. However, the distinction between unipolar and bipolar disorders was internationally recognised only in the 1960s. [32]

Recent evidence from clinical, epidemiological and molecular studies have challenged the current clear-cut unipolar-bipolar distinction [33]. Several studies have found that hypomanic symptoms are common in a substantial proportion of subjects suffering from a unipolar depressive episode [34]. On the other side, there are increasing evidence that bipolar depressive episodes and unipolar depressive episodes (that currently share the same diagnostic criteria and nosology) are not overlapping clinical entities.

The nosological boundaries of bipolarity have been expanded through the emerging concept of a clinically relevant broad **bipolar spectrum**. This term has been conceptualised as a clinical continuum ranging from affective temperaments to DSM-IV BD-I (a manic episode with or without a history of depression) and encompassing depression with history of spontaneous hypomanic episodes (DSM-IV, BD-II), cyclothymic depressions (*BD-II and a half*), antidepressant-associated hypomania (*bipolar III disorder*) and hyperthymic depressions (*bipolar IV disorder*) [35]. The term *cyklothymie* (cyclothymia) was firstly used by Kahlbaum to describe a mild form of bipolar disorder (a "partielle Seelenstörungen ", a partial mental disorder) characterized by highs and lows [36]. This view on cyclothymia is currently internationally accepted and recognised by ICD-10 and DSM-IV. However, in the German speaking psychiatry, although increasingly rare, cyclothymia can be used according to Schneider's meaning, indicating a full mental disorder, overlapping with the manic-depressive illness. Affective temperaments and their role in mood disorders are still controversial. The modern concept of affective temperaments is rooted in the German descrip-

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tive tradition. Kraepelin described four *fundamental states* (*'grundzustände'*): depressive, manic, irritable and cyclothymic [7]. Kretschmer expanded Kraepelin's notion of premorbid behavioural patterns to embrace the whole range of temperamental variants in the population. He theorised that psychoses "are only rare exaggerated editions of large wide-spread groups of healthy constitutions [that] have a genetic basis " [38]. Schneider regarded hyperthymic and depressive *psychopathic personalities* as extremes in a statistical sense, which represented much more than simply the underlying foundations of mood disorders [39]. In recent years there has been a rejuvenation of interest in the concept that certain affective temperaments may represent formes frustes or endophenotypic[8] manifestations of vulnerability to bipolar spectrum disorders. Akiskal et al postulated that temperamental dysregulation might constitute the link between predisposing familial-genetic factors and affective illnesses such as bipolar disorder [42]. They defined **affective temperament** as emotional reactivity that embraces both affective liabilities and assets and includes five dimensions of dysthymia, hyperthymia, cyclothymia, irritability and anxiety.

Recent advances in molecular genetics have provided new insights in the definition of the spectrum boundaries and challenged the still-in-use Kreapelian dichotomy between dementia praecox and manic-depressive insanity [43]. The bipolar spectrum can thus be extended to psychotic mood disorder, schizoaffective disorder, laying on a continuum with schizophrenia .

Despite Kreapelin's observations of subjects with clinical features that lied between manic-depressive insanity and dementia praecox, the first systematic studies on schizoaffective disorders are dated more than 60 years later [44]. Currently, the definition of schizoaffective disorder, bipolar type is controversial and its boundaries with bipolar disorder are very labile. Recent advance in molecular genetics has provided new important insight. Employing different definitions of schizoaffective disorder, bipolar type, Craddock et al in two different studies found that common variations at receptors within the gamma-aminobutyric acid system were associated with susceptibility to schizoaffective, bipolar type, when Research Diagnostic Criteria were applied [45, 46]. The methodology employed in these studies represented a shift of paradigm from a hypothesis driven descriptive approach to a data-driven, iterative approach [47] and is an important

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[7]temperaments"on the one hand frequently accompany the "free"intervals between attacks, on the other hand characterise the manic-depressive temperament in such cases also in which the full development of the malady is absent " [37]

[8]Akiskal et al, for example used the term *behavioural phenotype* to indicate traits that "best tap the familial-genetic diathesis of BD-II" [40]. The term endophenotype differed here from the more rigorous definition and use proposed by Walters and Owen [41]

tool for a new definition of psychiatric disorders.

In discussing postpartum episodes in relation to childbirth, **cycloid psychosis** is a recurring concept. Pfuhlmann et al [48] reported that about half of episodes of postpartum psychosis meet Leonhard's criteria for cycloid psychosis.

The term cycloid psychosis is not included explicitly in the current diagnostic systems. However, many characteristics of cycloid psychosis are met by the diagnostic categories of *acute polymorphic psychotic disorders, with or without symptoms of schizophrenia, F-23* in ICD-10 and *brief psychotic disorder, 298.8* in DSM-IV, although in both cases the episode has to last less than 1 month.

As many other concepts described in this chapter, the concept of cycloid psychosis is rooted in the German psychiatric tradition. Initially the term was used by Karl Kleist to label a form of psychosis that was not included in the Kraepelian dichotomy dementia praecox - manic-depressive illness [49] and that in many cases presented as an acute psychotic illnesses similar to schizophrenia, but with the episodic course of manic-depression. There is a paucity of information on the diagnostic validity of cycloid psychosis, however, it has been claimed that it is a separate nosological entity with longitudinal diagnostic stability [49]. Over the years two nosological positions have been alternating: the first supporting the view that cycloid is not a separate nosological entity and the second supporting the independence of cycloid psychosis from schizophrenia and bipolar disorder. Cycloid psychoses are phasic disorders with complete remission after each episode. Patients usually present with polymorphic clinical symptomatology that overlaps the symptomatology of organic psychoses. Karl Leonhard [50] described three characteristic forms of presentation: hyperkinetic-akinetic motility psychosis, excited-inhibited confusion psychosis and anxiety-happiness psychosis. In the database I analysed, episodes of cycloid psychosis were recorded and rated according to Perris and Brockington criteria [51]. These criteria were employed also by Kendell et al [52] in a milestone paper on postpartum disorders. I therefore list them in table 1.4.

The uncertainty in the definition of bipolar disorder(s) and in the limits of the bipolar spectrum influenced not only the design of my research, but also my lexical choices in this thesis. Expressing uncertainty around definitions is tedious (especially for the reader), but necessary. I use here the term *bipolar/mood disorders* to underline that, although the focus of the discussion is bipolar disorder, the boundaries between unipolar and bipolar mood disorders are unknown and probably not neat. I use the term bipolar depression to indicate an episode of DSM-IV major depression in subjects who have previously experienced a

Table 1.4: Perris and Brockington criteria for cycloid psychosis

1. Acute psychosis, not related to the drug use, to brain injury, with first onset between 10-50 years.
2. Sudden onset with rapid change from health to a full-blown psychosis within few hours/days
3. At least four of the following must be present:
i) Confusion, mostly expressed as perplexity or puzzlement
ii) Mood-incongruent delusions, mostly persecutory
iii) Hallucinations, often related to themes of death
iv) Pan-anxiety
v) Deeper feelings of happiness or ecstasy, most often with a religious coloring
vi) Motility disturbances of an akinetic or hyperkinetic type
vii) particular concern with death
viii) significant mood swings in the background that justify a diagnosis of affective disorders
4) Symptoms may change frequently during an episode and show bipolar characteristics.

manic/hypomanic/mixed episode.

1.3   Nosology of perinatal mood episodes

Contrary to pregnancy, the postpartum has been historically recognised as a period of great liability for psychiatric disorders and great emphasis has always been put on episodes occurring after childbirth.

Postpartum mood disorders are typically divided into three categories: the *baby blues*, postnatal depression and postpartum psychosis.

Baby blues are common after childbirth. Often depressive and hypomanic symptoms occur together, with mood swings ranging from elation to sadness, insomnia, tearfulness, crying spells, irritability, anxiety, and decreased concentration. Despite the inconsistency of the data in the current literature, it has been estimated that around 30-80% of women experience mood swings after delivery. Symptoms develop within a week postpartum and resolve within 2 weeks. Postpartum mood swings do not require treatment and there are many controversies as to their pathological relevance. However, they have been associated with subsequent postpartum depression and affective vulnerability (for a review on baby blues please see [53]). As I have already mentioned, in my research I used the DSM-IV criteria of disorder. Baby blues is not included in DSM-IV nor in ICD-10. Moreover, following the DSM-IV definition of what is a disorder reported above, baby blues does not significantly increase risk of suffering death, pain, disability, or an important loss of freedom nor there are solid evidence of behavioural, psychological, or biological dysfunction. Therefore, I did not investigate baby blues in my research

The term **postpartum depression** refers to the development of a depressive episode following childbirth and may form part of a bipolar or, more usually, a unipolar disorder. In contrast to baby blues, postpartum depression can last for months or even years and can result in significant impairment with severe long-term consequences for the mother and the entire family.

Postpartum psychosis is the most severe form of postpartum mood disorder. Although the disorder is not easy to define, the core feature is the acute onset of a manic, depressive or mixed affective psychosis in the immediate postpartum period. It is a psychiatric emergency. The epidemiology of

psychosis occurring after childbirth has changed over time and still changes over countries. Brockington [54] distinguished between three forms of postpartum psychosis:

1. Organic psychosis - including post-eclamptic and infective psychosis. With the introduction of antenatal care, this form has become rare in Western countries. I discuss the differential diagnosis of organic psychosis in chapter 3

2. Psychogenic psychosis is usually characterised by delusions and is associated with severe stress.

3. Bipolar/cycloid psychosis is currently the most common in the Western countries and is the object of this thesis. So, when I use the term *postpartum or postnatal psychosis*, I refer to this form.

Neither the term nor the concept of postpartum psychosis are present in DSM-IV or ICD-10. Figure 1.1 compares the modern classification of postpartum psychotic disorders with the clinical-historical concept of postpartum psychosis. According to Brockington, "the influence of ICD and DSM on postpartum psychosis has been adverse "and "has depressed research and the provision of the services ". DSM-IV severe manic episodes without psychotic features may be labeled as postpartum psychosis. On the contrary, chronic psychotic illness, such as schizophrenia, affecting the postpartum period, but with an onset before delivery are generally not considered episodes of postpartum psychosis. I use the term postpartum psychosis to define an episode of mania or affective psychosis occurring in the puerperium. I specify the length of the postpartum period in each analyses I discuss/ perform.
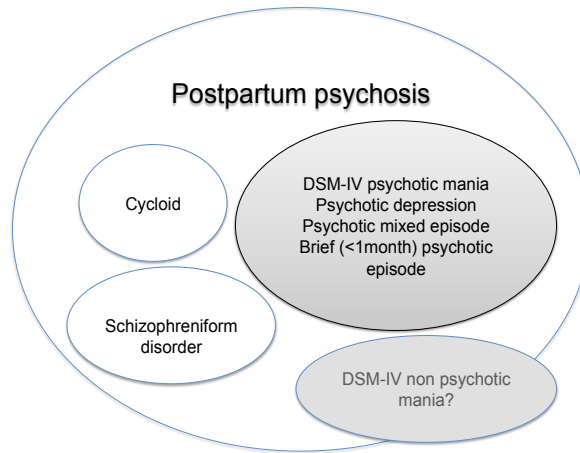
Figure 1.1: Postpartum psychosis in DSM-IV. Disorders included in the current DSM-IV postpartum onset specifier in grey. Postpartum psychosis includes also cycloid psychosis and schizophreniform disorders. However, episodes of cycloid that last more than a month are excluded by the current postpartum onset specifier. Similarly schizophreniform disorders are not covered by the onset specifier and cycloid is not a term employed by the DSM-IV. On the contrary, DSM-IV severe manic episodes without psychotic features may be labeled as postpartum psychosis.

Before describing the current nosology of perinatal disorders in ICD-10 and in DSM-IV I briefly list previous definitions in table 1.5, because they have been used in many studies that I report in the next chapters.

Although the approach to perinatal episodes is different in ICD-10 and DSM-IV, both assume that perinatal mood episodes are not separate nosological entities: postpartum depression and postpartum psychosis are not recognised as separate conditions.

DSM-IV has a course specifier - *with postpartum onset* which can be applied to a major depressive, manic, or mixed episode; or to brief psychotic disorder with an onset within 4 weeks after childbirth. The postpartum onset specifier cannot be applied to any other psychiatric diagnosis. Hypomania is excluded from the onset specifier, although, it has recently been argued that postpartum hypomania is clinically relevant and that the next version of DSM should consider a revision of the postpartum onset specifier to include it. Similarly, postpartum psychoses which are cycloid (and last more than a month) or schizophreniform

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Table 1.5: Nosology of perinatal mood disorders in previous classification systems

DIAGNOSTIC SYSTEM	YEAR OF PUBLICATION	CATEGORY	WHAT IS EXCLUDED	WHAT IS INCLUDED	NOTES
ICD-8	1967	Special category 294.4 "psychosis associated with childbirth"	Any psychosis classified elsewere (295-298 - schizophrenia, affective psychoses, paranoid states, other non-organic psychosis) and arising during the puerperium, episodes occurring in pregnancy	It includes only unspecified psychoses occurring within 6 weeks after delivery	Many psychiatrists ignored the restrictions (Brockington.)
DSM-II	1968	294.4	Any psychosis classified elsewhere and arising during the puerperium, episodes occurring in pregnancy	It includes only unspecified psychoses occurring after delivery	Similar to ICD-8
ICD-9	1975	In the obstetric section 648.4 "current .. mental disorders in the mother, classifiable elsewhere but complicating pregnancy, childbirth and the puerperium"		Mental disorders in pregnancy and the postpartum period	Many psychiatrists were not aware of the possibility, because it was in the obstetric section
DSM-III	1980	psychotic disorders not elsewhere classified	Any psychosis meeting the criteria for an organic mental disorder, schizophreniform disorder, paranoid disorder or affective disorder. No episodes occurring in pregnancy	Residual category	Becoming a parent as "psychosocial stressor "in axis IV - pregnancy ranked as a moderate stressor, childbirth as a severe stressor

are not covered by the onset specifier (figure 1.1).

In **ICD-10** the category *Mental and behavioural disorders associated with the puerperium, not elsewhere classified* (code F53) should be used only when unavoidable and includes only mental disorders associated with the puerperium (commencing within 6 weeks of delivery) that do not meet the criteria for disorders classified elsewhere[9]. Alternatively, disorders occurring within 6 weeks after childbirth, can be coded by adding to the presenting psychiatric episode code a second code (0.993 - mental diseases and diseases of the nervous system complicating the puerperium).

Current diagnostic systems do not allow episodes in pregnancy or later in the postpartum to be linked to childbirth. However, rather than the 4 or 6 weeks cut-off, a 6 month or 1 year postpartum period is commonly used in clinical practice. The exact length of time that the term *postpartum* denotes is controversial and is the main topic of chapter 7. The current definitions of perinatal onset in DSM-IV and in ICD-10 are, in fact, essentially arbitrary and more evidence-based criteria are needed.

Although pregnancy has thought to be a period of emotional well being, there is evidence, at least for depression that episodes are at least as frequent as at other time. Women with bipolar disorder face very difficult decisions about pregnancy: many of drugs used to keep them well are known teratogens, that is they can cause birth defects in children if taken in pregnancy. As I discuss in detail in the next chapter, euthymic women who discontinue antidepressant treatment during pregnancy have a five time higher risk of relapse than those who maintain drug [56]. Women with bipolar disorder have an even higher risk of recurrence in pregnancy, especially mixed recurrences. Discontinuation of treatment, especially if abrupt, is highly associated with the onset of a new episode in pregnancy, with more than 85% of women who discontinued mood stabilising therapy developing a new episode, versus only 37% in the group who continued therapy.

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[9]"This classification should be used only for mental disorders [..] that do not meet the criteria for disorders classified elsewhere [..] either because insufficient information is available, or because it is considered that special additional clinical features are present which make their classification elsewhere inappropriate" [55]

1.4 Summary

In this chapter I have explored some of the difficulties in the definition and nosology of mood episodes occurring in relation to childbirth. Confusion in the definitions of emotions and in the classification of mood disorders in general has probably had a negative impact on research into perinatal mood disorders (figures 1.2-4). The current categorical diagnostic systems do not consider perinatal disorders as separate nosological entities. There is no difference between episodes occurring after delivery or outside the puerperium. There is a neat difference between bipolar and unipolar disorders with no continuity between the two categories (figure 1.2). Episodes of hypomania, that are common in postpartum period, or cycloid/schizophreniform psychosis that have been associated with childbirth in the past are neglected by the current categorical diagnostic systems.

Postpartum episodes are not always recurrences of mood disorders occurring outside the perinatal period. Episodes neglected by DSM-IV such as cycloid psychosis and schizophreniform disorders are included, either as recurrence of a lifetime bipolar disorder, or as distinct entities, with no recurrences outside the puerperium. Postpartum depression can be either a recurrence of RMD or bipolar disorder or an isolated episode (figure 1.3). However, a first depressive episode after childbirth has been associated with an increased risk of a bipolar diathesis (please see [7] discussed in chapter 2)

One of the aim of this thesis was to explore different definitions of perinatal mood episodes and to compare them with current diagnostic criteria. I investigated a range of mood episodes and of definitions of puerperium to see whether the evidence support the current classifications.

Figure 1.2: Postpartum illness and mood disorders: PNEs as part of the unipolar-bipolar dichotomy. The current approach to postnatal mood episodes in DSM-IV is shown: there is no difference between episodes occurring after delivery or outside the puerperium. There is a neat difference between bipolar and unipolar disorders with no continuity between the two categories.
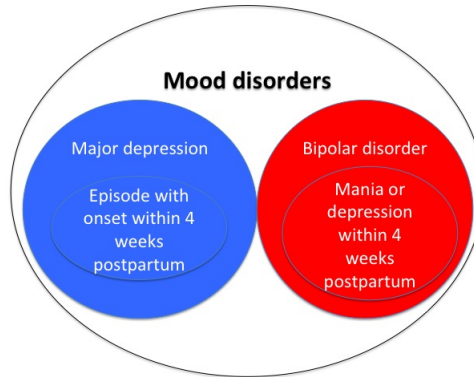
Figure 1.3: Postpartum episodes are not always recurrences of mood disorders occurring outside the perinatal period. Episodes neglected by DSM-IV such as cycloid psychosis and schizophreniform disorders are included, either as recurrence of a lifetime bipolar disorder, or as distinct entities, with no recurrences outside the puerperium. Postpartum depression can be either a recurrence of RMD or bipolar disorder or an isolated episode. However, a first depressive episode after childbirth has been associated with an increased risk of a bipolar diathesis (please see [7] discussed in chapter 2)
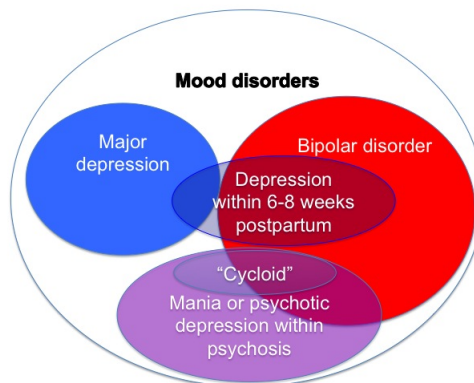
Figure 1.4: PNEs as part of the mood/bipolar disorder spectrum. Mood episodes are all part of a same nosological entity: the bipolar/mood disorder spectrum. Postnatal hypomania, that is currently neglected by DSM-IV, is included.
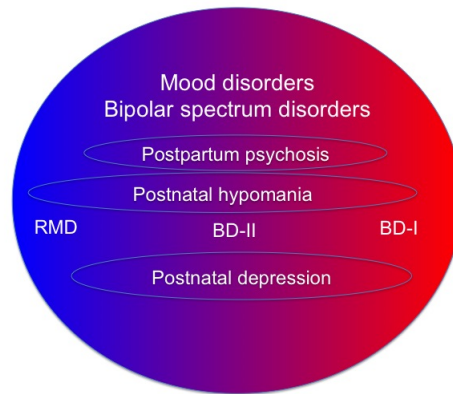
Chapter 2

Childbirth as a trigger for episodes of mood disorder

In the previous chapter I overviewed the complexity and the limitations that hinder the study of bipolar/mood disorders and introduced the debate on the nosological status of PNEs. In this chapter I expand the discussion on the childbirth trigger and critically review the literature on the following main research questions:

1. Is the perinatal period a period of increased risk of **onset** of bipolar/mood disorders? Is the risk similar across mood spectrum disorders?

2. Is the perinatal period a period of increased risk of **recurrence** of bipolar/mood disorders? Is the risk similar across mood spectrum disorders?

3. What period of time should be covered by the postnatal onset criterion? Should pregnancy be included?

These research questions were the main topic of my analyses on the Mood Disorder Research Project dataset.

As proposed by Kendell [52], quantitative studies on the effect of childbirth on psychiatric morbidity need to meet three methodological requirements: 1. an epidemiological sample 2. accurate information on women from the same pop-

ulation who do not develop any psychiatric disorders, despite the exposition to pregnancy and childbirth. 3. a large sample. Although many studies have been conducted over the years on bipolar disorder in pregnancy and the postpartum (table 2.1), only few meet Kendell's criteria. Therefore I dedicate an extensive part of this chapter to large register based studies. Large registry studies conducted in Scandinavia have given a major contribution to the topics approached in this chapter. In both Denmark and Sweden every resident is identified by a unique identification number that is used as personal identifier across all national registers. National registers include basic demographic information, but also medical information on admissions, diagnoses and treatment. Thanks to the unique identification number, register based studies have linked information contained in different registers in order to explore the link between childbirth and mental disorders.

Table 2.1: Studies reporting the rates of perinatal episodes in mood disorders.[2]

First Author,Year	Country	Sampling	Sample characteristics	Time window	Statistic	Outcome	N	%
Kendell 1987 [52]	UK	E	Pregnancies in women with prior history of manic or circular illness	90 days postpartum	Incidence	Psychiatric admissions	30	21.4
Blehar 1998 [57]	US	G	Parous women with prior history of BD-I		Lifetime prevalence	Severe emotional disturbance	186	~ 50
Viguera 2000 [58]	US, Italy	C	Pregnant women with prior history of BD-I, BD-II	Pregnancy	Incidence	Mania, or hypomania, or MDE	42	52.4
				24 weeks postpartum			20	70
Jones 2001 [59]	UK	G	Pregnancies in women with BD-I, or schizoaffective disorder, bipolar type	6 weeks postpartum	Incidence	Mania or psychosis	313	26

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Table 2.1 – *Continued from previous page*

First Author,Year	Country	Sampling	Sample characteristics	Time window	Statistic	Outcome	N	%
			Parous women with prior history of BD-I or schizoaffective disorder, bipolar type	Pregnancy	Lifetime prevalence	Any DSM-IV affective episode	152	7.2
				6 weeks postpartum		Mania or psychosis		38.2
						MDE or anxiety disorders		12.5
Freeman 2002 [60]	US	C	Parous women with prior history of BD-I or BD-II	Postpartum	Lifetime prevalence	Any DSM-IV mood episode	30	67
Eberhard-Gran 2004 [61]	Norway	E	Pregnancies in women with prior history of depression	Pregnancy-12 months postpartum	Incidence	EPDS >9	156	14.1
Cohen 2006 [56]	US	C	Pregnant women with prior history of MDD	Pregnancy	Incidence	MDE	201	43
Payne 2007 [62]	US	G	Parous women with prior history of BD-I	1 month postpartum	Lifetime prevalence	Mood symptoms [a]	514	22

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Table 2.1 – *Continued from previous page*

First Author,Year	Country	Sampling	Sample characteristics	Time window	Statistic	Outcome	N	%
			Parous women with prior history BD-II				83	22.9
			Parous women with prior history MDD				1283	20.3
Harlow 2007 [63]	Sweden	E	1st time pregnant women with prior history of BD-I	90 days postpartum	Incidence	Hospitalization	786	8.5
				Pregnancy		For BD		1.4
Viguera 2007 [64]	US	C	Pregnant women with prior history of BD-I or BD-II	Pregnancy	Incidence	MDE	89	38.2
						Hypomania		16.9
						Mania		6.7
Munk-Olsen 2009 [65]	Denmark	E	1st time pregnant women with prior history of BD	90 days postpartum	Cumulative incidence	Hospital re-admission		22
			1st time pregnant women with prior history of MDD	1 year postpartum				∼ 5
Colom 2010 [66]	Spain	C	Parous women with prior history of BD-I or BD-II	4 weeks postpartum	Lifetime prevalence	MDE	66	50

Continued on next page

Table 2.1 – *Continued from previous page*

First Author,Year	Country	Sampling	Sample characteristics	Time window	Statistic	Outcome	N	%
						Mania or mixed episode		16.7
Viguera 2011 [6]	US, Italy	C	Parous women with prior history of BD-I	6 months post-partum	Lifetime prevalence	DSM-III/IV Mania or Mixed episode		7.9
						DSM-III/IV MDE		19.2
						Psychosis		1.9
			Parous women with prior history of BD-II	6 months post-partum		DSM-IV hypomania		2.3
						DSM-III/IV MDE		28.7
			Parous women with prior history of MDD	6 months post-partum		DSM-III/IV MDE		16.1

2.1 Are there pregnancy or delivery specific triggers for the onset of bipolar/mood disorders?

Although the study by Kendell (1987) [52] was the first large systematic study meeting the above methodological criteria, it did not discriminate between first admissions and readmissions, and so I don't discuss it in this section. Two studies conducted on the Danish registries in recent years have investigated the risk of a first psychiatric episode in relation to childbirth in the general population. By linking information on the Danish Civil Registration system with information on the Danish Psychiatric Central Register, researchers were able to follow-up the entire Danish population for many years (Terp et al from 1973 until 1993 [67] and Munk-Olsen et al from January 1973 to 2005 [68]).

Terp et al (1998) [67] compared the rates of hospital admission within 3 months after childbirth with those in the general Danish female population, including parous and non parous women. The incidence for psychosis between 2 days and 3 months after delivery was 0.45/1000 deliveries. It is worth noting that women admitted within 1 day of delivery were not included in the nominator. The highest risk of first admission was found for bipolar disorder (ICD-8 codes 296-19, 296-39 - relative risk = 6.82 95% CI 4.22-10.42). The highest risk was for bipolar episodes occurring in the first month postpartum, while the risk was lower and more spread out across the first 3 months in women with unipolar depression (ICD-8 codes 296.09, 296.29).

Munk-Olsen et al (2006) [68] employed a different reference group, comparing rates of admission in women during pregnancy and in the first 11 months after childbirth with rates of admission in women who had given birth 11 to 12 months prior. The selection of a reference group of mothers presented an advantage compared to the choice of the general female population as in Terp et al [67]. In fact, risk factors involved in the onset of a mental disorder may influence also the likelihood of becoming a mother (*selection into parenthood*). They found, in fact, different patterns of admission between parent and non parent, with a strong interaction between age, parenthood and risk of admission. With the exception of pregnancies in early years (before 26 years of age), women with children had fewer psychiatric admissions than those without children. This

hypothesis was corroborated by a subsequent study on the same registries [69], that found that those who suffered with more severe disorders were less likely to become parents.

Although separate analyses were conducted on women giving birth to a second live-born child, the focus of the research was primiparae with a live-born child . The findings on hospital admissions are reported in figure 2.1.

Compared to admissions 12 months postpartum, there was an increased risk of admission for bipolar disorder in the first 2 months postpartum, but not in pregnancy or later in the postpartum. Similarly to Terp et al [67], the increased risk of admission with unipolar disorders was lower and persisted in the first 5 months postpartum. Pregnancy had a protective effect with a decreased relative risk of onset. The postpartum risk was only modestly increased for less severe episodes that did not require admission.

Several caveats need to be considered in the interpretation of the results of Terp et al [67] and Munk-Olsen [68] :

- In both studies, conducted on overlapping samples, diagnoses were made according to the ICD criteria. Therefore, they included 'mental and behavioural disorder associated with the puerperium, not elsewhere classified'. This is a composite category and it is possible that atypical forms of affective psychosis have been included in this category. Moreover, a study conducted on the same Danish Psychiatric Central Register [70] on the concordance between ICD-8 and ICD-10 found that the categories of bipolar and unipolar disorders in ICD-10 are broader and more comprehensive compared to those in ICD-8.

- Analyses of medical registries provided robust evidence on severe episodes, which required hospital admission. However, less severe episodes that required outpatient contact were not investigated by Terp [67]. Although Munk-Olsen [68] included separate analyses on outpatient contacts, it is still possible that women with less severe episodes may have not sought help in the health care system.

- Register studies, in general, rely on diagnoses made by clinicians in clinical settings without using the diagnostic instruments and procedures usually employed by researchers.

- Another problem that may lead to an underestimate of perinatal bipolar episodes is related to the current nosology of mood disorders. Bipolar
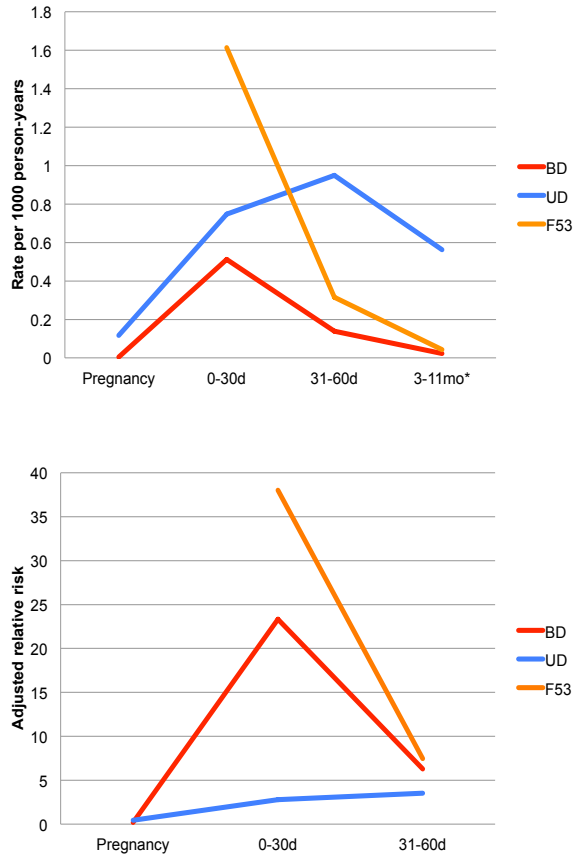
Figure 2.1: Risks of first-time hospital admission 0 to 12 months postpartum among primiparae in Munk-Olsen 2006 [68]. The top graph displays the rate of admission per 1000 person-years in pregnancy and the postpartum in primiparae without a previous psychiatric history and with a live birth. The bottom graph displays the relative risk of illness by period groups (pregnancy, first month, second month) compared with women who had given birth 11 to 12 months prior. I used Excel to draw the graphs. Abbreviations:UD: unipolar depression, BD: bipolar disorder, F53: mental and behavioural disorder associated with the puerperium, not elsewhere classified, for unipolar depression only 3-5 months, d:days, mo:months

depression is usually a 'longitudinal' diagnosis, made in subjects who are currently experiencing a depressive episode and who have a history of at least one manic episode. Thus, women experiencing depression as first lifetime episode are all initially labelled as unipolar. However, a study conducted on the same registries estimated that about 14% of women with first-time psychiatric contact during the first postpartum month for any type of mental disorder excluding bipolar disorder converted to a bipolar diagnosis within a 15-year follow-up period [7] compared to 4% of women with a first contact at other times. The risk was highest for admissions within 14 days postpartum (risk ratio adjusted for first diagnoses and family history of psychiatric illness =2.53 (95% CI 1.57-4.07) The association was stronger for hospital admission than for outpatient contacts.

In summary, despite some limitations, the studies conducted on the Danish registries provide robust evidence of an increased risk of psychiatric hospital admission in the first month postpartum, especially in primiparae with bipolar disorder.

2.2 Is the perinatal period a period of increased risk for a recurrence of bipolar/mood disorders?

2.2.1 Registry based studies

The first large study meeting the quality criteria listed above was conducted by **Kendell et al (1987)** [52] on the Edinburgh Psychiatric Case Register and Scottish maternity discharge data. Rates of psychiatric admission/contact in pregnancy and within 2 years after delivery were compared with the average admission rate of the same group of women two years before childbirth, using women as their own control group. Kendell et al [52] identified 486 women who had a psychiatric admission before their first delivery. Across psychiatric diagnoses, bipolar disorder (including mania and cycloid psychosis defined as in [51]) had the highest risk of readmission in the first 3 months after childbirth with 21.4% of deliveries affected. This study used diagnoses made according to the ICD-9 diagnostic criteria and differentiated between *depressed manic-*

depressive illness (ICD-9 296.3) and *depressive neurosis* (ICD-9 300.4)[3]. It found that, although the risk of admission for depressed manic-depressive illness was 13.3%, lower than the risk for mania or cycloid, but still higher than the risk for other disorders, including depressive neurosis (1.9%). Overall the risk of manic-depressive psychosis after childbirth was significantly higher than for any other psychiatric disorder (p=0.00008).

Terp et al [67], investigating clinical diagnoses made according to ICD-8 criteria, found much lower relative risks of readmission across all diagnoses than Kendell et al [52]. For *bipolar manic depressive psychoses* the relative risk was only moderately increased (1.86, 95% CI 1.43-2.39) between 2 and 28 days and it was even decreased between 29 and 91 days (0.38, 95%CI 0.25-0.56). For *unipolar manic depressive psychoses* the relative risk was not significantly different between 2 and 28 days (0.81, 95%0.48-1.28) and was moderately decreased between 29 and 91 days (0.65, 95% CI 0.44-0.92).

These contrasting results probably reflect the different reference groups chosen (the entire Danish female population in Terp et al [67] vs women acting as their own control in Kendell et al [52]). Both approaches have some limitations that need to be considered in the interpretation of the results. The choice of Terp et al [67] to include the entire female population as control group implied that the chances of becoming a mother were the same among women with mental disorders and women in the general Danish population (i.e. the authors did not consider what Munk-Olsen et al [68] called *selection into parenthood*). However, Laursen and Munk-Olsen [69] found in an overlapping sample that fertility was significantly impaired in women with psychiatric disorders. Using the Danish general female population as a reference, they found that the incidence rate of becoming a mother for the first time was significantly lower in women with unipolar depression (incidence rate ratio =0.57; 95% CI 0.55, 0.60) and even lower in those with bipolar disorder (incidence rate ratio =0.36; 95% CI 0.33, 0.40). Due to a similar mechanism of *selection into parenthood*, Kendell et al [52] estimates may be inflated. Kendell et al [52], in fact, used as denominator the same women 2 years before pregnancy. It is possible, however, that women who are well have more chances of getting pregnant and thus that the period before pregnancy is a period in which the rates of admission are lower than other times.

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[3]Depression precipitated by events in a person's life. Chronic affective disorder characterised by either relatively mild depressive symptoms or marked loss of pleasure in usual activities. It is not a synonym of DSM-IV or ICD-10 dysthymia. See [71] for a discussion and critique to the the current views on neurotic depression

Terp et al [67] supported this thesis by finding in the Danish sample that the admission rate before pregnancy (i.e. the reference group of the Scottish study) was significantly reduced in comparison to the admission rate in the general population (relative risk=0.08; 95% CI 0.07-0.09). The comparison between these two studies exemplifies a recurrent problem in studies investigating the link between childbirth and mental health: the choice of control groups can have dramatic consequences not only in the magnitude of the effect (here 10-fold lower in Terp et al [67] than in Kendell et al [52]) but also on the direction of the effect (here decreased risk for unipolar depression in Terp et al [67] and increased in Kendell et al [52]).

Two studies conducted in the last decade have acknowledged these limitations and used parous women in the general population as control group. The first study was conducted on the **Nationwide Swedish Hospital Discharge and Medical Birth registers** [63]. Similarly to Kendell et al [52] and Terp et al [67], the length of observation in the postpartum period was 3 months. Differently from the previous studies only primiparae were included. The overall incidence rate of admission for any psychiatric disorders was similar to the incidence reported in Terp et al [67], at around 0.1% of deliveries. The age-adjusted recurrence rate for admission with bipolar disorder in the postpartum was 8.5% (95% CI 6.22-10.70). Interestingly, and in contrast with previous findings, Harwol et al [63] reported more than twice as high rates of hospital readmission for schizophrenia (21.7%). Jones et al [72] pointed out that this marked discrepancy with previous studies may be due to several methodological factors. First, despite using diagnoses made according to ICD criteria as Kendell et al [52] and Terp et al [67], Harwol et al [63] did not separate unipolar manic-depressive illness from bipolar manic-depressive illness. As shown in the previous 2 studies and confirmed by a subsequent research [65], the risk of readmission for *bipolar manic-depressive illness* is at least 2-fold the risk for unipolar manic-depressive illness. Moreover, hospital readmissions in women with chronic psychoses such as schizophrenia may not be due to a new episode with acute onset within 3 months after childbirth but to other reasons such as necessity of assessing the parenting skills or close monitoring of women, with attempts to prevent an exacerbation by admission at the early signs of symptoms.

The most recent study was again a study conducted on the **Danish registries**. It investigated the hospital readmission during the first year after a live-born delivery. This study confirmed the interaction between parenthood and recur-

rences, with non parous women having significantly more recurrences than the parous counterparts. In this study primiparae with the same diagnosis who gave birth 6 to 11 months earlier were the reference group. The rates of recurrence in bipolar women were similar to those reported in previous studies at about 22%. The risk of readmission in the bipolar group was more than 8 times higher than the risk for any other disorder and maximised between 10 and 19 days postpartum (relative risk= 37.22; 95% CI, 13.58-102.04). In this study rates of readmission for unipolar depression were not intermediate between bipolar disorder and other mental disorders such as in the Scottish study and in Terp et al [67], but were lower than those for schizophrenia. The different risk profile for unipolar depression between studies may reflect the differences between ICD-8/ICD-9 and ICD-10 in the classification of unipolar depressive disorders. In ICD-10, in fact, the category *neurotic depression* was omitted and replaced mainly by the diagnoses of dysthymia but also by recurrent depression and depressive episode [73]. The inclusion of formerly labelled *neurotic depressions* in ICD-10 unipolar depression group is likely to underestimate the risk of recurrence in women with *unipolar manic depressive illness.*

In summary, there is solid evidence from register based studies that the risk of a hospital readmission for bipolar disorder is the highest among psychiatric disorders and it is significantly increased in the first month postpartum compared to other times. However, register-based studies have major limitations: i) they don't question the reliability of diagnosis -that relies on the opinion of clinicians, rather than on research instruments and methodologies and ii) are not able to investigate mental disorders that do not require admission to a public hospital. The issue of bipolar depression has not been explored by register studies, probably because it is difficult to examine, probably because it requires hospital admission less frequently than mania. Interestingly, a clinical study found that the majority of patients (57%, 34/60) referred for treatment resistant unipolar postpartum depression suffered from bipolar disorder [74]. For these reasons, clinical studies may provide further insights in the perinatal trigger.

2.2.2 Clinical prospective studies

The gold-standard for clinical studies aiming to estimate the rates of postpartum recurrence is a longitudinal design in which women with bipolar/mood disorders

are assessed and followed-up in pregnancy to establish the risk factors for a recurrence and after childbirth to see whether they have developed an episode of illness of not. Viguera et al [64] conducted an observational clinical cohort study on 89 women with DSM-IV bipolar disorder in pregnancy who were euthymic at conception. In this study the follow-up period was limited to pregnancy and no information was provided on episodes after childbirth. The recurrence rate of any episode of bipolar disorder in pregnancy was 71%, with women discontinuing the mood stabilising therapy at twice as high risk of a recurrence than those who continued the therapy. Moreover, about 3 in 4 (74%) episodes were depressive or mixed[4], with only 1 in 4 women having a clear cut manic/hypomanic episode.

The same research group conducted a similar study on recurrent major depression and found that 43% of women had a relapse in pregnancy [56]. Similarly to bipolar disorder, women who discontinued their medication had a increased risk of relapse compared to those who didn't (hazard ratio= 5.0; 95% CI 2.8-9.1; p< 0.001).The high rates of recurrence in pregnancy seem to be in contrast with the results of the register-based studies discussed above, in which pregnancy was protective against a relapse. However, the latter clinical studies assessed also less severe episodes, that did not require hospitalisation and reported only the raw rates, without comparing them with the rates in the postnatal period or at other times. Moreover the academic tertiary setting is not representative of the entire population at risk and may include only most severe cases. Both studies limited the sample to women who received a medical treatment prior to pregnancy and who then discontinued it or not. However, women with bipolar disorder or recurrent major depression who are well are not necessarily in contact with the services or taking any therapy. So the results of both studies may be inflated by the selection of particularly severe patients with highly recurrent illness. Unfortunately, Cohen reported the length of illness, the average number of episodes, the type of course of illness of the participants, but not other indicators of severity and it was impossible to establish if women with a more severe course were selected. However, it seems the case for the bipolar sample in Viguera et [64] where about 1 in 2 participants had an onset of the disorder before the age of 15 and about 30% reported more than 1 episode/year of illness

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[4]In this paper it is not clear what criteria were used to define a *mixed states*. The DSM-IV criteria are : A. The criteria are met both for a manic episode and for a major depressive episode (except for duration) nearly every day during at least a 1-week period B. The disturbance is sufficiently severe to cause marked impairment, or to necessitate hospitalisation to prevent harm to self or others, or there are psychotic features. C. The symptoms are not due to the direct physiological effects of a substance or a general medical condition (pregnancy is not considered a general medical condition!) [5] However, it is very unlikely that Viguera et al [64] used DSM-IV criteria, that are narrow and exclude BD-II

and about 40% reported prior rapid cycling.

2.2.3 Clinical retrospective studies

Given the paucity of informations from longitudinal studies, I also discuss 2 retrospective studies conducted again by Viguera et al [6, 58] on overlapping samples (that included also data from the longitudinal sample described above [64]). In the first study [58] the authors compared the rates of recurrence after lithium discontinuation in women who discontinued the therapy during pregnancy and in those who discontinued it outside the perinatal period. Rates of recurrence in pregnant women (52%) were similar to rates of recurrence in non-pregnant women (58%) during the first 40 weeks after lithium discontinuation, while postpartum recurrences were about 3 times more frequent than recurrences during an equivalent period of time for non-pregnant women (70% versus 24%). Interestingly, in accordance with the longitudinal study described above [64], depressive and mixed-dysphoric episodes were significantly more common among pregnant/postpartum women than in non-gravid subjects (63.16% versus 37.50%, p=0.02). More recently Viguera et al conducted a retrospective study on 1,162 women with DSM-IV BD-I (479 pregnancies/283 women), BD-II (641/338), or RMD (1,132/541) who were treated in three tertiary academic settings specialised in perinatal mood disorders [6]. The study derived several measures to assess the risk of recurrence. In the bipolar disorder group (either BD-I or BD-II), 23% of participants reported an episodes during pregnancy and 52% in the postpartum period, defined as within 6 months after childbirth. The rates were lower for unipolar depression, with 4.6% reporting an episode during pregnancy and 30% in the postpartum. In addition to the retrospective design, this study had the same limitations of the previous studies conducted by Viguera [58, 64]. It could also be argued that the conclusions are not generalizable because the sample was drawn from tertiary academic settings. Moreover, the definition and validity of 'mixed states' used by Viguera were not clear. The DSM-IV criteria for a mixed states implied a full-blown manic episode and thus mixed states should not occur in women with BD-II. However, mixed states affected 3.5% of women in the BD-II group during pregnancy and 22.5% after childbirth. Moreover, none of the participants with RMD or BD-II reported psychosis.

In summary, in women with bipolar disorder recurrences following childbirth

are significantly more common than at other times. With the exception of Harlow et al [63], studies found that bipolar disorder has the highest risk of recurrence across psychiatric disorders. Clinical studies investigating the symptomatology of the recurrences found that mixed and depressive episodes were more prevalent than mania. There is no evidence that pregnancy is a specific trigger for mood episodes. The high rates of recurrences in pregnancy observed by clinical studies are probably associated with the high rates of women discontinuing the medications during pregnancy.

2.3 What period of time should be covered by the postnatal onset criterion? Should pregnancy be included?

I have already discussed the current definition of postpartum onset in chapter 1. Here I summarise the evidence from registry and clinical studies on the length of the postpartum period. The studies I examined in the previous sections have all consistently reported an increased risk of hospital admission within the first month after childbirth. Results on a longer length of time after childbirth are controversial, but all univocally report a lower risk compared to the first month after delivery.

Less recent studies [75, 76] used a 6 months postpartum criterion. Kendell et al in the Scottish registry study [52] found that, although the admission rate maximised in the first month, it was still higher than before pregnancy for 2 years after delivery and proposed a 3 months criterion.
A lot of debate has been generated on whether there is a *lucid interval* between delivery and the onset of postpartum psychosis[5].
Paffenbarger [76] reported that only one third of women with postpartum psychosis had the onset in the first week postpartum and less than 70% of women with postpartum psychosis had an onset within 4 weeks. On the opposite side, Brockington et al [77] and Heron et al [78] argued against a lucid interval. In a clinical retrospective study conducted on women with a history of postpartum mania or affective psychosis within 4 weeks postpartum [6] 73% of participants

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[5]I use the term postpartum psychosis because the studies I discussed are antecedent to the DSM-IV and ICD-8 classifications and used different diagnostic criteria for 'postpartum psychosis'

[6]This sample was part of the Mood disorder research project

recalled the first manic symptom within 3 days postpartum and about 95%
within the first 2 weeks. The results are, however, not generalizable, as women
were recruited as part of a project on bipolar disorder and the majority of them
suffered from both perinatal and non perinatal recurrences. It is an important
limitation, because, as argued in a review based on follow-up studies by Chau-
dron and Pies [79], although the majority of episodes of postpartum psychosis
occur in women with bipolar disorder, this is not the case for all episodes.
Bergink et al recently conducted a prospective study on a small cohort (n=57)
of women admitted to a mother and baby unit for postpartum psychosis [7],
without a history of bipolar disorder or psychosis outside the postpartum pe-
riod [80]. For 45 patients this was the first psychotic episode. Although a
previous history of postpartum disorders had no effect on time of onset, there
were significant differences according to the polarity of mood symptoms. Pa-
tients without depression had a significantly earlier onset of psychosis (median
= 7 days; interquartile range = 4-10) than patients with psychotic depression
(median=18 days; interquartile range = 7-21). Unfortunately the groups were
very small (only 7 women had prominent depressive psychotic features) and
solid conclusions cannot be drawn. Moreover, as in Heron et al [78], women
who had an episode of psychosis later in the postpartum were not included
in the studies and thus it was not possible to determine whether a 1 month
postpartum criterion was too narrow. However, a similar pattern was reported
in previous studies that found that women with manic episodes were admitted
more quickly than those with depressive psychosis [81–83].

There is a lack of information on the time-to onset of bipolar depression. In
registry studies that considered only unipolar depression, the definition of de-
pressive episodes varied significantly and may be in part responsible for the
lack of consistent results. Insights on the length on the postpartum period in
RMD are provided by a family study conducted on the Mood Disorder Research
Project dataset. Forty et al [84] studied 120 sibling pairs with RMD and found
that the familiality for postpartum depression maximised when a postpartum
definition of 6-8 weeks was applied. One of the major aims of my research was
to partially fill this gap in knowledge on bipolar postpartum depression and
on whether lifetime diagnosis made any difference in the time-to onset between
unipolar and bipolar depression.

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[7]defined as DSM-IV depressive disorder with psychotic features, mania with psychotic
features, mixed episode with psychotic features, psychotic disorder not otherwise specified
(NOS), or brief psychotic disorder with onset within 4 weeks after delivery

2.3.1 Pregnancy

Registry based and clinical studies found that pregnancy was a 'protective' period with a reduced risk of new onset disorders and recurrences. A prospective clinical study found high recurrence rates in pregnancy in women who discontinued the medications [64]. However, the high recurrence rates in pregnancy were similar to the rates of recurrences in women who discontinued the therapy outside the perinatal period. Moreover, in a retrospective clinical study Viguera et al [6] reported that the postpartum/pregnancy risk ratio in unipolar depression was higher (3.68, 95% CI=3.16-4.30) than that in BD-II (1.68, 95% CI=1.20-2.01) and in BD-I (1.52, 95% CI=1.15- 2.03). Although there is no consistent evidence of an increased risk of bipolar/mood episodes in pregnancy, I analysed in my research also information on pregnancy onset for a reason of completeness and clinical utility. Depression in pregnancy, in fact, could be less prevalent than depression in the postpartum period, but, there is increasing evidence that it has long-term negative consequences on the offspring. The longitudinal, community-based South London Child Development Study followed up until the age of 16, 25 children who were exposed to maternal depression in utero and 95 who were not. Antenatal depression was associated with an about 4-fold increased risk of maltreatment in the offspring, not necessarily perpetrated by the mother. Although antenatal depression was not associated with subsequent psychopathology in the offspring, children who were exposed to depression in utero and who were also maltreated had a 12 times greater risk of developing psychopathology than the non exposed counterpart [85].

2.4 Summary

In this chapter I have reviewed the literature on the childbirth trigger of episodes of mood disorders. For women who have never suffered from any mental disorders, the first month postpartum is a period of increased risk of hospital admission for mania or affective psychosis. Similarly, for women who have a previous history of bipolar disorder, the first month postpartum is a period of increased risk of hospital readmission. The majority of studies reported that the association with childbirth shows some specificity for bipolar disorder. Postpartum non bipolar episodes in women with no psychiatric history are associated with an increased risk of further episodes of bipolar disorder. Although there is a lot of evidence on the association between childbirth and admission for ma-

nia, there is a paucity of information on less severe episodes. Moreover, lack of consensus on the terminology used to defined postpartum episodes and on the reference groups has led to some inconsistencies.

Chapter 3

Clinical characteristics of perinatal mood episodes

In the previous chapters I overviewed some of the epistemic and nosological difficulties that raise when we investigate perinatal mood disorders. In this chapter I provide a schematic overview on the clinical aspects of postnatal depression and postpartum psychosis in bipolar disorder. I particularly stress the diagnostic features and the risk factors involved in the liability to postnatal episodes, because they were key factors in designing the prospective study that I discuss in chapters 10 and 11.

3.1 Postpartum psychosis

3.1.1 Aetiology and pathophysiology

A range of factors has been suggested to increase vulnerability to postpartum psychosis:

Genetic factors There is robust evidence that the vulnerability to the triggering of affective psychosis by childbirth aggregates in families and may define a genetically relevant subtype of bipolar disorder [59, 86]. Evidence from family studies suggests that episodes of postpartum psychosis are a

marker for a more familial form of bipolar disorder [87] and that a specific
vulnerability to the puerperal triggering of bipolar disorder is familial [59].
Evidence from a linkage study indicated the possible location of a suscep-
tibility gene on chromosome 16 [86]. Particular candidate genes, such as
those involved in the serotoninergic [88,89], hormonal [90,91], and inflam-
matory pathways [92], have been also investigated.

Obstetric risk factors An increased risk of postpartum psychosis has been re-
ported with primiparity, pregnancy and delivery complications, caesarean
section, female baby and shorter gestation period. However, findings are
consistent only for primiparity [93]. The bias that women with a severe
postpartum episode may be less likely to go on to have further children
is unlikely to be the sole, or even the main, explanation [93]. Given that
there is little evidence of an association between postpartum psychosis
and psychosocial factors, the possibility remains that the effect of primi-
parity is, at least in part, due to biological differences between first and
subsequent pregnancies. It is of particular interest the overlap with other
pregnancy related disorders, such as pre-eclampsia, that have also been
reported to occur more frequently in first pregnancies. Hormonal, im-
munological and other biological differences between first and subsequent
pregnancies are therefore interesting targets for further investigation into
the aetiology of postpartum psychosis. This is the main topic of chapter
9.

Changes in medications Women with bipolar disorder often come off mood
stabilizers, such as lithium, preconception or in early pregnancy because
of concerns over toxicity to the foetus. A survival analysis comparing
women with bipolar disorder who stopped taking lithium because of preg-
nancy compared with age-matched non-pregnant women who disconti-
nued lithium for other reasons, reported similar rates of recurrence during
the first 40 weeks after lithium discontinuation for both groups. How-
ever, among subjects who remained stable over the first 40 weeks after
lithium discontinuation, postpartum recurrences were 2.9 times more fre-
quent than recurrences in non-pregnant women during weeks 41-64 (70%
versus 24%) [58]. Thus, the increased risk of recurrence following child-
birth for women with bipolar disorder does not appear to be merely a
result of stopping mood-stabilizing medication.

Hormonal factors The lack of evidence implicating psychosocial factors and
consideration of the abrupt onset during a time of major physiological

change suggest that biological, possibly hormonal, factors are important. The role of several hormones (including estrogens, progesterone, prolactin, follicular stimulating hormone and luteinizing hormone) has been considered, but the evidence pointing to hormones in the aetiology of postpartum psychosis is predominantly circumstantial.

Sleep deprivation A plausible hypothesis is that the sleep deprivation of delivery and the immediate postpartum period is responsible for puerperal triggering of illness. Sleep loss can effectively trigger the onset of mania in people with bipolar disorder and sleep loss is, of course, common for new mothers. In a small study flawed by many methodological limitation (chart review with no direct measure of sleep, and use of a healthy control without psychiatric history rather than a comparison group of at-risk women), Sharma et al found that postpartum psychosis was associated with longer duration of labour and and nighttime delivery. In the group of women with postpartum psychosis insomnia was the most frequent and usually the earliest symptom [94].

3.1.2 Prevention

Screening for risk factors

In addition to a history of bipolar disorder or postpartum psychosis, other risk factors for postpartum psychosis include having a first-degree relative who has experienced postpartum psychosis and having a first-degree relative with bipolar disorder [95].
For women who themselves have a history of mood disorder, particularly bipolar disorder, a family history of a severe postpartum episode is very important and may indicate a risk in excess of 50%.
For women who have themselves not suffered with psychiatric illness, it is not so clear that a family history is relevant with a risk of postpartum psychosis in low single figures. While this represents a considerable increase on the population risk of around 1 in 1000, it is unclear whether extensive efforts to identify women who are well but with a family history is a worthwhile strategy. It is not in doubt, however, that family history is an important consideration in women with a personal history of bipolar disorder.
Because of the relapsing and remitting nature of bipolar disorder, women at high risk are often currently well and not in contact with mental health services

and will fail to recognise the serious risks of the situation. Thus, all women should be screened for known important risk factors at their antenatal booking visit. Protocols should be put in place to ensure that women at potential risk receive a formal risk assessment and management plan [95].

Management of women at high risk

Women at high risk of postpartum psychosis need very careful care before conception, throughout pregnancy and during the postpartum period. The high risk of illness in the weeks following delivery in a woman with a history of bipolar disorder must be recognised both by healthcare professionals and by the woman herself.

Preconception The possibility of future pregnancy should be considered in all women with bipolar disorder who are of childbearing age. The risks of illness following childbirth should be discussed with women and the importance of seeking help emphasised. Decisions about continuing or stopping medications before, or during, pregnancy are difficult and should be the result of a detailed and individualised risk analysis [95]. Although there are significant concerns about the teratogenic effects of the medications used to treat bipolar disorder, the risks of stopping medication must also be considered. Data suggest that women with bipolar disorder who stopped medication during pregnancy were more than twice as likely to experience a recurrence than those who remained on medication [64].

During pregnancy and after childbirth Perhaps the most important aspect of care is to maintain close contact and review during the perinatal period. Women at high risk, even if they are well, should be referred in pregnancy for psychiatric assessment and monitored regularly for at least 3 months following delivery. Psychiatric services should have priority care pathways for pregnant and postpartum women and care by multiple psychiatric teams should be avoided [96]. It may also be important to address other avoidable factors that may increase risk - such as decreasing general levels of stress and paying attention to sleep in late pregnancy and the early postpartum weeks. For women with a history of bipolar disorder who have been off medication in pregnancy the introduction of prophylactic medication in the immediate postpartum period should be considered. Some evidence exists for the use of lithium in this

context, but the few studies have been open and retrospective and there are practical problems with reaching therapeutic levels quickly to cover the period of risk. These issues have led some perinatal psychiatrists to use typical or atypical antipsychotics as prophylaxis [97].

3.1.3 Diagnosis

Examination

The distinctive clinical features include sudden onset and rapid deterioration. The vast majority of episodes has its onset within 2 weeks of delivery, with over 50% of symptom onsets occur on days 1-3 [98]. The clinical picture often changes rapidly, with wide fluctuations in the intensity of symptoms and severe swings of mood. Common symptoms and signs include: 1) A wide variety of psychotic phenomena such as delusions and hallucinations, the content of which is often related to the new child. 2) Affective (mood) symptoms, both elation and depression. 3) Disturbance of consciousness marked by an apparent confusion, bewilderment or perplexity.

Differential diagnosis

- Primary cerebral or systemic disease (e.g. eclampsia or infection) should be excluded. The misattribution to psychiatric disorder has led to a number of deaths in new mothers [96].

- Exogenous toxic substances or hormones: History of therapeutic use and/or abuse of known causative substances or hormones, other symptoms and signs specific to the substance or substances involved should be investigated. Urine drug screen may be positive in substance abuse and identifies the substance taken, although it is not definitive for drug misuse.

- Other psychiatric disorders of the puerperium:

    - Minor mood disorders (mood swings)

    - Postpartum depression

The tendency for all postpartum episodes to be labeled as postnatal depression can lead to suboptimal care and, in some cases have dramatic consequences on mothers and babies. The last Confidential Enquiries into Maternal Deaths in the United Kingdom reported that 8 out of 11 women, who committed suicide after suffering for postpartum psychosis, were initially diagnostisized as suffering for anxiety or mild depression or adjustment disorder [96]. Any psychotic symptoms, particularly delusions or hallucinations, substantially increase risk for both mother and child. The woman should be referred for a same day emergency appointment so that a detailed risk assessment can be carried out.

3.1.4 Treatment

Hospital admission

Postpartum psychosis is a psychiatric emergency. The clinical picture may mislead, quickly become extremely severe and vary significantly from hour to hour. Patients are usually admitted for treatment. Even women with the most supportive of families are likely to require hospital admission. The National Institute for Health and Clinical Excellence (NICE) guidelines 23 recommend that women within a year of childbirth should be offered admission to a specialist mother and baby unit, however, the provision of services across the United Kingdom is patchy and for the majority of women there is no option of admission with her baby [99].

Pharmacological treatment

A range of psychotropic medication may need to be employed. The treatment used depends on a number of factors, including the symptoms that the woman experiences, her level of disturbance and her previous response to medication. For many women the severity of the illness does not allow breastfeeding. If breastfeeding is being considered, factors in the baby such as prematurity and systemic illness should be considered in addition to the particular properties of the medication itself. Limited data suggest that the use of lithium during breastfeeding is not as problematic as once thought but it tends to be avoided because of the risk of toxicity in the infant.

3.1.5 Prognosis

The short-term prognosis for postpartum psychosis is generally good. However, women need to be counselled about the risks they run of a further puerperal or non-puerperal episode. This will include discussing the need for longer-term mood stabilising medication and other measures that can reduce the risk of recurrence. Despite the high risk of recurrence following further deliveries, many women make the decision to become pregnant again and it is our strongly held view that women with PP, or indeed bipolar disorder more generally, should not be told that they should not have children.

Risk of non-puerperal recurrences

There is a paucity of information on rates of non-puerperal recurrences. Robertson et al [100] found that, following the index episode of postpartum psychosis, 62% of women experienced at least one non-puerperal affective episode of mania, depression or hypomania during a median period of observation of 9 years from recovery.

Complications

Neglect of the baby Referral to safeguarding teams should not be routine, but should take place as the result of a risk assessment. Extra vigilance and care are required in these cases, as it may increase the risk of deterioration in the mother's mental health and suicide [97].

Infanticide Infanticide is a very rare complication. The past two Confidential Enquiries into Maternal Deaths in the United Kingdom didn't report any infanticide in mothers suffering from postpartum psychosis .

Suicide According to the Eight Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom, psychosis was the most common diagnosis in woman who committed suicide after childbirth [96].

3.2   Postpartum depression

There is a paucity of evidence on bipolar depression. However, the topic cannot be neglected, given the high rates of depressive recurrences in the perinatal period in bipolar disorder. The data reported in this section are mostly based on unipolar samples. The few studies on bipolar depression are reported in the last paragraph.

3.2.1   Aetiology and pathophysiology

The aetiology of postpartum depression is poorly understood but is likely to involve an interaction between psychological, social, and biologic factors. For non psychotic episodes of major depression, a specific relationship with child-birth has been challenged [101]. It has been argued that depression is no more common following childbirth, that the clinical presentation is no different from that for depression occurring at other times, and that the treatment options are the same. However, a proportion of women with postpartum depression may be vulnerable to a specific puerperal trigger.

Hormonal factors   No major differences in the hormonal profile of women who develop postpartum depression have been reported [102]. However, it has been suggested that women who become depressed postpartum may have an abnormal sensitivity to the normal physiologic changes of child-birth [103].

Exaggerated immune response It has also been suggested that the inflammatory response after labor and delivery may be exaggerated in women who develop postpartum depression [104].

Genetic factors Vulnerability to postpartum depression within 8 weeks of delivery may be familial [84]. For women without a personal history of major depression, however, the importance of a positive family history is less clear [105]. An Australian twin study reported that genetic factors accounted for 26% to 49% of variance in postpartum depressive symptoms [106]. A study suggested that genetic variation on chromosomes 1q and 9p might increase susceptibility to broadly defined postpartum mood symptoms in a sample of women with both unipolar and bipolar disorder [107].

Sleep disruption A strong association between infant sleep patterns, maternal fatigue, and new-onset depressive symptoms in the postpartum period has been suggested. Therapeutic interventions to reduce sleep deprivation in the early weeks postpartum have been tried [108].

Previous psychiatric history A previous history of psychiatric illness, either in pregnancy or lifetime, has been strongly associated with postpartum depression. Postpartum depression is more likely to occur in patients with a history of previous depression or anxiety [105, 109–112]. Discontinuing psychopharmacological treatments increases the risk of postpartum depression in patients with depression or a bipolar disorder [58]. Women who experience prenatal depression have about a fivefold increased risk of developing postpartum depression [113], while women who experience prenatal anxiety have a threefold increased risk [113].Two longitudinal studies also found that hypomanic symptoms at day 3 predicted depressive symptoms at 6 weeks postpartum [114, 115].

Psychosocial factors There is a strong association between recent life events and postpartum depression. In the presence of clear psychosocial adversity and mild to moderate postpartum depression, the risk of subsequent depressive episodes depends on the persistence of the adverse circumstances [116]. Emotional and instrumental supports have been negatively correlated with postpartum depression [105, 109, 112, 117, 118] while perceived social isolation was strongly predictive of depression in the postpartum period in a sample of black women with low incomes [119]. Marital problems during pregnancy and the lack of a supportive partner have been found to moderately increase the risk of postpartum depression [112]. Low income, financial strain, unemployment, and low social status have a small but significant predictive effect on postpartum depression [112, 119].

3.2.2 Prevention

Intensive professional postpartum support individually targeted at at-risk mothers may be beneficial. Although the evidence base is small, it may be appropriate to offer antidepressant prophylaxis to some women with a strong history of depression [116]. Current guidelines, however, do not recommend psychosocial interventions routinely as part of prenatal and postpartum care [99]. An argument can be made for a lower threshold for access to psychological ther-

apies during pregnancy and the postpartum period arising from the changing risk-benefit ratio for psychotropic medication at this time.

Management of women at risk

Advice about future risk should be tailored to the individual patient [116]. It is important to give relevant information to women with an existing mental illness who are planning a pregnancy or are pregnant, as well as to those women who develop an episode during pregnancy or the postpartum period [99]. This should include the impact of the disorder and its treatment on both the woman herself and her baby and a full discussion of the risks and benefits of medication [99].

3.2.3   Diagnosis

Screening

Suspected mild and moderate depression can be assessed and managed in primary care. Depression should routinely be sought in all women in the perinatal period [99, 120]. Risk factors should be identified.

The Bromley Postnatal Depression Scale [121], the Edinburgh Postnatal Depression Scale [122], and the Postpartum Depression Screening Scale [123] are self-reported measures specifically designed to screen for depression in the postpartum period. The Edinburgh Postnatal Depression Scale had been most widely studied. It has been psychometrically tested extensively in postpartum women and used throughout the world. Sensitivity and specificity of cutoff points showed marked heterogeneity between different studies. Sensitivity results ranged from 34% to 100% and specificity from 44% to 100%. The cutoff score of >12 has an overall positive predictive value of 57% and negative predictive value of 99%. Other tools such as the Beck Depression Inventory [124] may have value but require further research [125]. These screening tools should be used to identify women who need further clinical assessment.

The United Kingdom National Institute for Health and Clinical Excellence [99, 120] recommends that healthcare professionals (including midwives, obstetricians, health visitors, and general practitioners) should ask 2 questions to identify possible depression (Whooley questions), at the woman's first contact with primary care, at her first prenatal appointment, and postnatally (usually at 4 to 6 weeks and 3 to 4 months).

US guidelines stress the importance of routinely assessing patients for depression but do not provide a definitive recommendation as to how patients should be screened and which tools should be used [120].

Symptoms

Patients may present with a history of depressed mood, anhedonia, weight changes, sleep disturbance, psychomotor problems, low energy, excessive guilt, loss of confidence or self-esteem, poor concentration, or suicidal ideation [126]. Depressed mood is to a degree that is abnormal for the person, present for most of the day, and largely uninfluenced by circumstances.

There is evidence of a relationship between postpartum depression and obsessive-compulsive symptoms, particularly unwanted intrusive thoughts of hurting the newborn [127]. In one study of 37 women with postpartum depression, 57% reported obsessional thoughts, of which 95% had an aggressive content. The most frequent content of the aggressive thoughts was causing harm to their newborns or infants. The presence or number of obsessional thoughts or compulsions was not related to severity of the depressive episode [128]. In another study, of the 41% of women with postpartum depression who reported aggressive obsessive thoughts, 5% had actually acted in an aggressive way toward their child. However, it must also be noted that the prevalence of aggressive thoughts among postpartum women without depression is 6.5% [129]. Psychotic symptoms occurred in 4% of episodes in one study [130]. These include hallucinations, delusions, confused and disturbed thoughts, and a lack of insight and self-awareness. They can substantially increase risk of self-harm or harm to the baby, particularly if the delusions or hallucinations relate to the baby.

Physical exam is required to assess the patient's general medical status but does not reveal any specific features of depression. However, examination of the skin may reveal stigmata of trauma, self-injury, or drug use.

- Minor mood disturbance (postpartum blues or baby blues, mood swings)

- Postpartum psychosis. Any psychotic symptoms substantially increase the risk of self-harm or harm to the baby, particularly delusions or hallucinations that relate to the baby. The core feature of postpartum psychosis is the acute onset of a manic or depressive psychosis in the immediate postpartum period. Postpartum psychosis is a psychiatric emergency and can develop rapidly into a very severe condition.

- Internistic conditions, such as anemia and thyroid dysfunctions.

3.2.4   Treatment

Guidelines recommend a stepwise approach to the treatment of postpartum depression [99], although it is important that women with severe illness receive appropriate treatment quickly rather than working through various levels of treatment. Treatment can be effectively organised via primary care.
Referral to specialist mental health services is reserved for patients with suicidal ideation, thoughts of harming the child, severe disease, and/or features that raise suspicion of bipolar illness. Before treatment decisions are made, healthcare professionals should discuss with the patient the absolute and relative risks associated with treating and not treating the mental disorder in relation to breastfeeding, the evolutionary risk of the illness and the impact on the mother-child relationship.

For a woman who develops mild or moderate depression[1] during the postpartum period, the following should be considered [99, 126]:

- Self-help strategies (guided self-help, computerised cognitive behavioural therapy, or exercise)

- Brief cognitive behavioural therapy or interpersonal psychotherapy

- Antidepressants are recommended if the patient declines psychological therapy, if it is unavailable or does not work, or if the woman has a prior history of severe depression [99, 126].

For a woman who develops a severe postpartum depressive episode or a moderate postpartum depressive episode with a prior history of severe depression, the following should be considered [99, 126]:

- Cognitive behavioural therapy or interpersonal psychotherapy

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[1]Depression is defined as mild, moderate, and severe as follows: Mild: few if any symptoms more than the number required for diagnosis of depression with minor functional impairment. Moderate: more than the required number of symptoms for diagnosis of depression with greater intensity and moderate impairment in functioning. Severe: many more symptoms than required for diagnosis of depression with intense functional impairment [5]

- Antidepressant therapy if preferred by the patient

- Combination treatment if there is no, or a limited, response to psychological or drug treatment alone.

The local availability of psychological therapies is an important factor when determining which treatment to offer, as waiting times can be lengthy. It is vital to treat women with severe illness promptly, which often necessitates the use of antidepressant drugs [99, 126].

Non-pharmacologic therapy

A Cochrane meta-analysis of 10 trials of psychological and psychosocial interventions [98] concluded that peer support and non-directive counselling, cognitive behavioural therapy, psychodynamic psychotherapy, and interpersonal psychotherapy are all effective in postpartum depression. Women requiring psychological treatment should be seen for treatment quickly, ideally within 1 month of initial assessment [99].

Pharmacologic therapy

Specific evidence for the pharmacologic management of postpartum depression is limited [116]. Antidepressants are often prescribed for postpartum depression according to the same principles delineated for other types of major depressive disorder, despite a limited number of controlled studies. However, in breastfeeding women the risk-benefit balance of antidepressant drugs is altered, and psychological therapies are therefore preferred if possible [99]. If antidepressant therapy is given, patients require close mood monitoring in case a hypomanic or manic episode is triggered.

Treatment depends on the patient's preference, previous responses to treatment, local availability of psychological therapies, the severity of the illness, and the risks involved. Certain antidepressants are considered safer than others in breastfeeding women, but in general the long-term outcomes for babies exposed to maternal antidepressant treatments are unknown.

Emerging Therapies

A Cochrane review on oestrogens and progestins for preventing and treating postpartum depression suggests that synthetic progestins may be used with significant caution in the postpartum period and that oestrogen therapy may be of modest value [131]. However, oestrogens have not been rigorously evaluated, and further research is warranted, given the increased risk of thromboembolism associated with their use.

3.2.5 Prognosis

Differing definitions of postpartum depression across studies make it difficult to interpret prognostic information. Outcomes depend on the severity and nature of the symptoms. Episodes of postpartum depression last 3 to 6 months on average, but a few women remain depressed at 1 year [116].

Risk of further episodes

Women with a first episode of postpartum depression have a higher risk of subsequent postpartum depression (41% vs. 18%) but a lower risk of depression outside the postpartum period (38% vs. 62%).
In the presence of clear psychosocial adversity and mild to moderate postpartum depression, the risk of subsequent depressive episodes depends on the persistence of the adverse circumstances [116]. If the adversity was a discrete life event, such as the breakdown of a relationship, and has been resolved, then the risk of future postpartum depression may be low. However, the risk of future episodes in this situation depends not only on the life event itself but also on a wide range of patient-specific psychological and biologic factors [116].
Early-onset depression (within the first 6-8 weeks), severe depression, and depression with bipolar or psychotic symptoms suggest the presence of a specific puerperal trigger, and the risk of subsequent postpartum episodes may be higher in these patients [100].

Complications

Impaired bonding with infant A strong correlation exists between postpartum depression and impaired interaction and bonding between mother and infant. Avoiding or impaired bonding with the baby, a lack of feeling of attachment toward the infant, and a sense of numbness are important features to consider. Impaired maternal-infant bonding has a negative impact on infant development and may also affect later child development. It also adds to the mother's sense of shame and guilt. Infant exposure to maternal depression has been shown to have negative consequences behaviourally, cognitively, and emotionally. Affected infants demonstrate restricted facial expression and fewer interests. Treatment of maternal depression reduces depression, anxiety, and disruptive behaviour in the child, whereas no treatment results in worsening of these symptoms. Comorbidity with a personality disorder increases the risk of dysregulated infant behaviour [132].

Neglect of the baby, maltreatment or infanticide Situational and environmental factors might increase or decrease risk. Any history of attempted suicide or harm to the baby, any psychotic symptoms substantially increase risk, particularly delusions or hallucinations that relate to the baby. In these cases, the patient should be referred for a same-day emergency appointment so that a detailed risk assessment can be carried out [116].

Suicide is much more common than infanticide in new mother with severe psychiatric disorders. A preliminary assessment of the risks of suicide can be made by assessing the current mental state and any situational and environmental factors that might increase or decrease risk [116]. Also in these cases, the patient should be referred for a same-day emergency appointment so that a detailed risk assessment can be carried out.

3.2.6 Postpartum depression in bipolar disorder

Postpartum depression most often occurs in the context of a unipolar depressive illness. However, episodes of mood disorder following childbirth are very common in women with bipolar disorder, and a small proportion of postpartum depressive episodes are bipolar. The consequences of missing a diagnosis of bipolar disorder can be particularly serious, as treatment with antidepressants

may precipitate mania, a mixed state, or rapid cycling, and thereby increase the risk for admission to a psychiatric hospital [4]. It has been reported that 54% of 56 outpatients seen consecutively with the referral diagnosis of postpartum depression were re-diagnosed as having a lifetime diagnosis of a bipolar disorder [133]

Screening should include questions about a family history of bipolar disorder. Atypical features [5] , racing thoughts, and psychotic symptoms during a depressive episode should raise suspicion of a bipolar disorder [4].

In addition to asking questions about high mood and related symptoms in the history, questionnaires can also be used. There is no screening instrument designed specifically for use before or after delivery in women with bipolar disorder [134]. Self-reported measures used to screen for bipolar disorder in the general population include the Altman Self-Rating Mania Scale [135], the Highs [115], the Mood Disorder Questionnaire [136], and the Screening Assessment of Depression-Polarity [137]. Although no screening tool has been definitively shown to be superior [138], the Mood Disorder Questionnaire [4,138] and Highs [4] are the most promising tools and have already been studied in perinatal populations. The Mood Disorder Questionnaire incorporates all pertinent information included in the other scales with the addition of an assessment of irritability and impulsive behaviour. Once the risk of bipolar disorder is recognised, it is necessary to follow up with a more comprehensive psychiatric assessment.

Insufficient research has been conducted on the treatment of postpartum bipolar depression, so definitive recommendations cannot be made [4].Treatment with antidepressants should be avoided, as it has been associated with a highly unstable course of illness. Mood stabilisers may pose a risk to the baby during breastfeeding. Specialty consultation with a psychiatrist familiar and comfortable with managing mood disorders during and following pregnancy is recommended.

In summary, bipolar depression following childbirth is an important but neglected topic. I extensively investigate depression in bipolar disorder throughout the thesis.

Chapter 4

Summary and objectives

"The problems of language here are really serious"

Werner Heisenberg [139]

There is very strong, clear and consistent evidence of a specific relationship between bipolar disorder and childbirth. New mothers in the general population are over 23 times more likely to be admitted with an episode of mania in the first postpartum month [68]. A previous history of admission with bipolar is associated with an even larger increased risk of postpartum admission (relative risk 37.2) [65]. Women with bipolar disorder have at least a 1 in 4 risk of suffering a severe recurrence following delivery. Women with bipolar disorder and a previous personal or family history of a severe postpartum episode are at particularly high risk with more than 1 in 2 deliveries affected [95].

Despite the high prevalence of less severe forms of illness, the study of postpartum bipolarity beyond postpartum psychosis has been largely ignored [4, 140]. Misdiagnosis of bipolar depression as major depressive disorder during the postpartum period appears to be common and the consequences particularly serious [74]. Treatment with antidepressants, in fact, may precipitate mania, a mixed state, or rapid cycling and thereby increase the risk for psychiatric hospitalisation.

Although a number of potential risk factors for postpartum triggering have been established, the work to date has been in retrospective samples and has not examined a number of potential factors that are likely to be involved.

In summary, the link between bipolar disorders and childbirth has firmly been established only for severe psychotic episodes, while there is no robust evidence for less severe, but more prevalent forms. Even for severe episodes, risk factors and mechanisms underpinning the relationship between bipolar episodes/disorders and childbirth are poorly documented. My PhD project sought to address these deficiencies. The project revolved around the childbirth trigger of bipolar disorder. The uncertainty in the definitions and classification of mood disorders (within and outside the perinatal period) was the major conundrum in my research, so much attention was paid in exploring possible models to conceptualise perinatal episodes of bipolar disorder.

Aims of the PhD project were:

- To investigate in a large existing dataset perinatal bipolar episodes and to compere them with those in women suffering with RMD. I focussed my analyses on

    Rates of perinatal episodes I estimated the lifetime prevalence, the incidence during and after each pregnancy and the morbidity risk. Then I explored differences between lifetime diagnoses of BD-I, BD-II and RMD.

    Timing of onset of episodes in pregnancy and within 6 months postpartum. I estimated and compared survival curves across types of episode (mania, non psychotic depression, psychotic depression) and lifetime diagnoses (BD-I, BD-II and RMD).

    Specificity of the postpartum trigger I explored the lifetime course of mood disorders in relation to the episodes occurring after childbirth and tested the hypothesis that childbirth is not a specific trigger and episodes occur after delivery only by chance.

    Link between parity and PNEs and its potential implications for the aetiology and nosology of perinatal mood disorder. I estimated the rates of PNEs across types of episode (mania and psychotic depression, non psychotic depression) and lifetime diagnoses (BD-I, BD-II and RMD), explored the influences of potential biases and compared the rates between first and subsequent pregnancies.

- To design and pilot a prospective study aimed to recruit a large, well characterised sample of women with bipolar disorder preconception or in early pregnancy and to monitor them through pregnancy and the postpartum. The aims of the full blown prospective study were:

  - to establish the proportion of women who suffer a severe episode of psychiatric illness

  - to characterise the clinical features of episodes occurring in the postpartum

  - to explore the influence of a range of variables on the vulnerability to develop an episode of severe illness in pregnancy or the postpartum

The aims of the pilot study were:

- to establish the effectiveness of the recruitment methods

- to test the adequacy of the assessment tools

- to estimate the variability in the outcomes to calculate the sample size

- to assess the feasibility of the large scale study and to modify the current research protocol in order to increase the chance of success in recruiting and following-up women

Part II

Perinatal mood episodes in a large dataset of women with mood disorders

Chapter 5

Methods

In this chapter I first describe the recruitment and assessment of participants included in the Mood Disorders Research Project database, then provide a brief overview of the principal statistical methods employed in the analyses.

5.1 The Mood Disorder Research Project

The retrospective data that I analysed were drawn from the Mood Disorder Research Project database. The Mood Disorder Research Project is jointly run by the University of Birmingham (Dr Lisa Jones and Dr Katherine Gordon-Smith) and Cardiff University (Professor Nick Craddock, Dr Ian Jones and Dr Liz Forty). The Mood Disorders Group - called also the Bipolar Disorder Research Network (BDRN - see bdrn.org) - has extensive experience of recruiting large numbers of individuals with unipolar and bipolar disorder for clinical and genetic studies and has collected data on more than 6000 people with mood disorders over a 20-year period.

The database collected information on individuals who took part in different sub-projects (figures 5.1, 5.2 and 5.3). Although the main structure of the dataset remained unchanged, a number of variations in the inclusion criteria and in the variables assessed have been occurred over the years (table 5.1).

As stated in the background section, a clear-cut distinction between bipolar and unipolar disorders is currently controversial. Thus, although this thesis is focused on bipolar disorder in relation to pregnancy and postpartum, I in-

cluded in the analyses a sample of women with RMD to explore differences and similarities between unipolar and bipolar disorder. Strategies of ascertainment and duration of recruitment differed across sub-studies, thus in my analyses the sample sizes of the BD-I, BD-II and RMD group differed (figures 5.2 and 5.3).
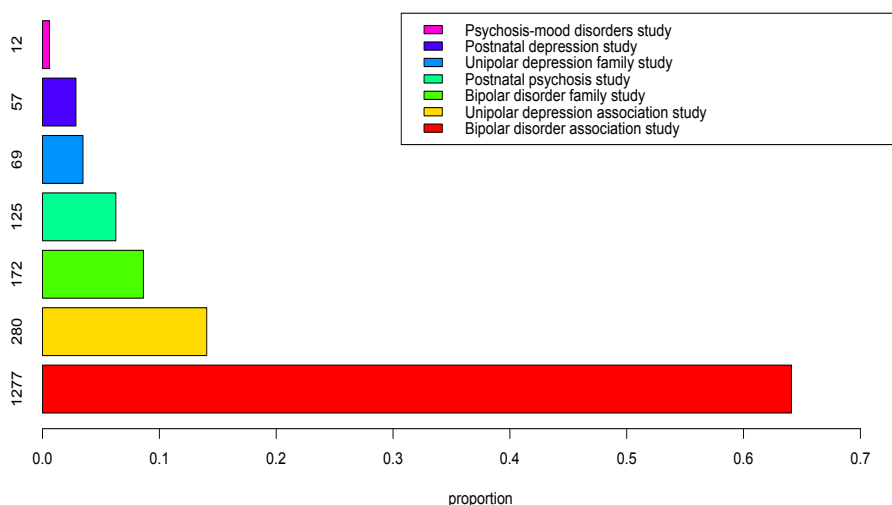
Figure 5.1: Distribution of participants according to study in which they have originally been recruited. The numbers on the left refer to number of participant, while the bars display the proportions. Only parous women with bipolar I disorder, bipolar II disorder or recurrent major depression and a history of mood disorder prior to menopause were included in the present analyses. If multiple members from the same family took part to the project, only probands (index cases) were included, i.e. only one member for each family was included.

5.1.1 Recruitment

Participants were recruited using both systematic and non-systematic recruitment methods (figure 5.4). In the current analyses, 26 % of the sample was recruited systematically. No differences emerged in the rates of broadly defined perinatal episodes between systematically and not systematically recruited women ($\chi^2 = 0.56$, df $= 1$, p-value $= 0.45$).

Systematic recruitment Systematic recruitment involved the identification of participants through screening of community mental health teams across

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Table 5.1: Information collected by initial project in with participants were recruited[a]

Variables	BD GWAS N	BD GWAS %	BD FAM N	BD FAM %	PND N	PND %	PP N	PP %	PSYCH-MOOD N	PSYCH-MOOD %	UD GWAS N	UD GWAS %	UD FAM N	UD FAM %
Sample size	1277		172		57		125		12		280		69	
Participants with any PNE	917		100		56		125		10		193		37	
Age at interview	1276	99.9%	166	96.5%	57	100.0%	123	98.4%	12	100.0%	252	90.0%	69	100.0%
Age at impairment	1218	95.4%	169	98.3%	56	98.2%	123	98.4%	11	91.7%	278	99.3%	69	100.0%
Perinatal history	1277	100.0%	172	100.0%	57	100.0%	125	100.0%	12	100.0%	280	100.0%	69	100.0%
N of perinatal episodes	783	61.3%	46	26.7%	33	57.9%	89	71.2%	10	83.3%	214	76.4%	48	69.6%
N of episodes	1050	82.2%	152	88.4%	56	98.2%	100	80.0%	11	91.7%	244	87.1%	68	98.6%
pregnancy by pregnancy ratings	1061	83.1%	57	33.1%	46	80.7%	106	84.8%	12	100.0%	241	86.1%	56	81.2%
First episode perinatal/not	1155	90.4%	87	50.6%	55	96.5%	119	95.2%	12	100.0%	269	96.1%	65	94.2%
Age at first perinatal episode	618	67.4%	56	56.0%	16	28.6%	20	16.0%	5	50.0%	44	22.8%	17	45.9%
DSM-IV	1277	100.0%	172	100.0%	57	100.0%	125	100.0%	12	100.0%	280	100.0%	69	100.0%
Deliveries	1185	92.8%	70	40.7%	57	100.0%	120	96.0%	12	100.0%	270	96.4%	69	100.0%

[a]Abbreviations: BD GWAS: bipolar disorder association study, BD FAM: bipolar disorder family study, PND: study on postpartum depression. PP: study on postpartum psychosis, PSYCH-MOOD: study on mood and psychosis, UD GWAS: unipolar depression association study, UD FAM: unipolar depression family study, PNE: perinatal episodes of the total number of participants with at least one perinatal episode

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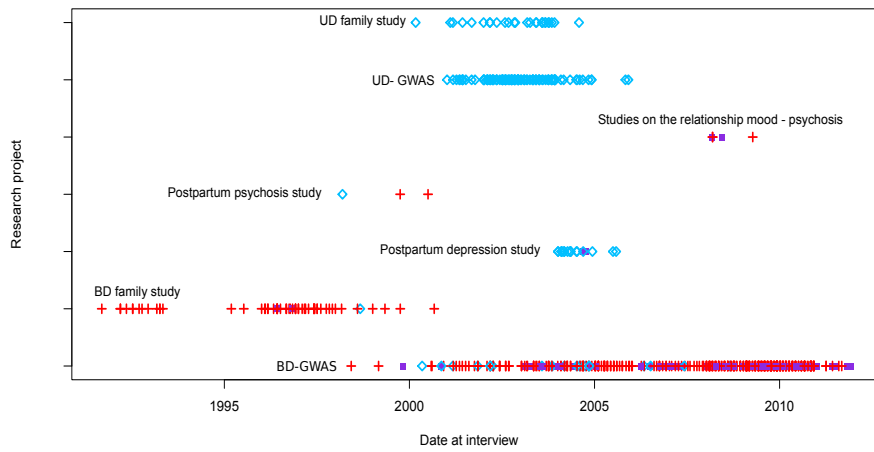
Figure 5.2: Distribution of participants by project, year of inclusion and lifetime diagnosis. Each symbol represents one participant. Information on date of interview was missing for 794 women in the BD-GWAS project, 110 in the BD family study, 36 in the postpartum depression study, 122 in the postpartum psychosis study, 7 in the study on the relationship between mood and psychosis, 180 in the UD-GWAS and 43 in the UD family study. Symbols colours reflect lifetime diagnoses of DSM-IV BD-I (red), BD-II (purple), RMD (blue). Abbreviations: BD: bipolar disorder, GWAS: genome wide association study, UD: unipolar depression
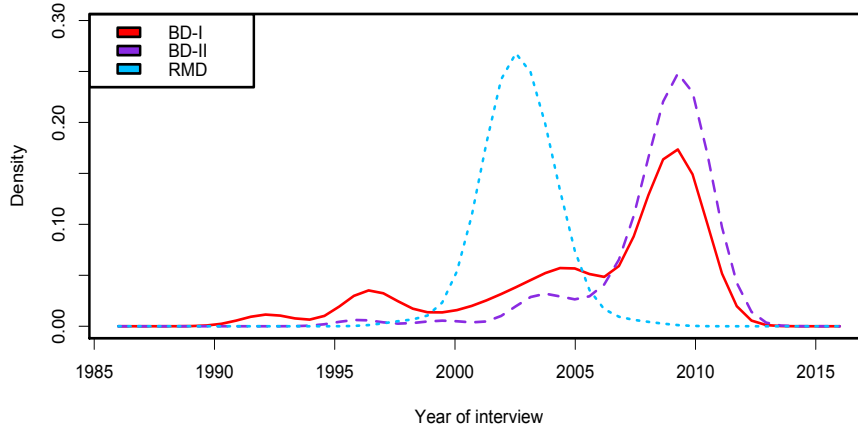
Figure 5.3: Kernel density plot of participants by year of interview and lifetime diagnosis. A kernel density estimate is a good graphical summary of the shape of the data, in which each observation x_i is replaced by a copy of the function $k()$ shifted so that it is centred at x_i, and scaled by a factor h called 'bandwidth'. The function $k()$ has got the following characteristics: i) $k(x) \geqslant 0 \; \forall$ x, ii) $\int_{\infty}^{-\infty} k(x) \, \mathrm{d}x$ iii) k is concentrated around 0. Differently from the previous graph, this one does not display the count of participants, but the proportion of participants recruited by year and by lifetime diagnosis. From the graph it can be inferred that the overrepresentation of women with BD-I was due to a longer time of recruitment and to a more intensive recruitment in more recent years. Women with RMD were recruited intensively over a shorter period of time. The majority of women with BD-II were recruited in recent years.

the United Kingdom (UK). At the discretion of the responsible medical officer, all participants deemed suitable for inclusion were invited to participate. More than 20 Mental Health Trusts and Boards throughout the UK were involved in the recruitment and the recruitment was supported by the Mental Health Research Network (http://www.mhrn.info/).

Non-systematic recruitment Participants were recruited non-systematically via the media (television, press, radio and internet) and via patient support organisations (Bipolar UK and Action on Puerperal Psychosis). I provide here a description of Bipolar UK and Action on Puerperal Psychosis because I have been in contact with them for the recruitment of participants in the longitudinal study I describe in chapter 10 and 11.

Bipolar UK (former MDF The Bipolar Organisation) Bipolar UK is the only England & Wales based charity aimed to specifically

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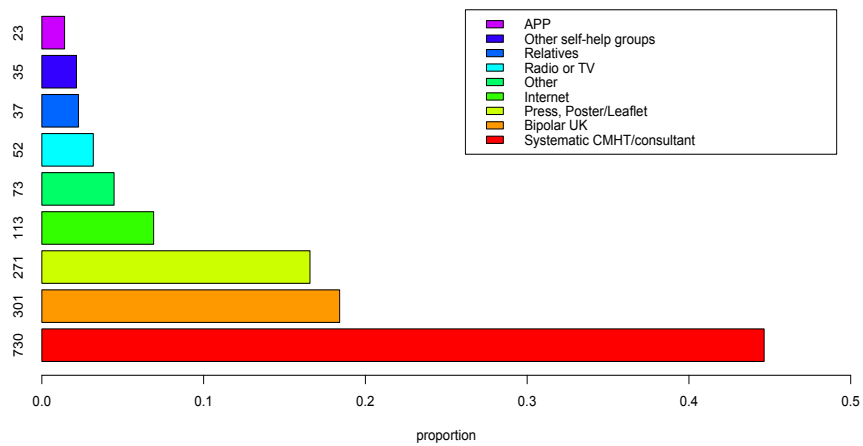
Figure 5.4: Distribution of participants according to method of recruitment. The numbers on the left refer to number of participant, while the bars display the proportions. Only parous women with BD-I, BD-II or RMD and a history of mood disorder prior to menopause were included in the present analyses. If multiple members from he same family took part to the project, only probands (index cases) were included, i.e. only one member for each family was included. Abbreviations: APP: action on postpartum psychosis, CMHT: community mental health team

support individuals suffering from bipolar disorder, their families and carers. Explicit objectives of the charity are to promote "the improvement of treatments and services to promote recovery "and to "develop partnerships with other organisations concerned with mental health "(http://www.bipolaruk.org.uk/). Bipolar UK was established in 1983 and currently provides support to over 65,000 people/year (data from http://www.bipolaruk.org.uk/history-of-the-charity.html). Pendulum is the magazine published quarterly by Bipolar UK and provides also evidence-based information.

There is a close collaboration between Bipolar UK and BDRN. In 2010 BDRN hosted a national conference for Bipolar UK at the University of Birmingham Medical School, with around 350 delegates from all over UK taking part (http://bdrn.org/?p=648). Moreover, Professor Nick Craddock and Dr. Ian Jones have collaborated with Bipolar UK and written for the Pendulum magazine, providing scientific contributions.

Action on Postpartum Psychosis Action on Postpartum Psychosis (APP) is a charity based in UK and a network of women who have experienced postpartum psychosis. An explicit objective of APP is to "facilitate research into all aspects of postpartum psychosis ". APP was set up by Professor Ian Brockington and Mrs. Jackie Benjamin in 1996 in Birmingham and currently has about 600 members throughout the UK including a number of women worldwide. Today, APP is run by a team of women who have experienced postpartum psychosis, clinicians and researchers from the University of Birmingham and Cardiff University. Dr. Ian Jones is the current chair of APP. APP publishes the annual APP magazine with information about research and events. The magazine contains adverts and updates on the BDRN study. The previous and current editions of the magazine are available for free at http://www.app-network.org/news-events/newsletters/.

5.1.2 Inclusion criteria

All participants were aged 18 years or over and provided written informed consent after complete description of the study.
Participants were excluded from the original studies if they: i) had a lifetime

diagnosis of intravenous drug dependency; ii) had only experienced affective illness as a result of alcohol or substance dependence; and iii) had only experienced affective illness secondary to medical illness or medication.

The major depression studies aimed to recruit a sample of participants with clear-cut unipolar depression. Thus, in addition to the general criteria, individuals in the recurrent major depression group were excluded if they i) had a first or second degree relative with a clear diagnosis of bipolar affective disorder or schizophrenia, schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorders or schizoaffective disorder, or ii) had ever experienced mood incongruent psychosis or psychosis outside of mood episodes.

Participants were included in the current analyses if they i) had a lifetime diagnosis of DSM-IV BD-I, BD-II or RMD and ii) were parous, having given birth to at least one live child.

As I was interested in mood disorder episodes in the reproductive years, women were excluded from the current analyses if they reported an age of onset in the post-menopausal period. A cut-off of 50 years old was set, according to the mean European age at menopause [141].

The analyses presented in the next chapters were conducted on different subsamples, according to the research hypothesis that was tested. Figure 5.5 provides a flow chart aimed to help the reader throughout the different research hypotheses.

5.1.3   Assessment

Team members involved in the interview, rating and diagnostic procedures were all research psychologists or psychiatrists.
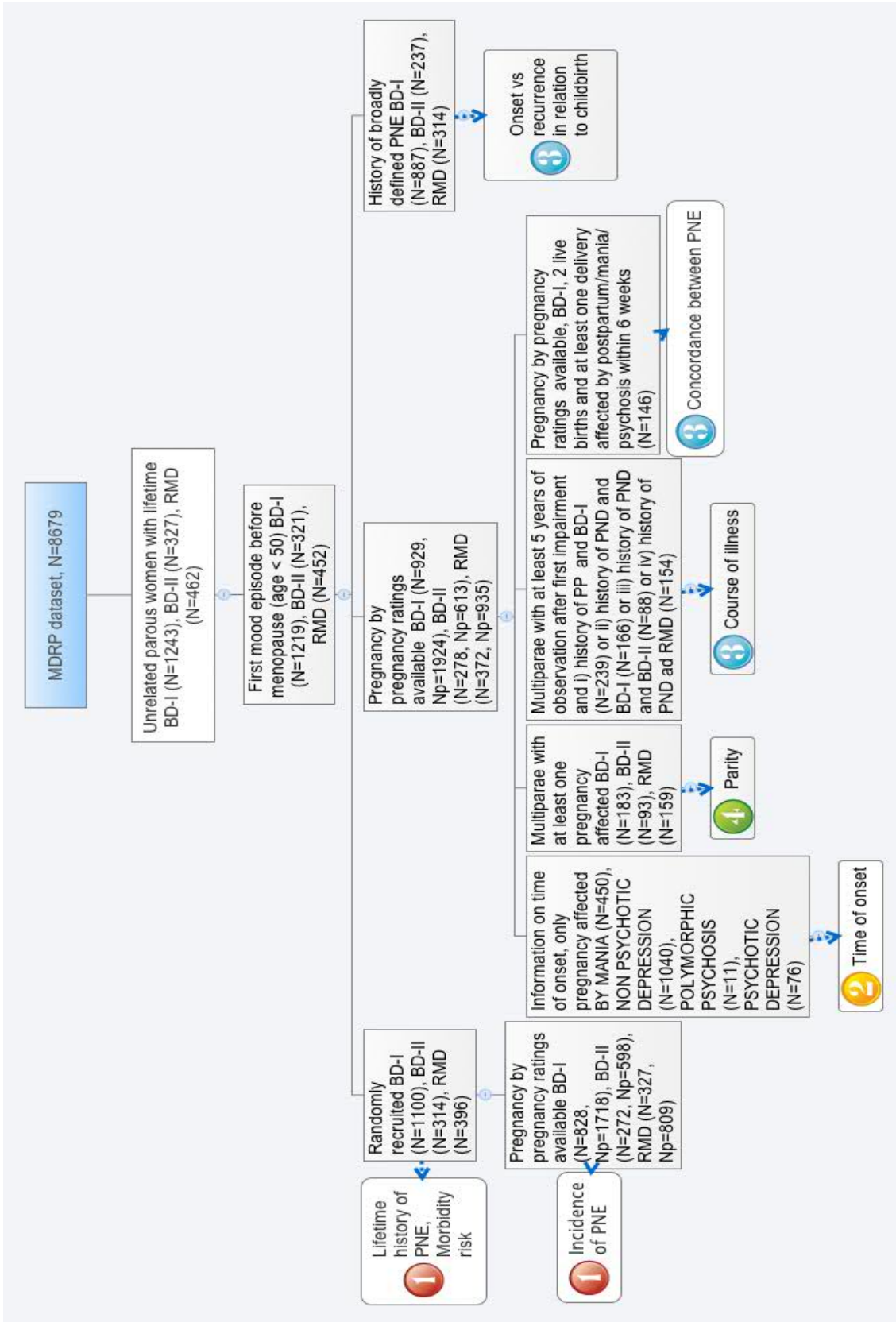
Figure 5.5: Flow chart showing the sub-samples used in the analyses. In the rounded rectangles the topics that were investigated using that particular sub-sample. The numbers in coloured circles indicate the chapter in which the analyses are reported: 1: analyses reported in chapter 6, 2: analyses reported in chapter 7, 3: analyses reported in chapter 8, 4: analyses reported in chapter 9. Abbreviations: N:number of women, Np: number of pregnancies. The graph was produced using XMind, a brainstorming and mind mapping software tool (www.xmind.net/)

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Interview

Subjects, who agreed to take part, were interviewed in a place convenient for them, usually their own house. The interview lasted about an hour and a half and included:

- The **life chart** for the systematic collection of retrospective information about the course of illness, life events and treatment. An example of life chart is given in figure 5.6.

- The **Schedules for Clinical Assessment in Neuropsychiatry** (SCAN) are a set of semi-structured clinical interviews developed by the World Health Organization and widely used to assess and diagnose psychiatric disorders among adults [142]. The approach is bottom-up and no diagnosis-driven frames are applied in grouping the symptoms, with each symptom assessed in its own right. The Mood Disorder Research Project interview contained the sections on mania, depression and psychosis. Each section contains obligatory general questions about symptoms of that particular section, followed by more specific questions to be answered if the general questions were affirmative or if the interviewer has got doubts. The rating is done by comparing the answers given by the interviewee with the definitions of the symptoms given in a glossary. The definitions in the glossary largely follow Jasper's criteria [22]. In my research I considered episodes rather than symptoms. Possible rating for episodes according to the SCAN interview are: current episode, representative episode, in which symptoms were more severe, lifetime ever. Although SCAN alone can be used to produce a DSM-IV or a ICD-10 diagnosis, in the Mood Disorder Research Project other sources of information were jointly employed.

- Details of **family history** of mental disorders

- Information about **lifetime history of PNEs** of illness.

- Participants recruited more recently were also asked **pregnancy by pregnancy** questions about the relationship of episodes of illness to childbirth.

If the participant consented, part of the interview was audio recorded for consistency and training purposes.
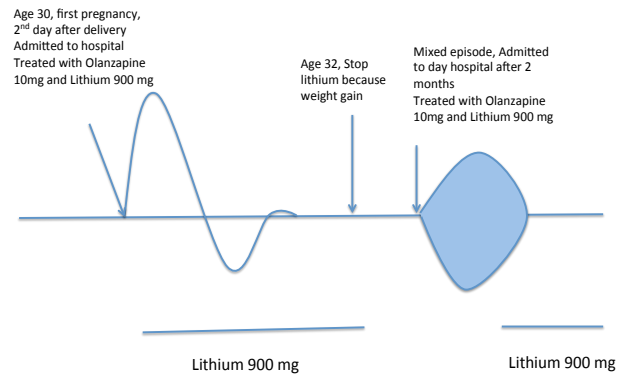
Figure 5.6: Example of a life chart. Although systematic, the collection of information did not follow the graphic and the structured approach of Leverich and Post [143]

Questionnaires

Participants were left with a set of questionnaire, which took around half an hour to be completed. Questionnaires included measures of:

- Current mood (Beck Depression Inventory and Altman Self-Rating Mania Scale)

- Life events prior to onset (Brief Life Events Questionnaire) and childhood life events (Coddington Life Events Questionnaire)

- Personality and temperament (Eysenck Personality Questionnaire, Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego. Auto-questionnaire)

- Alcohol and substaces use

However, in my analyses I used only information collected during the interview.

Case notes review

Psychiatric case-notes were available for 78% of participants and were also reviewed.

Estimate of lifetime diagnosis and clinical variables

Based on the information collected during the interview, in the questionnaires and by reviewing the case-note, best-estimate lifetime diagnoses were made according to DSM-IV, ICD-10 and key clinical variables, such as age at onset and number of episodes, were rated. In cases where there was doubt, diagnostic and clinical ratings were made by at least two members of the research team blind to each other's rating. Inter-rater reliability was formally assessed using 20 cases. Mean kappa statistics [1] were 0.85 for DSM-IV diagnoses and ranged between 0.81 and 0.99 for other key clinical categorical variables; mean intra-class correlation coefficients were between 0.91 and 0.97 for key clinical continuous variables.

5.2 Analytical strategies

> "[..] to deal with uncertainty successfully we must have a kind of
> tentative humility. We need a lack of hubris to allow us to see data
> and let them generate, in combination with what we already know,
> multiple alternative working hypotheses. These hypotheses are then
> modified as new data arrive. The sort of humility required was well
> described by the famous Princeton chemist Hubert N. Alyea, who

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[1]Kappa statistic is a quantitative measure of agreement between observers. It is calculated as the standardised difference between the observed agreement p_o and the agreement that would be expected to be present by chance alone p_e.

$$k = \frac{p_o - p_e}{1 - p_e}$$

where

$$p_o = \frac{concordant_{observations}}{total_{observations}}$$

and

$$p_e = \frac{n_1 m_1}{n^2} + \frac{n_0 m_0}{n^2}$$

is the expected agreement with m_1 and n_1 the positive results in the observers m and n and m_0 and n_0 the negative results in the observers m and n. Kappa assumes values between -1 and 1. With negative values indicating agreement less than chance, 0 agreement as expected by chance and positive values agreement more than chance and 1 perfect agreement.

once told his class, 'I say not that it is, but that it seems to be; as it now seems to me to seem to be.' "

Howard Wainer [144]

Analysing retrospective data on reproductive events is a complex task. In this chapter I discuss the principal statistical methods I employed in the analyses of the retrospective dataset. I do not provide here a detailed account of the specific statistical methods that I used in the different analyses, because I describe them in the appropriate chapters along with the results of the analyses.

Analyses were performed using R version 2.13.0 (Copyright 2011 by The R Foundation for Statistical Computing). Graphics were also produced with R. When an unusual type of graph is presented, explanations are provided in the caption.

Methodology and results are reported according to the statistical guidelines of the British Medical Journal[2] and of the STROBE project [3]. These guidelines recommend to prefer confidence intervals for effect sizes to p-values when reporting the results of comparisons. However, I calculated and report also p values, as the majority of papers I reviewed relayed their conclusions on p values. In accordance to the STROBE and BMJ guidelines, I emphasise that the results of my analyses need to be interpreted in the light of the following considerations, sometimes dismissed in medical research: i) percentages where the denominator is small (for example less than twenty) are of little value ii) a lack of significance is not an evidence of no effect and iii) odds ratios instead of relative risks should be calculated as a measure of effect when retrospective information is analysed (such in the case of my analyses).

5.2.1 Estimates

Figure 5.7 summarises the estimates I report in the next chapters. In the background section I argued that the choice of the reference group (i.e. the denominator in the ratios) has been a major source of bias and heterogeneity across studies. So, in my research I paid special attention to the choice of the reference groups. I chose a 99% confidence interval (99%CI) estimator instead of the usual 95% because I wanted to have greater confidence that my estima-

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[2]http://bmjopen.bmj.com/site/about/guidelines.xhtml
[3]http://www.strobe-statement.org/index.php?id=available-checklists

tions contained the population parameters. Confidence intervals for estimates were imputed using the Clopper-Pearson exact[4] method (function `exactci` in the package `PropCIs` [147]). The Clopper-Pearson exact method relies on the assumption of a binomial distribution. There are several algebraically identical formulae to calculate the Clopper-Pearson confidence intervals, including:

$$B(\alpha/2; x, n - x + 1) < \theta < B(1 - \alpha/2; x + 1, n - x) \qquad (5.1)$$

where x is the number of successes, n is the number of trials, and $B(p; v, w)$ is the p_{th} quantile from a beta distribution with shape parameters v and w. [5] I chose the Clopper-Pearson exact method because it is one of the most commonly used. It is accurate when $np > 5$ or $n(1 - p) > 5$.

5.2.2 Comparative analyses

The comparative analyses I conducted are summarised on table 5.2. I tested more than one hypothesis simultaneously, incurring in problems of multiple testing. [6] In fact, I investigated many variables (presence of PNE, time of onset of PNE, order of pregnancy, lifetime diagnosis etc) and grouped participants in many ways (by lifetime diagnosis, by pregnancy outcome, by having a first lifetime episode in the perinatal period etc). Although I had to control for multiple comparisons, it is "cleary impractical, if not impossible to control errors to a small level over the entire set of potential comparisons " [150].

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[4]The term exact refers to the fact that the estimate is based directly on the cumulative probabilities of the binomial distribution rather than any approximation to the binomial distribution [145]. Neyman pointed out that "exact probability statements are impossible in the case of the binomial distribution ". [146]

[5]The beta distribution is a family of continuous probability distributions defined on the interval [0, 1] parametrized by two positive shape parameters, denoted by v and w, that appear as exponents of the random variable and control the shape of the distribution

[6]For a comprehensive overview on multiple comparisons I used two text books: [148, 149]

Figure 5.7: Estimates reported in the thesis

	LIFETIME DIAGNOSIS	EPISODES CHARACTERISTICS	TIME OF ONSET	REFERENCE GROUP
Estimates of PNE				
LIFETIME HISTORY OF PNE	DSM-IV BD-I DSM-IV BD-II DSM-IV RMD	HIERARCHICAL APPROACH ⊖ NARROW DEFINITION / INTERMEDIATE DEFINITION / BROAD DEFINITION		total number of women by lifetime diagnosis
MORBIDITY RISK OF PNE	DSM-IV BD-I DSM-IV BD-II DSM-IV RMD	Any PNE		total number of women by lifetime diagnosis ⊕
INCIDENCE RATES OF PNE	DSM-IV BD-I DSM-IV BD-II DSM-IV RMD	non psychotic depression manic or mixed episode psychotic depression SURVIVAL CURVES	pregnancy within 6 weeks postpartum between 6 weeks and 6 months postpartum	total number of pregnancies by lifetime diagnosis
INCIDENCE BY PARITY ORDER	DSM-IV BDI DSM-IV BD-II DSM-IV RMD	manic or mixed episode or psychotic depression non psychotic depression	pregnancy within 6 weeks between 6 weeks and 6 months postpartum	total number of first/second/third/fourth pregnancies by lifetime diagnosis
LIFETIME ONSET IN THE PERINATAL PERIOD	DSM-IV BD-I DSM-IV BD-II DSM-IV RMD	Any PNE		total number of women per lifetime diagnosis total number of women with perinatal episodes by lifetime diagnosis

Table 5.2: Summary of the comparative analyses presented in the thesis[8]

SUBJECT	CHAPTER	SAMPLE	Ho	NOTES	N IND H_0	N nIND H_0
		Parous women with a lifetime diagnosis of either BD-I, BD-II or RMD & with first mood episode before menopause &				
Lifetime prevalence of PNE	6	Randomly recruited BD-I (N=1100), BD-II (N=314), RMD (N=396)	no difference in lifetime prevalence of PNE between BD-I, BD-II and RMD		1	3
Morbidity risk of PNE	6	as above	no difference in morbidity risk of PNE between BD-I, BD-II and RMD		1	3
Pregnancy incidence of PNE	6	Pregnancy by pregnancy ratings available BD-I (N=828, Np=1718), BD-II (N=272, Np=598), RMD (N=327, Np=809)	no difference in incidence of PNE between BD-I, BD-II and RMD		1	3

Continued on next page

Table 5.2 – *Continued from previous page*

SUBJECT	CHAPTER	SAMPLE	Ho	NOTES	N IND H_0	N N_INDH_0
Time of onset in BD-I	7	583 post BD-I	No difference between time of onset of M, BD-I pD and BD-I npD		1	3
Time of onset of npD	7	678 perinatal /584 post npD	No difference in time of onset of npD between BD-I, BD-II and RMD		1	3
First lifetime episode in the postpartum	8	History of broadly defined PNE BD-I (N=887), BD-II (N=237), RMD (N=314)	Proportion of women with lifetime onset in the perinatal period is similar across mood disorders		1	NA
Specificity of the childbirth trigger in relation to lifetime course		Multiparae with $\geqslant 5 years$ of observation after 1_{st} impairment and i) history of PP and BD-I (N=239) or ii) history of PND and BD-I (N=166) or iii) history of PND and BD-II (N=88) or iv) history of PND ad RMD (N=154)	rates of episodes occurring outside the perinatal period per year are similar to the rates of deliveries affected	analysis conducted separately for each lifetime diagnosis and for PP and PND in BD-I	4	NA

Table 5.2 – *Continued from previous page*

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SUBJECT	CHAPTER	SAMPLE	Ho	NOTES	N IND H_0	N $N_I NDH_0$
Concordance between PNE	8	Pregnancy by pregnancy ratings available, BD-I, 2 live births and $\geqslant$ 1 delivery affected by post-partum/mania/psychosis within 6 weeks (N=146)	The proportion of women experiencing 2 PNE of different polarity is similar to the proportion of women experiencing 2 episodes of the same polarity		1	NA
Parity and PNE	9	Multiparae with at least one pregnancy affected BD-I (N=183), BD-II (N=93), RMD (N=159)	Proportion of first pregnancies affected by PP/PND similar to the proportion of second pregnancies affected by PP/PND.	$\forall$ lifetime diagnosis, and $\forall$ onset groups[1]	12^3	NA
Parity PNE	9	Multiparae with at least one pregnancy affected BD-I (N=183), BD-II (N=93), RMD (N=159)	as above, but by lifetime onset (postpartum v other times)	secondary to the previous analyses	2^3	NA

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[8] Abbreviations: BD-I bipolar I disorder, BD-II bipolar II disorder, RMD recurrent major depression, t_i time-to-onset, M mania, pD psychotic depression, npD non psychotic depression, 1 first perinatal period, 2 second perinatal period, PP: postpartum psychosis defined as DSM-IV mania or DSM-IV psychotic depression or, cycloid psychosis, defined according to [51] preg: in pregnancy, post: postpartum, IND: independent, $nIND$:not independent, H_0 null hypothesis, [1] in pregnancy, within 6 weeks postpartum, between 6 weeks and 6 months postpartum, [2] maximum number of possible analyses, but only those promising at the exploratory analyses were conducted, [3] number of analyses actually conducted, on the basis of previous significant findings

Multiple testing

Three major multiple testing problems arose from my analytic plan:

1. **Multiple independent analyses** . It is the set of minimal hypotheses that did not imply the truth of any other hypothesis in the set.

2. **Hierarchical sets** Some hypotheses were components of others (for example, in the parity analyses, the hypotheses tested on the subgroups of multiparous with at least a pregnancy affected were a subgroup of the hypotheses tested on the general sample).

3. **Pairwise comparisons** For each analysis in which I rejected the null hypothesis I examined the differences between pairs of groups (post hoc analyses).

The main problem was to establish the number of K independent hypotheses I tested, or, looking from another prospective, the number of families of hypotheses (i.e. set of hypotheses to treat as a family and for which errors were controlled jointly) and how many hierarchical sets I had. Moreover, different independent hypotheses were tested on overlapping, but not identical datasets. So a unique one step correction for all analyses I performed would have been too conservative.

Once I determined the number K **independent hypotheses**, I calculated a corrected P value using the Bonferroni correction. The Bonferroni method is the most user-friendly single step approach to correct for multiple testing. However it has got its limitations: i) it is counter-intuitive, because the interpretation of findings depends on the number of other tests performed, ii) the general null hypothesis that all the null hypotheses are true is rarely of interest, iii) it is highly conservative, with a high probability of rejecting the alternative hypothesis of an effect when it is true (i.e. high probability of committing a type 2 error).

For **correlated multiple tests** the Bonferroni correction is inappropriate, because of the reasons explained above. I therefore used a two-steps approach . Initial global comparisons between groups (BD-I, BD-II and RMD) were performed using the analysis of variance for normally distributed variables and the non parametric Kruskall-Wallis analysis of variance for continuos variables that were not normally distributed. For categorical variables I employed contingency tables and χ^2 statistics. If groups were not homogenous at the Bonferroni corrected P value, I run further analyses and, according to the characteristics of

the variables, I used:

- the least significant difference - Tukey's method when variables were normally distributed and groups were of similar size,

- the least significant difference - Scheffe's method when variables were normally distributed, but groups differed in size

- for non parametric continuous variables I used rank sums and calculated the standard error as

$$p_{adj} = \frac{pK(K+1)}{2}$$

  where K is the number of groups (in this case 3)[9]

- for categorical variables I used the function `fisher.multcomp` from the package `RVAideMemoire`.

Logistic regression

I used logistic regressions for many inferences[10]. Logistic regression is a generalised linear model for binary response variables, based on the logit transformation of a proportion. As a response variable I used PNEs, classifying each observation as a *success* (having a PNE) or a *failure* (not having a PNE). The definition of PNE varied across analyses and could include only certain subtype of PNEs.

In logistic regression models the odds for a participant with independent variables specified by X is

$$\frac{P(X)}{1 - P(X)}$$

where, in my analyses, P denotes the probability of a PNE (the definition of PNE varied across analyses). Thus, an odds is the probability that a PNE occurred over the probability that it did not occur. In the logit function the parameters α and β_i can be interpreted in terms of log odds. The odds ratio is the ratio between two odds and the probabilities in the odds ratio are all defined

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[9]I derived the formula from [148], Chapter 9, Distribution-Free and Robust Procedures pages 242-247

[10]Almost all the analyses I conducted were on categorical data. As a main reference book I used [151]

as risks. In the case of logistic regression

$$ROR_{X1,X2} = \frac{odds\,for\,X_1}{odds\,for\,X_0} = \frac{e^{\alpha + \sum \beta_i X_{1i}}}{e^{\alpha + \sum \beta_i X_{0i}}} \tag{5.2}$$

5.2.3 Dealing with dependent measures

Multiple deliveries from one individual could not be considered independent observations. In order to compare differences in rates of deliveries affected across diagnostic groups, I used the Mantel-Haenszel methodology for repeated measurements data. The null hypothesis of *no partial association* between lifetime diagnosis and perinatal episode was that the occurrence of PNEs (response variable) was distributed at random with respect to the factor levels (i.e. lifetime diagnoses), for each of the stratum levels indexed by 1st, 2nd, 3rd, 4th pregnancy. I was interested in the extent to which the null hypothesis could be rejected in favour of the hypothesis that the distribution of PNEs differed in nonspecific patterns across diagnoses. Thus, the general association Mantel-Haenszel test statistic (GA) was employed (for a general overview of Mantel-Haenszel methods, see [152]).

Similarly, in the multivariate analyses I took into account possible within subject effects. I used a generalized mixed model approach (package `lme4` [153]), introducing a parameter that identified each subject (random effect). If deliveries from the same woman were independent events, the variance of the random effect should be zero. This null hypothesis was tested with the Wald Z statistic test.

If in the mixed models the variance of the random effect was close to zero, univariate comparisons were performed using contingency tables and χ^2 statistics or Fisher Exact test for categorical variables, t-test for normally distributed quantitative variables and non-parametric rank tests for those not normally distributed. When in the mixed models the variance of the random effect was close to zero, the random effect was dropped from the final model and a generalized linear model was fitted (function `glm`).

In case of multiple imputed datasets, the function containing a within subject effect was modelled by using the specification `logit.mixed` in the `zelig` command [154] (see the section on multiple imputations below).

Mixed effect models for survival analyses using the Cox method are discussed

in chapter 7.

5.2.4   Dealing with missing values

Missing values are common in medical research and a vast literature has been produced on the topic. Missing values are usually classified according to the cause of missingness:

Missing completely at random (MCAR) : missing values are equally and randomly distributed across the dataset. MCAR data cause loss of power, but do not influence the inferences, because missing values in cases have the same characteristics of missing values in controls.

Missing at random (MAR) : missing values are associated with certain known factors. However, these factors are not necessarily measured in the experiment. In this case, to obtain unbiased inferences, analyses need to be corrected for the variable responsible of the missing values.

Missing Not at Random (MNAR) : the causes of missingness cannot be related to any variable known by the researcher. This is the most damaging cause of missingness.

Graham & Donaldson [155] simplified this classification, according to the causes of missingness:

Accesible, in which the causes of missingness are known and have been measured (this category included MCAR and part of the MAR, where information for the responsible factor are available)

Inaccessible, in which the causes of missingness have not been measured.

In my analyses I investigated the presence of accessible factors. However, the most common scenario is that both accessible and inaccessible factors account for missing data. I therefore used multiple imputations techniques to handle missing data. Multiple imputation replaces each missing value/missing cell with M values in the dataset/data matrix and creates M complete data sets. The M complete sets obtained through multiple imputations contain the same observed values of the original data set, while missing values there replaced with a distribution of M imputations that reflect:

- the natural variability in the missing values. The imputed values, in fact, are estimated on the basis of the variables correlated with the missing data and causes of missingness

- the uncertainty about the estimation by creating M different datasets that contain different versions of the missing values and then observing the variability between missing values.

I chose multiple imputation over other techniques for the following reasons:

- It minimises the detrimental effect of inaccessible mechanisms [155];

- It produces better inferences than list-wise deletion. Excluding cases with missing values using a list-wise deletion process would lead not only to loss of power and of valuable information that was partially collected for these cases, but also to biased inferences;

- It has been shown to be robust for not normally distributed variables;

- It performs well in the presence of high rates of missing data;

- It is an intuitive method and a package was available in R.

I used multiple imputations in all analyses involving variables with missing values, with the exception of the time-to-onset coded as a continuous variable in weeks, because i) the distribution violated the assumption of normality, ii) transformations to normality didn't work and iii) the difference between the distribution of imputed values and the actual values was too large (see below for an explanation of the diagnostic techniques).

Amelia II [156], the statistical package I used to compute multiple imputation, in fact, requires two assumptions: i) multivariate normality ii) data MAR. Thus, I first checked whether there were factors that could have been accounted for the pattern of missingness and whether the normality assumption was met, then I used Amelia II to replace missing values using multiple imputations. Using the `amelia` function, I imputed priors and bounds to improve the imputations. A detailed description of the theory behind Amelia II computation of missing values is beyond the scope of this thesis. In addition to the Amelia II reference guide [156], I referred to [157] as a general reference guide on missing data. Here I explain in very lay terms only the terminology and the formulae that are necessary to interpret the results. I focus on the Expectation-Maximization

```
            ┌─────────────────────────────┐
            │  Dataset with missing values │
            └─────────────────────────────┘
```
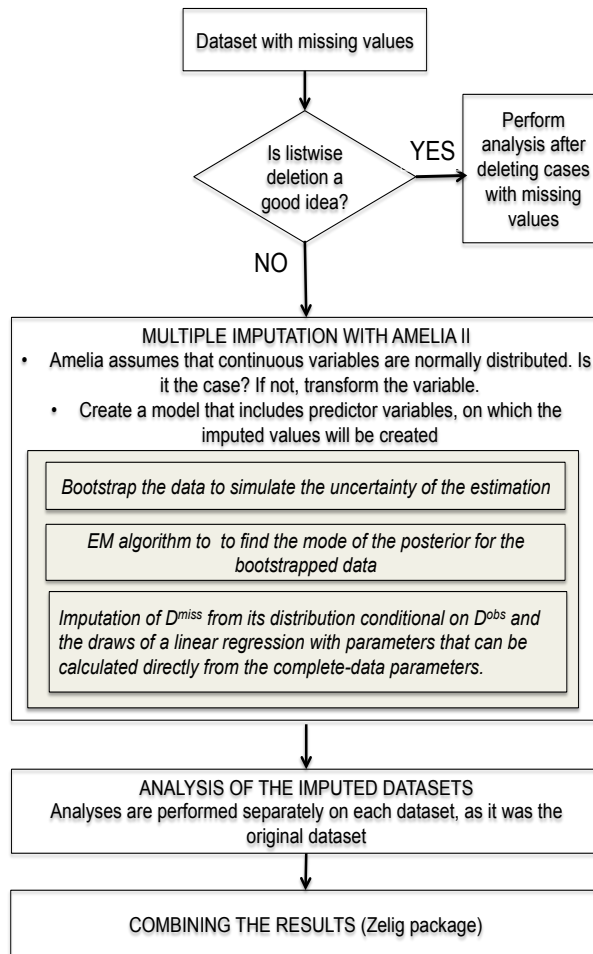
Figure 5.8: Flow chart of the multiple imputations process

(EM) algorithm, rather than on the bootstrap step, because this is a key concept to understand not only the results, but also possible problems rising from the imputations algorithm.

Expectation-Maximization (EM) algorithm

Given a density function $f(\mathbf{x} \mid \Phi)$ that is is governed by the set of parameters Φ and a data set of size N, supposedly drawn from this distribution, i.e., $\mathcal{X} =$

$\mathbf{x_1}, ..., \mathbf{x_N}$, the likelihood function

$$f(\mathcal{X} \mid \Phi) = \prod_{i=1}^{N} f(\mathbf{x_i} \mid \Phi) = g(\Phi \mid \mathcal{X}) \qquad (5.3)$$

The likelihood is a function of the parameters Φ where $\mathcal{X}$ is fixed.

The aim of the maximum-likelihood estimation problem is to find the Φ that maximizes g

The EM algorithm is a iterative method of finding this maximum-likelihood estimate of the parameters Φ of an underlying distribution from a given data set when the data is incomplete or has missing values.

An incomplete dataset implies 2 sample spaces: $\mathcal{Y}$ and $\mathcal{X}$ and a *many $\rightarrow$ one* mapping from $\mathbf{y} \rightarrow \mathbf{y(x)}$ from $\mathcal{X}$ to $\mathcal{Y}$, with $\mathbf{x}$ being the complete data and $\mathbf{y}$ the observed data, $\mathbf{x}$ is known only to lie in $\mathcal{X}(\mathbf{y})$. In other words, the subset of $\mathcal{X}$ is determined by the equation $\mathbf{x} = \mathbf{y(x)}$. Let $f(\mathbf{x} \mid \Phi)$ be a family of sampling densities depending on the parameters Φ and $g(\mathbf{x} \mid \Phi)$ its corresponding family of sampling densities. The complete-data $f(... \mid ...)$ is related to the incomplete-data $g(... \mid ...)$ by the function [158][11]

$$g(\mathbf{x} \mid \Phi) = \int_{\mathcal{X}(\mathbf{y})} f(\mathbf{x} \mid \Phi) d\mathbf{x} \qquad (5.4)$$

As the term suggests, the EM algorithm is an iterative process that consists on a iteration step followed by a maximization step. The aim of the EM algorithm is to find the values of Φ that maximises $g(\mathbf{x} \mid \Phi)$. There are many possible complete data specifications $f(\mathbf{x} \mid \Phi)$ that generate $g(\mathbf{y} \mid \Phi)$ given the incomplete data specification $g(\mathbf{x} \mid \Phi)$.

E-step The EM algorithm first finds the expected value of the complete-data log-likelihood $\mathbf{log}g(\mathcal{X}, \mathcal{Y} \mid \Phi)$ with respect to the unknown data $\mathcal{Y}$ given the

---

[11]The paper is wrongly cited in the seminal paper on Amelia II. Although the paper by Dempster et al [158] is the seminal paper on EM algorithm, I also refer here to the *Gentle tutorial* by Bilmes [159]

observed (constant) data $\mathcal{X}$ and the current parameter estimates:

$$\mathcal{Q}(\Phi, \Phi^{(i-1)}) \tag{5.5}$$

where $\Phi^{(i-1)}$ are the current (constant) parameters estimates that are used to evaluate the expectation and Φ are the new parameters that are optimized to increase $\mathcal{Q}$. Φ is a normal variable while $\mathcal{Y}$ is a random variable governed by the distribution $f(\mathbf{y} \mid \mathcal{X}, \Phi^{(i-1)})$.

M-step M-step maximizes the expectation computed in the first step.

$$\Phi^{(i)} = \arg\max_{\Phi} \mathcal{Q}(\Phi, \Phi^{(i-1)}) \tag{5.6}$$

where arg max is the argument of the maximum, i.e. the set of values of Φ for which the function $\mathcal{Q}(\Phi, \Phi^{(i-1)})$ attains its maximum value.

These two steps are repeated as necessary. Each iteration increases the log-likelihood and the algorithm is guaranteed to converge to a local maximum of the likelihood function.

Diagnostics

I inspected the multiple datasets with graphical methods of overimputations and overdispersion diagnostic.

Overimputation involves sequentially treating each of the observed value as if it was missing. Hundreds imputed values for that 'missing value' are created. Then by plotting observed values over imputed values (for that missing value) it is possible to inspect whether the observed values fall within the region where it would have been imputed if it had been missing. It was possible to compute overimputations only for one continuos variable at time. I report two examples of overimputation diagnostics from the Amelia II reference guide [156] in figure 5.8.
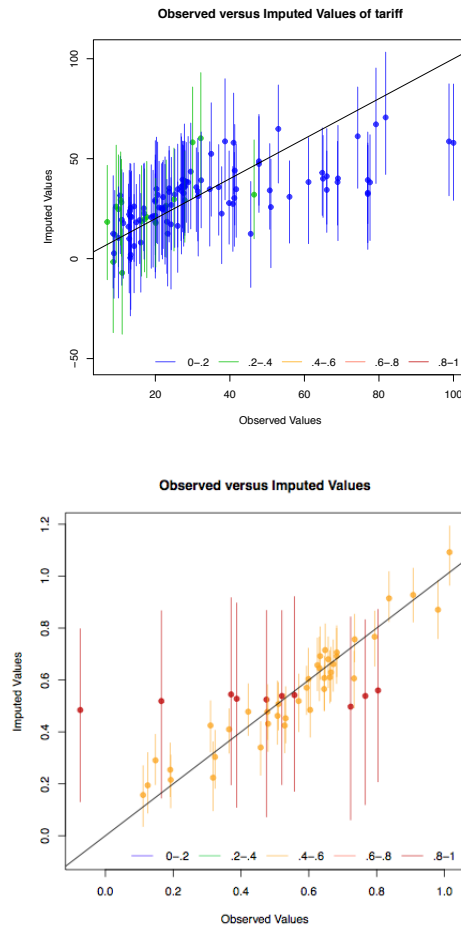
Figure 5.9: Examples of overimputations diagnostic. The vertical lines represent the 90% confidence intervals detail where an observed value would have been imputed if it had been missing from the dataset, given the imputation model. The dots represent the mean imputation. The colour of the line (as coded in the legend) represents the fraction of missing observations in the pattern of missingness for that observation. The regression line $x = y$ indicates perfect agreement, (all the true observed values fall on this line). By checking how many of the confidence intervals cover the regression line, I can see how often the imputation model can confidently predict the true value of the observation. In part A, the majority of confidence intervals fall on the regression line and there is less than 20% of covariates missing for each value imputed. In part B, the observations with fewer covariates observed (in red) have a higher variance across imputed values. The example is taken from [156]

Overdispersion diagnostic is used to make sure that the imputations do not depend on the starting values. The EM algorithm is deterministic. Thus, the point in the parameter space where it starts can impact where it ends. However,

this is irrelevant when the likelihood has only one mode. If the EM algorithm has problems finding a global maximum, starting values can effect imputations. In this scenario, the algorithm recognise the starting values as the maximum, unaware that there is a global maximum farther away. So, by running the EM algorithm from multiple, dispersed starting values, I checked that the EM chains converged. Convergence is a good sign (i.e. a well behaved likelihood), because it means that the algorithm recognises the global maximum.[12]. The diagnostic tracks the convergence of M EM chains which start from various overdispersed starting values. I report two examples of overdispersion diagnostic from the Amelia II reference guide [156] in figure 5.10. The parameter space of the imputation model is high-dimensional. However, the plot can track no more than 2 principle components and their change over the iterations of the EM algorithm. Thus, the plot is a lower dimensional summary of the convergence and is subject to all the drawbacks of summaries.

Analyses of the multiple imputed datasets

First I analysed each imputed dataset as it was a primary completed dataset. Then, I analysed multiple imputed datasets. The imputations used by the multiple imputation method are conditional draws rather than conditional means. They therefore provide valid estimates for a wide range of estimands, if the imputation model is good [157]. The combined estimate for any parameter θ over M imputed datasets is

$$\bar{\theta}_M = \frac{1}{M} \sum_{m=1}^{M} \hat{\theta}_m \tag{5.7}$$

The variability associated with this estimated has two components: the average within-imputation variance,

$$\bar{W}_M = \frac{1}{M} \sum_{m=1}^{M} W_m \tag{5.8}$$

and the between-imputation component,

$$\bar{B}_M = \frac{1}{M-1} \sum_{m=1}^{M} (\hat{\theta}_m - \bar{\theta}_M)^2 \tag{5.9}$$

---

[12]For a in depth mathematical explanation of the convergence properties of the EM algorithm, I referred to [160]

However, for matter of brevity I report for each estimate only the total variability associated with $\bar{\theta}_M$,

$$T_M = \bar{W}_M + \frac{M+1}{M} B_M \qquad (5.10)$$

When possible, I used the `Zelig` package [161] to calculate these estimates. I run mixed regression models with `logit.mixed` [154] if a random effect was required, otherwise I computed logistic regressions with `logit` [162].
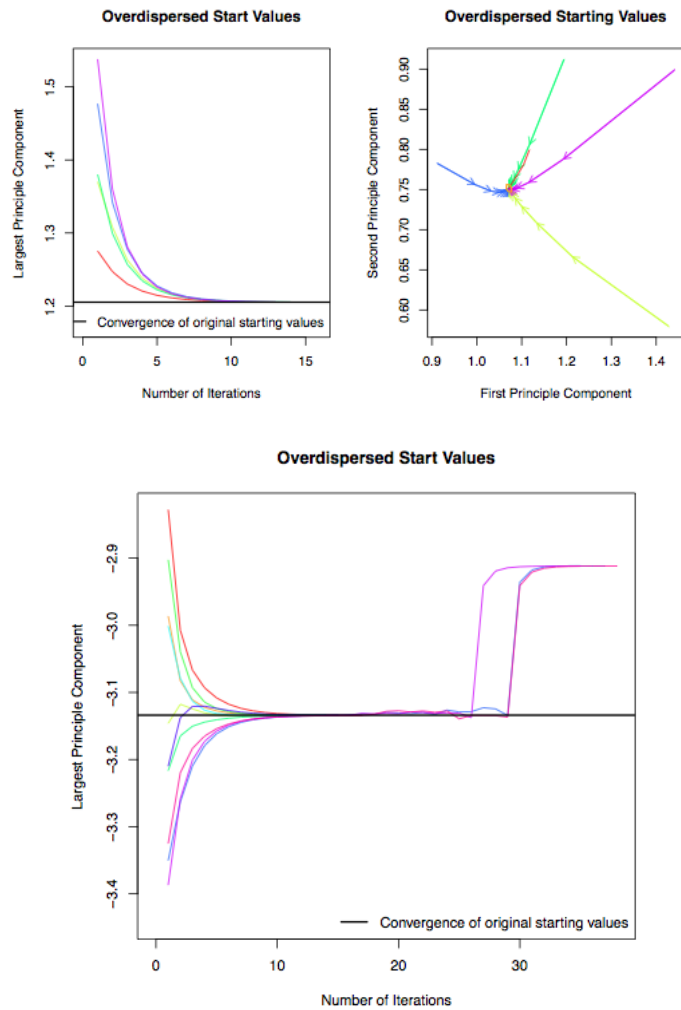
Figure 5.10: Examples of overdispersion diagnostic. Part A All chains converge to the same point, and thus starting values are not affecting the EM algorithm. On the left the x- axis represents the iteration number of the chain. The y-axis represents movement in the (very high dimensional) parameter space. The plot shows the movement of the chain on the y-axis over time (given by the iteration number on the x-axis). The black horizontal line is the point where the first EM chain converges. Thus, we are checking that the other chains converge close to that horizontal line. On the right: Two dimensional parameter space using the first two principal components of the end points of the EM chains. The distance between iterations is marked by the distance between arrowheads on each chain. The convex hull indicates the point of convergence for the first EM chain. The hull is scaled to be within the tolerance of the EM algorithm. Thus, we should check that the other chains end up in this hull. Part B: a problematic EM algorithm, where chains are converging to one of two different modes, depending upon the starting value. The example is taken from [156]

Chapter 6

Rates of perinatal episodes across the bipolar/mood disorder spectrum

In the background section I argued that, i) although lot is known on severe postnatal mood episodes, the literature presents some discrepancies and that ii) the gap in knowledge is wider for the less severe, but more prevalent, forms, that have been almost neglected by research and clinical practice. In this chapter I move beyond the rates of postpartum psychosis in BD-I, to examine the occurrence of a wider range of PNEs in BD-I, BD-II and RMD. I first estimate the lifetime rates, the morbidity risk, the rates in relationship to each pregnancy of PNEs. I then explore differences in rates across the unipolar-bipolar spectrum.

6.1 Methods

6.1.1 Inclusion criteria

Recruitment and assessment of participants have been already described in chapter 5.

Participants were included in the current analyses if they i) had a lifetime di-

agnosis of DSM-IV BD-I or BD-II or RMD and ii) had at least one full term delivery. Some participants in the mood disorder project dataset were recruited specifically due to a history of severe postpartum illness. Including these women would have inflated the rates of postpartum episodes, as, by definition, they were ill in the postpartum period. I therefore excluded women from the current analysis who were recruited on the basis of having a postpartum episode. The inclusion criteria were met by 1810 parous women, 1100 with BD-I, 314 with BD-II and 396 with RMD.

Participants recruited more recently (N= 1427) were also asked pregnancy by pregnancy questions about the relationship of episodes of illness to childbirth. I was therefore able to report lifetime rates of perinatal episodes in the whole sample, and report rates per delivery in a majority (78.8%) of women.

6.1.2 Assessment

Lifetime occurrence of perinatal episodes

For the lifetime PNE rating I employed three overlapping and hierarchical definitions of perinatal episode:

Narrow definition History of at least one episode of mania / hypomania, or mixed episode or affective psychosis all with onset within 6 weeks of delivery

Intermediate definition History of at least one episode meeting narrow criteria or major depressive episode with onset within 6 weeks of delivery

Broad definition History of any major mood disorder with onset in pregnancy or within 6 months of delivery.

Women were rated on a lifetime basis into the narrowest category that applied for any of their pregnancies. The 6-week onset cut-off is consistent with previous studies [84], includes both DSM-IV and ICD-10 definitions of the postpartum period, and was chosen as a compromise between very narrow (onset within 1 or 2 weeks) and very wide (onset within 6 months) definitions that have been used in previous studies of postpartum episodes.

Pregnancy by pregnancy ratings

For women with pregnancy by pregnancy information the following episodes were rated, according to DSM-IV criteria: mania/mixed episode, hypomania, major depression with psychotic symptoms, and non-psychotic major depression. Time-to-onset of PNEs was also recorded. However in this chapter I report the estimates for a broad definition of the perinatal period, including episodes occurring in pregnancy and within 6 months after childbirth. Then, in the next chapter I explore the rates of deliveries affected by mood episodes employing survival curves to address the issue of the time of onset.

6.1.3   Analytic plan

Estimation of rates and morbidity risk of perinatal episodes

I calculated interval estimates for

- Lifetime prevalence of PNEs, defined according to the narrow, intermediate and broad definition described above;

- Morbidity risk of broadly defined PNEs;

- Incidence rates of PNEs occurring in pregnancy or within 6 months after childbirth.

Estimation of the morbidity risk   The lifetime prevalence of PNEs underestimates the lifetime morbid risk of PNEs, as at the time of the assessment some participants who had not experienced any episodes in relation to childbirth will go on to have further pregnancies and PNEs. The morbidity risk of PNEs is the probability (expressed as percentage) that a woman with a diagnosis of mood disorder will develop a PNE if she survives and has children through the entire period at risk (in this case represented by the distribution of the age at first PNE). To obtain an indirect approximation to disease expectancy, the Strömgren's method was employed. The Strömgren's estimator is defined as:

$$SO - MR = \frac{A}{\sum_{i=1}^{n} D(a_i)} \tag{6.1}$$

where a_i is the age at the time of the interview and $D(a_i)$ is the corresponding conditional probability of being affected by age a_i, given that an individual is affected. The Strömgren's denominator sums the proportion of risk for onset that the individual has experienced, rather than the proportion of risk period time. It assumes that the conditional age-at-onset distribution for affected individuals (i.e. age at first PNE) is known and it is normally distributed (see figure 6.1).

Age at first perinatal episode
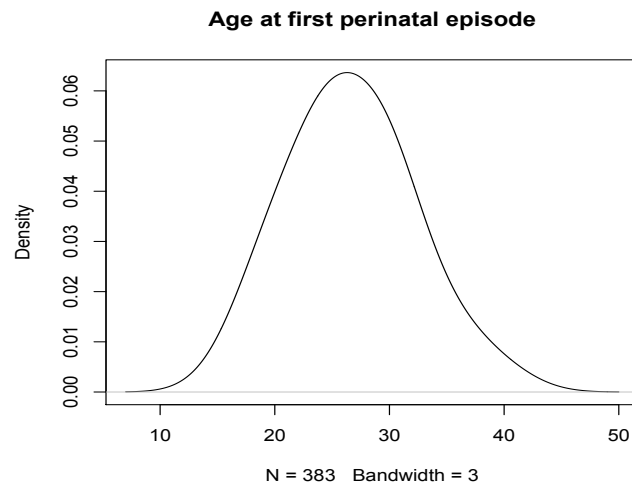
(a) Kernel density estimate
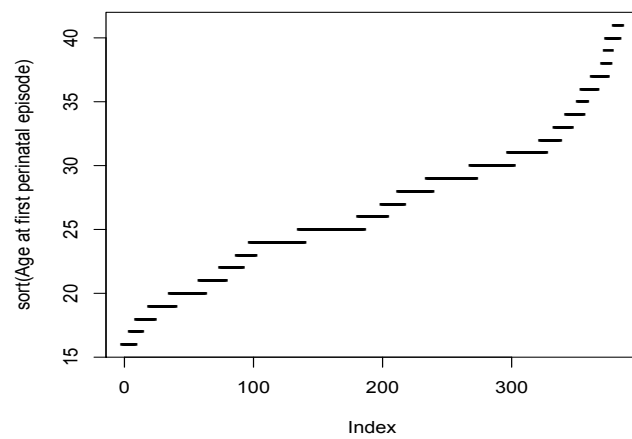
(b) Index plot of the sorted values

Figure 6.1: Age at onset of first PNE, N=383, mean 26.6 years, sd 5.37, range 16-41. PNE was defined as any mood episode occurring in pregnancy or within 6 months after childbirth. Age at onset did not differ across lifetime diagnostic groups (df= 1, F= 0.025, p=0.9) or between perinatal mania (N=58, mean 28.3, sd 4.95) and perinatal depression (N=169, mean 26.5, sd 5.34, t=-1.4284, p=0.16)

Comparative analyses

I tested the null hypotheses that there were no differences between BD-I, BD-II and RMD in i) lifetime prevalence; ii) morbidity risk; iii) incidence rates of PNEs.

Because I tested 3 independent hypotheses, I set the level of significance for the independent analyses testing to p=0.05/3=0.017. This significance level is consistent with the conservative approach used above for estimations.

The Mantel-Haenszel methodology for repeated measurements data was used to compare differences in rates of deliveries affected by a PNE across diagnostic groups.

6.2 Results

Demographic and clinical characteristics of the sample are shown in table 6.1. As explained in detail in chapter 5, women with BD-I were overrepresented because of the ascertainment strategy and the duration of each sub-study from which the samples were drawn. The focus of the bipolar disorder recruitment was in mental health services, where it is more likely to identify individuals with BD- I than BD-II. The studies recruiting bipolar probands were also longer than the study recruiting RMD. Women with BD-I, BD-II and RMD had similar age at interview and age at first pregnancy. Age at onset of mood disorder (defined as first episode of mood disorder resulting in significant impairment), number of pregnancies and number of deliveries significantly differed across lifetime diagnostic groups. Women with BD-II reported a significantly earlier age at onset than women with either BD-I or RMD (Tukey multiple comparisons of means: $p < 0.001$ and $p < 0.001$ respectively). The BD-I group had significantly fewer deliveries than the BD-II group (Wilcoxon rank sum test with continuity correction W = 127534.5, p = 0.007) and than the RMD group (Wilcoxon rank sum test with continuity correction W = 147729.5, p = $p < 0.001$).

6.2.1 Lifetime occurrence of perinatal illness

I examined the lifetime occurrence of three definitions of PNE (table 6.2, figures 6.2 and 6.3). Although the narrow definition of PNE was predominantly found in women with BD-I, under the broad definition more than $\frac{2}{3}$ of women in all

Table 6.1: Sample characteristics. Women recruited for the projects on postpartum psychosis and postpartum depression were excluded from the current analyses.

LIFETIME DIAGNOSIS	BD-I		BD-II		RMD	
	N	%	N	%	N	%
PARTICIPANTS	1100	60.8	314	17.3	396	21.9
PROJECT						
BD association study	945	85.9	297	94.3	36	9.1
BD family study	146	13.2	15	4.8	11	2.8
PND study	0		0		0	
PP study	0		0		0	
Relationship mood - psychosis	9	0.8	3	0.9	0	
UD association study	0		0		280	70.7
UD family study	0		0		69	17.4
	MEAN	**SD**	**MEAN**	**SD**	**MEAN**	**SD**
AGE AT INTERVIEW (years)	48.8	11.3	47.7	11.63	48.8	11.26
AGE AT FIRST IMPAIRMENT (years)	24	8.59	21.6	8.51	25.3	8.57
AGE AT FIRST PREGNANCY (years)	24.7	4.96	24.5	5.86	24.3	5.33
	MEDIAN	**MIN, MAX**	**MEDIAN**	**MIN, MAX**	**MEDIAN**	**MIN, MAX**
DELIVERIES PER WOMAN	2	1,10	2	1,6	2	1,6

[a]Abbreviations: BD:bipolar disorder, UD:unipolar depression, BD-I: DSM-IV bipolar I disorder, BD-II: DSM-IV bipolar II disorder, RMD: recurrent major depression

three diagnostic groups reported at least one episode of illness during pregnancy or postpartum. With the broad definition of PNE, there were not significant differences across lifetime diagnostic groups (χ^2= 6.03, df = 2, p = 0.05).

Table 6.2: History of PNEs in women with mood disorders. Hierarchical definitions of perinatal episode: i)Narrow: an episode of mania / hypomania, a mixed episode or an affective psychosis all with onset within 6 weeks of delivery ii) Intermediate: those women meeting the narrow criteria plus those with a history of an episode of major depression with onset within 6 weeks of delivery iii) Broad: a history of an episode of any major mood disorder with onset in pregnancy or within 6 months of delivery.

LIFETIME DIAGNOSIS	BD-I			BD-II			RMD		
HISTORY OF PNEs	N	%	99%CI	N	%	99%CI	N	%	99%CI
Narrow	338	30.7	27.2-34.4	30	9.5	5.8-14.6	0		0.0-0.1
Intermediate	595	54.1	50.2-58.0	141	45	37.6-52.3	179	45.2	38.7-51.8
Broad	768	69.8	66.1-73.3	231	74	66.7-79.7	258	65.1	58.7-71.2

6.2.2 Morbidity risk of perinatal episodes

Using the Strömgren's estimator, the morbidity risk for broadly defined PNEs didn't differ across lifetime diagnoses and was 72.3% (99%CI 68.7%-75.2%) in the BD-I group, 76.6% (99%CI 69.8%-82.6%) in the BD-II group and 67.2% (99%CI 60.7%-73.3%) in the RMD group (figure 6.4).

(a) Bipolar I disorder (N=1100)

(b) Bipolar II disorder (N=314)
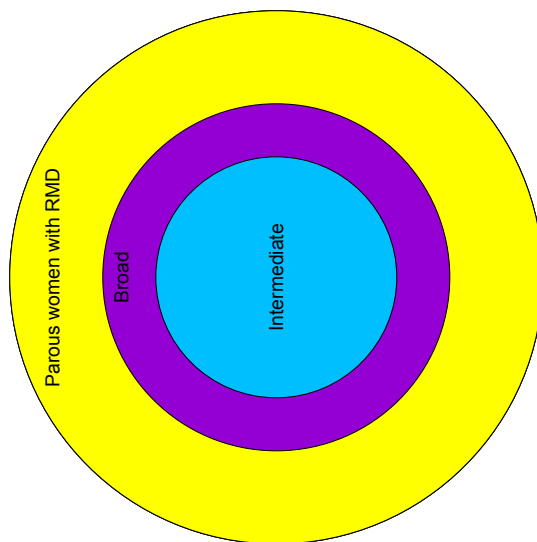
(c) Recurrent major depression (N=396)

Figure 6.2: Lifetime perinatal episodes in parous women with mood disorder. Hierarchical definitions of perinatal episode: i) Narrow: an episode of mania / hypomania, a mixed episode or an affective psychosis all with onset within 6 weeks of delivery ii) Intermediate: those women meeting the narrow criteria plus those with a history of an episode of major depression with onset within 6 weeks of delivery iii) Broad: a history of an episode of any major mood disorder with onset in pregnancy or within 6 months of delivery. The graph was built using the gridSVG library in R
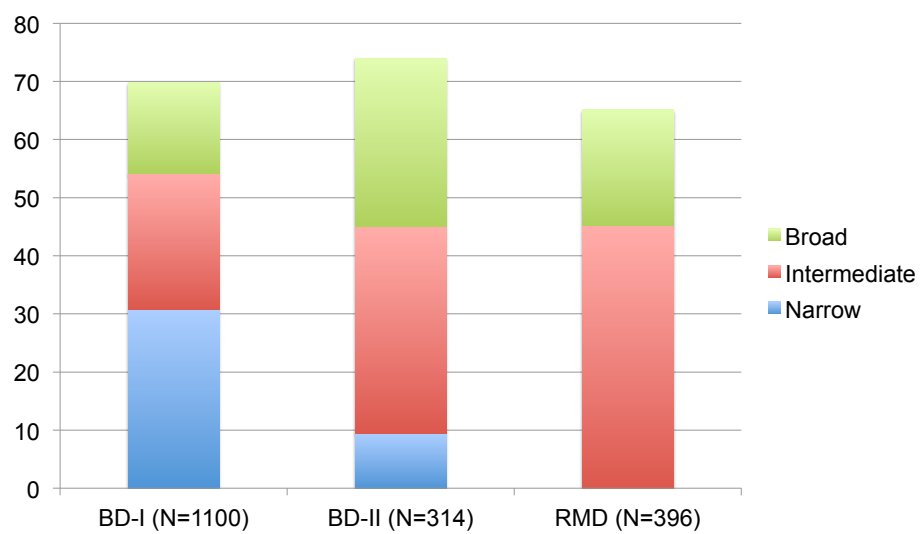
Figure 6.3: Lifetime perinatal episodes in parous women with mood disorder. Hierarchical definitions of perinatal episode: i) Narrow: an episode of mania / hypomania, a mixed episode or an affective psychosis all with onset within 6 weeks of delivery ii) Intermediate: those women meeting the narrow criteria plus those with a history of an episode of major depression with onset within 6 weeks of delivery iii) Broad: a history of an episode of any major mood disorder with onset in pregnancy or within 6 months of delivery.
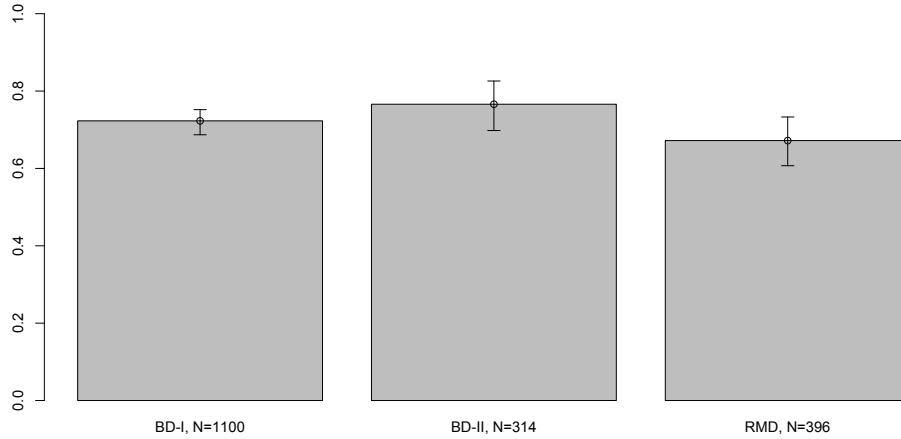
Figure 6.4: Morbidity risk of PNEs by lifetime diagnosis. Vertical bars represents 99% confidence intervals. On the y axis the morbidity risk of PNEs expressed as $SO - MR = \frac{A}{\sum_{i=1}^{n} D(a_i)}$ where a_i is the age at the time of the interview and $D(a_i)$ is the corresponding conditional probability of being affected by age a_i, given that an individual is affected.

6.2.3 Incidence rates of perinatal episodes

Pregnancy by pregnancy information was available for 3125 pregnancies from 1441 women (table 6.3).

Table 6.3: Incidence of perinatal episodes by live birth delivery in women with mood disorder.

LIFETIME DIAGNOSIS	DSM-IV BD-I			DSM-IV BD-II			DSM-IV RMD		
	(N=828) (Nd=1718)			(N=272) (Nd=598)			(N=327) (Nd=809)		
DELIVERIES AFFECTED WITH:	N	%	99%CI	N	%	99%CI	N	%	99%CI
PP	350	20.4	17.9-23.0	20	3.3	1.7-5.7	14	1.7	0.8-3.3
PND	433	25.2	22.5-28.0	230	38.5	33.3-43.7	315	38.9	34.5-43.5
ANY PNE	844	49.1	46.0-52.3	269	45	39.7-50.3	332	41	36.6-45.6

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Around 1 in 5 pregnancies in women with BD-I were complicated by a manic episode or a psychotic depression in pregnancy or within 6 months postpartum. Episodes of perinatal major depression were even more common in bipolar women, affecting 1 in 4 pregnancies. Looking at broadly defined episodes of PNE, women with BD-I had a statistically significant higher incidence of broadly defined PNEs than women with RMD (Mantel-Haenszel χ^2= 10.13, df = 1, p = 0.001). However the effect size was small (OR=1.32, 99%CI=1.06-1.66). I found no difference in the incidence rates between BD-I and BD-II (Mantel-Haenszel χ^2= 2.43, df = 1, p = 0.12) or between BD-II and RMD (Mantel-Haenszel χ^2= 1.36, df = 1, p = 0.24)

6.3   Summary

In this chapter I investigated the rates of PNEs in a large, well-characterised clinical sample of women with mood disorders. The lifetime prevalence of PNEs was high across all disorders, affecting more than 2 women out of 3 in all diagnostic groups. When information on each pregnancy was studied, women with BD-I reported more PNEs than women with RMD. In women with BD-I episodes of mania/psychosis affected about 1 in 5 perinatal periods and episodes of major depression were even more common, affecting 1 in 4 perinatal periods.

Chapter 7

Time of onset of perinatal mood episodes

In this chapter I report the analyses I conducted on the timing of onset of PNEs. In the background section I have argued that

- Although the majority of studies reported that episodes of postpartum psychosis occur soon after childbirth, the presence of a *free interval* after delivery and the period in which the incidence of postpartum depression maximises are controversial

- There is a lack of information on bipolar postpartum depression and no previous studies have compared bipolar and unipolar postpartum depression

- The literature has either focussed on episodes occurring in pregnancy or episodes occurring in the postpartum period. Only the large retrospective study conducted by Viguera et al that I reviewed in the background section examined the rates of mood episodes in pregnancy and in the postpartum period [6].

I therefore explored the time-to-onset of PNEs across the mood disorder spectrum. I reported the rates of episodes occurring in pregnancy and after childbirth, using different definitions of postpartum onset. I sought to replicate Viguera's [6] findings on the postpartum-pregnancy risk ratio and to quan-

tify the proportion of episodes that would be included in current definitions of postpartum onset. Then I explored the survival curves for postnatal mania/psychosis in BD-I and for postnatal depression across the unipolar - bipolar spectrum to test whether empirical data supported the current definitions of postpartum onset rather than the hypothesis that different postpartum onset criteria should be used for mania and depression.

7.1 Methods

Recruitment and assessment of participants have been already described in chapter 5. Participants were included in the current analyses if they i) had a lifetime diagnosis of DSM-IV BD-I or BD-II or RMD and ii) had at least one DSM-IV major depressive, manic, or mixed episode in pregnancy or after a live birth.

7.1.1 Analytic plan

First I estimated the proportion of episodes occurring in pregnancy and within 6 months after childbirth by lifetime diagnosis. I also employed three mutually exclusive definitions of postpartum onset: 4 weeks (as in the DSM-IV), 6 weeks (as in the ICD-10) and 6 months (commonly used in the clinical practice). Then, I used survival analyses to:

- estimate time-to-onset of i) manic or mixed episodes, ii) non psychotic depression and iii) psychotic depression;

- compare time-to-onset of i) postnatal manic or mixed episodes, ii) postnatal non psychotic depression and iii) postnatal psychotic depression in women with BD-I. Given that, by definition, women with RMD do not experience manic episodes, and there were only few episodes of psychotic depression in the BD-II group (N= 9) and in the RMD group (N=18), I compared survival curves according to the type of episode only in the BD-I group.

- compare time-to-onset of postnatal depression between lifetime diagnosis (BD-I, BD-II, RMD). I aimed to test the hypothesis that the DSM-IV lifetime diagnosis is not associated with the time of onset of postpartum

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depression. I limited the comparisons to the postpartum period, because the survival curves including the entire perinatal period showed a peak of incidence in the immediate postpartum and the majority of episodes occurred after childbirth.

Table 7.1 lists the hypotheses I tested. I performed 3 independent groups of tests, so the initial P value threshold using the Bonferroni correction was $0.05/3=0.017$[1].

Survival analyses

In order to perform any survival analysis two outcome variables are needed:

- a time variable: t_i=time-to-onset of the postnatal episode

- a censoring variable: c_i=1 if the postnatal episode occurred or c_i=0 if the postnatal episode did not occur by the time t_i

First, I employed the Kaplan-Maier estimator to estimate the survival function. It is a non parametric method (and thus does not require any mathematical assumptions about the underlying hazards) and provides an intuitive graphical presentation. As already discussed in previous chapters, affected pregnancies from the same individual are not independent events. Thus, I fitted a mixed effect Cox model to test the null hypothesis of no difference between survival functions and to explore the influence of parity order and within subject variations. I used the `coxme` function of the `coxme` library and I compared the fit of different models [163]. I limited these analyses to the first 2 pregnancies, because there were not many cases among subsequent pregnancies.

---

[1]Comparative analyses on 1) episodes occurring in pregnancy v episodes occurring postpartum 2) survival curves in BD-I 3) survival curves for perinatal depression

Table 7.1: Hypotheses tested

QUESTION	H_0	SAMPLE
How many episodes in preg and how many post in BD-I?	no differences between proportion of M/pD/nPD occurring in preg and M/pD/nPD occurring post	394 BD-I M, 40 BD-I pD, 318 BD-I npD
Is there any difference between survival curves for postM, post pD and post npD in BD-I? Is there any within subject effect?	Survival curves for M, pD and npD in BD-I are similar, no within subject effect	583 post BD-I
How many npD did occur in pregnancy and how many post? Was there any difference across the mood disorder spectrum? Is parity order associated with t_i?	no differences between $npDpreg/npDpost$ ratio across BD-I, BD-II and RMD	678 perinatal np
Is there any difference between survival curves for npD across lifetime diagnoses? Is there any within subject effect?	no differences between npD survival curves across BD-I, BD-II and RMD, no within subject effect	678 perinatal /584 post npD
Any difference in t_i between 1st and 2nd	t_i similar between first and second PP	61 women with both first and second perinatal period affected by PP
	t_i similar between first and second npD	125 women with both first and second perinatal periods affected by npD

7.2 Results

Information was available for 1332 affected pregnancies from 695 women (table 7.2).

Table 7.2: Sample charachteristics

LIFETIME DIAGNOSIS	BD-I		BD-II		RMD	
NUMBER OF WOMEN	421		105		169	
NUMBER OF PREGNANCIES	761		190		381	
	N	**%**	**N**	**%**	**N**	**%**
ORDER OF PARITY						
First	421	55.3	105	55.3	169	44.5
Second	230	30.2	51	26.8	126	33.1
Third	77	10.1	22	11.6	65	17.1
Fourth	33	4.3	12	6.3	21	5.5
PERINATAL DIAGNOSIS						
Mania, hypomania or mixed episodes	394	51.8	7	3.7	0	
Psychotic depression	40	5.3	9	4.7	18	4.7
Non-psychotic depression	318	41.8	173	91.1	362	95.0
Polymorphic psychosis	9	1.2	1	0.5	1	0.5

7.2.1 Perinatal episodes in bipolar I disorder

Mania The vast majority (342/394, 86.8%) of manic episodes occurred within 4 weeks postpartum, about 90% (353/394) within 6 weeks. Only 5.1% (20/394) of episodes occurred in pregnancy - test of proportion for episodes occurring in pregnancy v episodes occurring in the postpartum $\chi^2 = 316.3$, df = 1, p < 0.001.

Non-psychotic depression Although episodes of postpartum non psychotic depression were still overrepresented in comparison with episodes during pregnancy (42/318, 13.2%) , only 64.1% (204/318) occurred within 4 weeks postpartum, while about 1 in four episodes occurred later after childbirth (72/318, 22.5%) - test of proportion for episodes occurring in pregnancy v episodes occurring in the postpartum $\chi^2 = 170.7$, df = 1, p< 0.001.

Psychotic depression 22.5% (9/40) episodes of psychotic depression occurred in pregnancy, 62.5% (25/40) within 4 weeks - test of proportion $\chi^2 = 11.0$, df = 1, p= 0.001

Cycloid psychosis There were only 9 episodes of cycloid psychosis. All of them occurred in the postpartum period, with 8/9 (88.9%) occurring within 4 weeks after delivery.

Figure 7.1a displays the survival curves for perinatal episodes in BD-I according to the type of episode (mania, psychotic depression, cycloid psychosis and non-psychotic depression) while figure 7.1b is focused on the postpartum period. I used Cox mixed analysis, including only first (N=379) and second deliveries (N=204) and excluding episodes occurring in pregnancy and episodes of cycloid psychosis, because of the small sample size. There was a significant random effect (Integrated loglik = 65.3, df= 4,$p < 0.001$; Penalized loglik= 110.4, df= 24.9, $p < 0.001$), so I compared survival curves in the following model:

```
coxme(survival object ~ type of episode + parity order + (1|ID))
```

and

```
survival object <- with(BD-I , Surv(t, episode))
```

The random effect is specified in the formula by a parenthesised expression which contains a vertical bar separating effects on the left (in this case the intercept) from grouping variables on the right (in this case the subject ID). I found that survival curves for mania and psychotic depression were similar (z=-1.63, p=0.1) while non-psychotic depressive episodes had a significantly later onset in the postpartum (z=-6.8, $p < 0.001$). Moreover, postnatal episodes occurring in primiparae had an earlier onset than those occurring in multiparae (z=-3.01, $p < 0.001$).
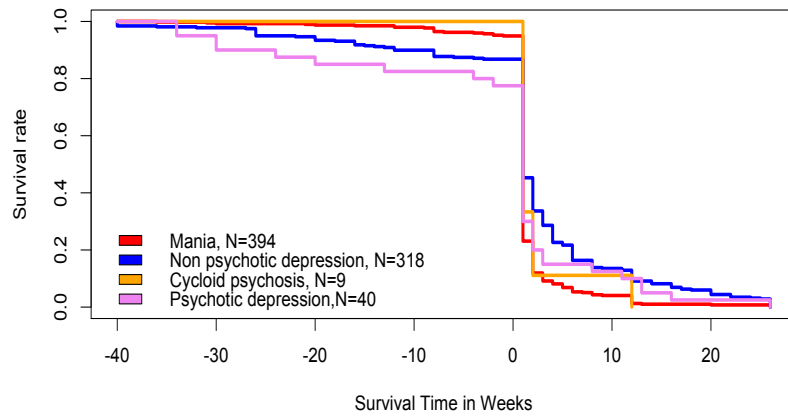
(a) Perinatal period
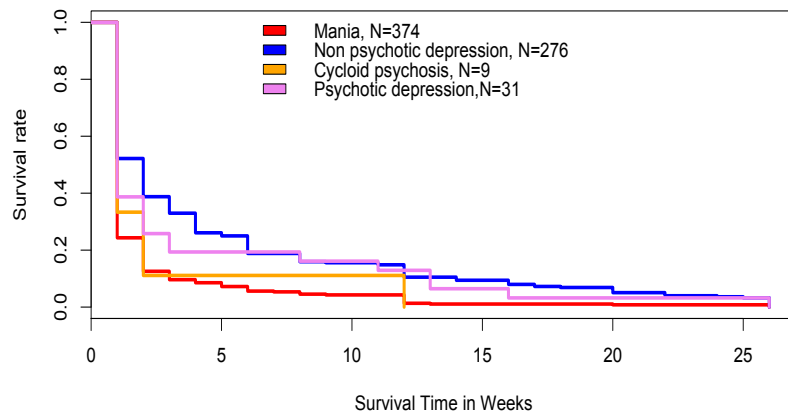
(b) Postnatal period

Figure 7.1: Survival curves for perinatal episodes in BD-I according to the type of episode. Part a) includes also pregnancy, while part b) includes only postpartum episodes. Survival curves for postpartum mania and psychotic depression were similar (z=-1.63, p=0.1) while non-psychotic postpartum depression had a significantly later onset in the postpartum (z=-6.84, df=1, $p < 0.001$).I excluded cycloid psychosis from the analysis because of the small sample size.

7.2.2 Perinatal non psychotic depression across the mood disorder spectrum

Given that, by definition, women with RMD do not experience manic episodes, and there were only few episodes of psychotic depression, further survival analyses were conducted for non psychotic depressive episodes alone. I aimed to examine the question of whether the time to onset of perinatal depression differed BD-I, BD-II and RMD.

The majority of episodes of perinatal depression occurred in the postpartum period across all diagnostic group (figure 7.2a). However, women with BD-II had a larger proportion of episodes occurring in pregnancy than women with BD-I (Fisher's Exact Test for Count Data p=0.02, OR 1.8, 99%CI 0.91- 3.49 - not significant after Bonferroni correction) and than women with RMD (Fisher's Exact Test for Count Data p = 0.001, OR 2.3, 99%CI 1.17- 4.59). I summarise the distribution of postpartum episodes, employing different definitions and according to lifetime diagnoses in figure 7.2b.
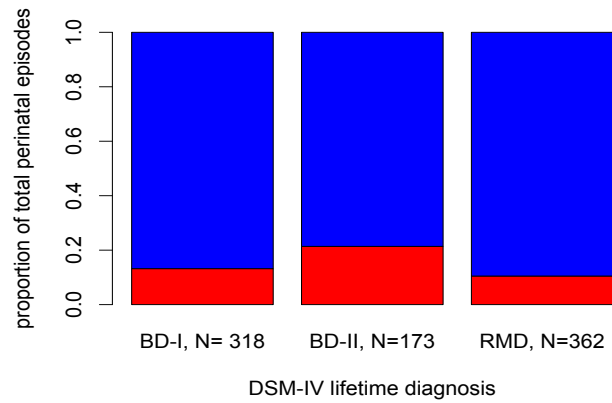
(a) Non psychotic depression occurring in pregnancy (red) and in the postpartum (blue)
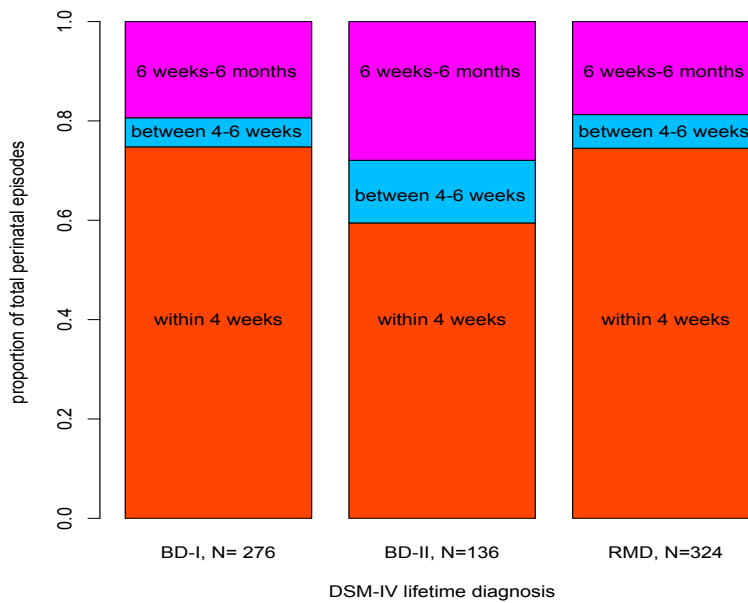
(b) Postpartum non psychotic depression according to different onset criteria

Figure 7.2: Part a): Staked bar plot of the proportion of perinatal non psychotic depression occurring in pregnancy and in the postpartum period. Women with BD-II had a larger proportion of episodes occurring in pregnancy than women with RMD (Fisher's Exact Test for Count Data p=0.001, OR 2.3, 99%CI 1.17-4.59). Part b): Staked bar plot of the proportion of postpartum episodes according to different onset definition

Figure 7.3a shows the survival curves for perinatal non psychotic depression according to lifetime diagnosis. I used the Cox mixed methodology to compare survival curves for depression across lifetime diagnoses in the following model:

```
coxme(survival object ~ DSM-IV diagnosis + parity order + (1|ID))
```

and

```
survival object <- with(postnatal depression, Surv(t, episode))
```

Including the entire perinatal period in the analysis, there were no differences between lifetime diagnoses, nor between first and second perinatal periods (Integrated loglik =18.8, df =4, p= 0.0009, Penalized loglik =389.1, df=162.85, $p < 0.001$).

I then analysed survival curves for postnatal depression (figure 7.3b). Again, I found a within subject effect (Integrated loglik =25.1, df= 4, p< 0.001, Penalized loglik= 318.1, df=130.9, p< 0.001). Women with BD-I and RMD had overlapping survival curves (z=0.13, p=0.9), while women with BD-II displayed a delayed onset of non psychotic depressive episodes (z=-2.71, p= 0.007 v BD-I). Postnatal episodes occurring in primiparae had an earlier onset than those occurring in multiparae (z=-2.46 p=0.014).
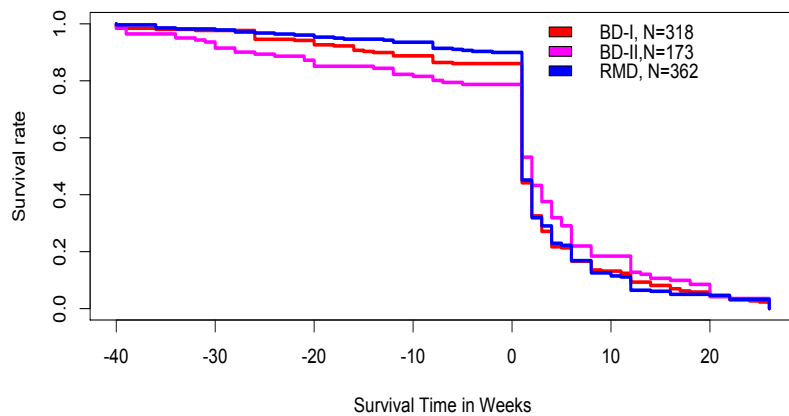
(a) Perinatal period
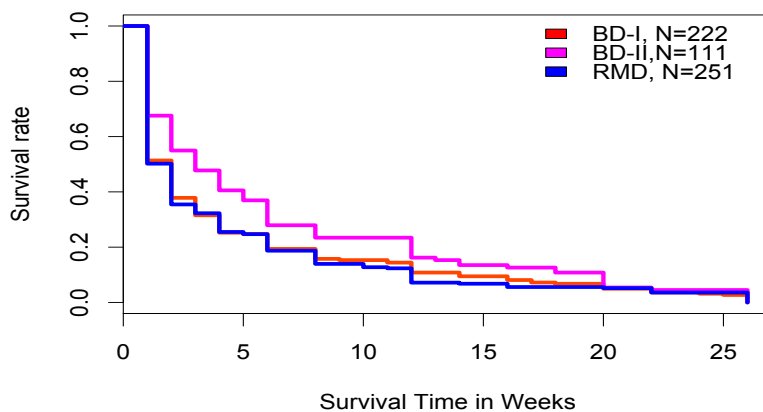
(b) Postnatal period

Figure 7.3: Survival curves for perinatal depression according to lifetime diagnosis Part a) includes also pregnancy, while part b) includes only postpartum episodes. Women with BD-I and RMD had overlapping survival curves (z=0.13, p=0.9), while women with BD-II displayed a delayed onset of non psychotic depressive episodes (z=-2.71, p= 0.007 v BD-I).

7.2.3 Was there any differences in onset between first and subsequent pregnancies in women with more than one episode?

I selected two sub-samples of women having both their first and second pregnancy affected by either perinatal mania/psychosis (N=61) or perinatal non psychotic depression (N=135). I merged the sample with mania with that of psychotic depression and cycloid psychosis to have a sample size suitable for statistical inference. I labelled this category as 'affective psychosis'. I tested the hypothesis that having an episode in the first perinatal period is associated with a shorter latency between childbirth and the onset of a second perinatal episode. Using Cox mixed models, there were no differences in the survival curves between first and second episode of perinatal affective psychosis (Likelihood ratio test=0.13, df=1, p=0.7) and of perinatal non psychotic depression (Likelihood ratio test=0.33, df=1, p=0.6).

7.3 Summary

In this chapter I explored the time to onset of perinatal episodes.

- I examined how many perinatal episodes occurred in pregnancy and how many in postpartum and found that the majority of PNEs occurred in the postpartum period

- I examined how many postpartum episodes met various postpartum onset criteria and found that the majority of PNEs in women with BD-I and RMD occurred within 4 weeks after childbirth.

- In BD-I I compared the survival curves for manic/mixed, psychotic depressive, and non psychotic depressive episodes and found that there was a correlation between the phenomenology of the episode and the time of onset, with a significantly shorter latency for manic and psychotic episodes.

- I compared survival curves for perinatal depression in BD-I, BD-II and RMD. Women with BD-I and RMD had overlapping survival curves, while for BD-II, onsets of PNEs were more spread out over the perinatal period

with more onsets in pregnancy and later in the postpartum.

- I explored differences in onset between first and subsequent pregnancies in women with more than one episode and found that episodes occurring after first pregnancies had a shorter latency than episodes occurring after subsequent pregnancies. The effect was stronger for episodes of BD-I.

a

Chapter 8

Is childbirth a specific trigger for mood disorders?

> "It is certain that among furious lunatics, there are more women than men. A new subject of research. Does this difference originate in the sequelae of childbearing, in the nervous sensations accompanying lactation?"
>
> Jacques Tenon [164]

The high incidence rates in the perinatal period reported in chapter 6 do not necessarily implicate that childbirth is a specific trigger, because bipolar disorder and RMD are recurrent illnesses and high occurrence rates may be common also outside the perinatal period. The cross-sectional observation of a PNE needs, in fact, to be put into the context of the longitudinal lifetime course of the disorder in order to establish the strength of the association between childbirth and bipolar/mood disorders. Similar high rates of PNEs can have different diagnostic validity, according to the lifetime course of the illness. Figure 8.1 and 8.2 exemplify some possible scenarios.

In this chapter I investigate the specificity of the childbirth trigger and report the analyses I conducted in order to:

1. estimate the proportion of parous women with mood disorders who had their first episode in relation to childbirth (as exemplified in figure 8.2) versus women in which PNEs were recurrences of a pre-existing mood
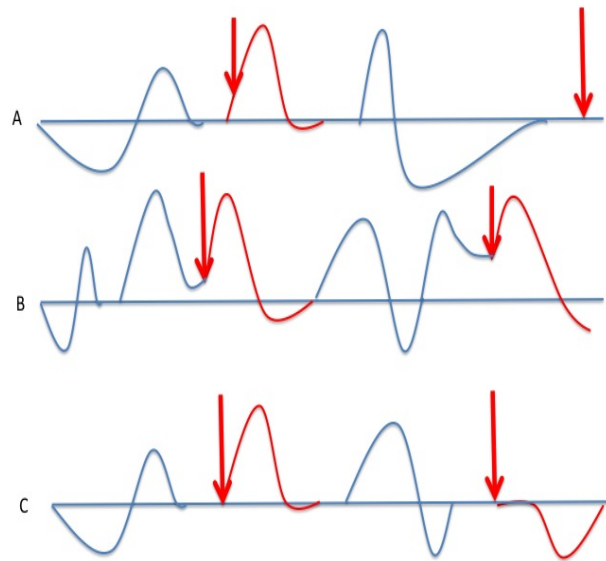
Figure 8.1: Perinatal recurrences of mood disorders.Red arrows represent child-birth. Episodes occurring in temporal relation with childbirth are not necessarily caused by psychological and biological changes occurring in relation to childbirth, but may be a consequence of the recurrent course of mood disorders and be in temporal relation to childbirth just by chance. Here I exemplify three possible scenarios in which childbirth is not necessarily a specific trigger for an episode. **Part A** Chronic illness, in which, although the participant reported to be ill after childbirth, the episode may have been part of an ongoing episode, or **part B** a relapse (i.e. a full syndrome before a full remission from a previous episode was reached) or **part C** a recurrence that only by chance happened in relation to childbirth, given the high rates of recurrence of the condition. In fact it has been shown in a sub-sample of participant with BD-I drawn from the mood disorder research project database that 36% of participants with an early onset and 21.6% of those with a mid onset had rapid cycling and more episodes and a worse course of illness than participants in the late-onset group. [165]

disorder (as exemplified in figure 8.1);

2. test the association between lifetime course of illness and PNEs and compare the rates of episodes occurring in relation to childbirth with the rates of episodes occurring at other times outside the perinatal period;

3. test whether the vulnerability was specific to postpartum mania/psychosis (as in figure 8.2B) and postpartum non-psychotic depression or it was a general vulnerability to PNEs in which a woman experienced mania after
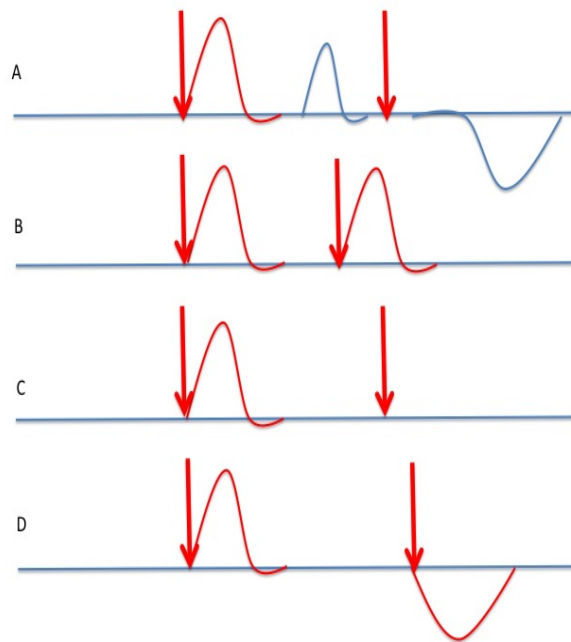
Figure 8.2: Perinatal onset of mood disorders. Red arrows represent childbirth. Even the onset of the disorder in relation to childbirth does not necessarily imply that childbirth is the trigger for that episode or for the disorder in general. In fact the onset of bipolar disorder occurs in most of the cases in the reproductive age and a first episode may occur only by chance in relation to childbirth. In these cases women develop a bipolar illness, in which recurrences are not related to reproductive events **(part A)**. Among women who have episodes only in relation to childbirth, there are three possible scenarios: 1) childbirth is a strong and specific trigger, causing only one type of recurrence after each pregnancy (here manic, **part B**), 2) it can act as a trigger after one pregnancy, but not after other pregnancies **(part C)** or 3) it can act as an unspecific trigger by triggering episodes with different phenomenology within the same woman **(part D)**. The latter three patterns can be identified only in women with at least 2 deliveries.

one pregnancy and non-psychotic depression after an other (as in figure 8.2D).

8.1 Results

As I was interested in PNEs in relation to the lifetime course of illness, I included in the current analyses only women with a lifetime history of broadly

defined PNEs[1]. The sample consisted of 887 women with BD-I, 237 women with BD-II and 314 women with RMD. The association between PNEs and lifetime diagnoses was consistent with my findings in chapter 5 and is summarised by the mosaic plot in figure 8.3.

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[1]See chapter 6 for a definition of broad PNE
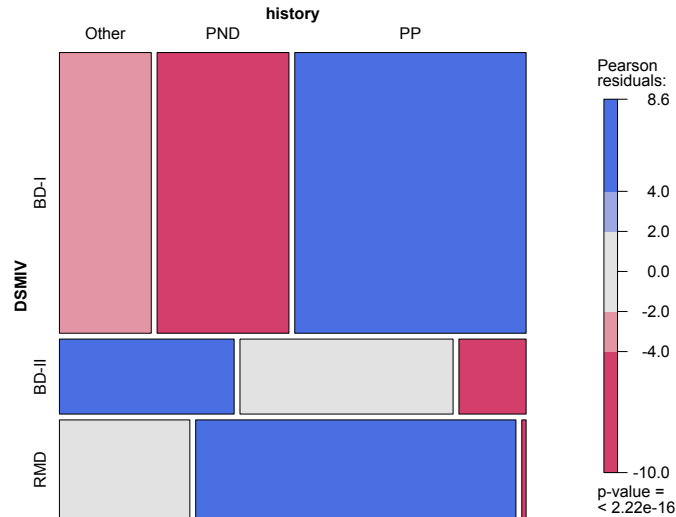
Figure 8.3: History of perinatal episodes according to lifetime diagnosis. Only women with a lifetime history of PNEs were included in the analyses (N=1438). The total area of the mosaic plot represents the total sample size. The plot is divided first into horizontal bars whose widths are proportional to the probabilities associated with the first categorical variable (in this case the DSM-IV diagnosis). Then each bar is split vertically into bars that are proportional to the conditional probabilities of the second categorical variable. Colours display the deviations (residuals) from a model in which PNEs and lifetime diagnoses are independent events. Deep blue corresponds to residuals are greater than +4, indicating much greater frequency in those cells than would be found if PNE and lifetime diagnosis were independent. Deep red corresponds to the residual lower than -4, indicating that that combination of PNE and lifetime diagnosis is extremely rare under the hypothesis of independence. The standardized Pearson residual for a cell $_{ij}$ is $r_{ij} = \frac{O_{ij}-E_{ij}}{\sqrt{E_{ij}(1+p_{i+})(1-p_{+j})}}$ where O is the observed count, E the expected count and p the marginal proportions. The overall Pearson χ^2 statistic is just the sum of squares of the residuals. The plot was produced using the library `vcd`. Abbreviations: BD-I: bipolar I disorder, BD-II:bipolar II disorder, RMD: recurrent major depression, PP: history of mania or brief psychotic episode with mood symptoms within 6 weeks postpartum, PND: history of postnatal depression within 6 weeks postpartum, Other: history of mood episode in pregnancy or between 6 weeks and 6 months after childbirth. A hierarchical approach was used

The dataset used for the analyses reported in this chapter contained many missing values. Figure 8.4 displays the missing values according to the pattern of missingness. I did not identify any variable that was completely responsible for the missing data. I therefore assumed that data were missing due both accessible and inaccessible factors. My assumption was based on a large amount of literature (see for example [166]), that suggested that this is the most plausible scenario . Missing data were handled according to the algorithm presented in chapter 5. Dealing with missing data and multiple imputation is complex and computationally demanding, so I preferred to produce separate multiple datasets for each hypothesis I tested. This approach allowed me a better control and produced more stable datasets.
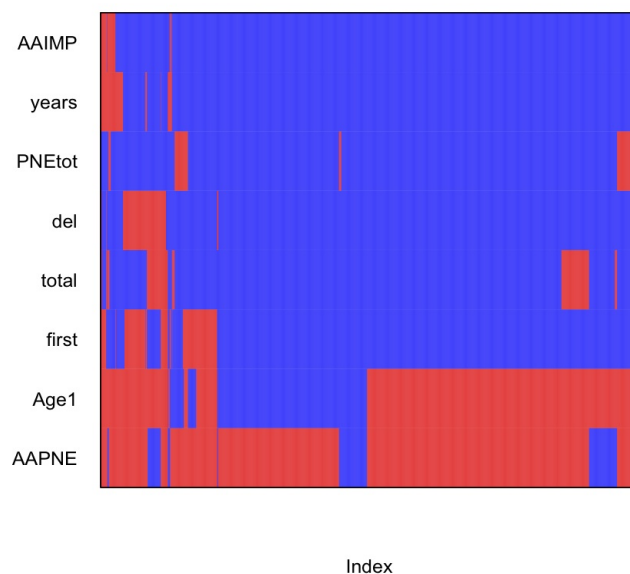
Figure 8.4: Missingness pattern plot obtained with the function `missing.pattern.plot` in the package `mi` [167]. Only variables containing missing values are shown. The observed values are plotted with blue and the missing values are in red. Variables and cases are ordered by proportion missing and clustered by similar missingness pattern. Abbreviations: AAPNE: age at first perinatal episode, del: number of deliveries, PNEtot: total number of postpartum episodes within 6 weeks after childbirth, years: years of illness, total: total number of episodes lifetime, Age1: age at first pregnancy, first: whether perinatal episode is a recurrence or the first lifetime episode, history: history of perinatal episodes

8.1.1 Onset of mood disorder or recurrence of a pre-existing disorder?

Information on whether a PNE was the first lifetime episode or a recurrence of a pre-existing mood disorder was available for 1187/1438 (82.6%) women. Because missing values were overrepresented in BD-I (χ^2= 12.22, df = 2, p = 0.0022 and figure 8.5), the `Amelia` package was employed to perform multiple imputations and the `Zelig` package for the inferences (please see chapter 5 for a broader discussion on dealing with missing values).
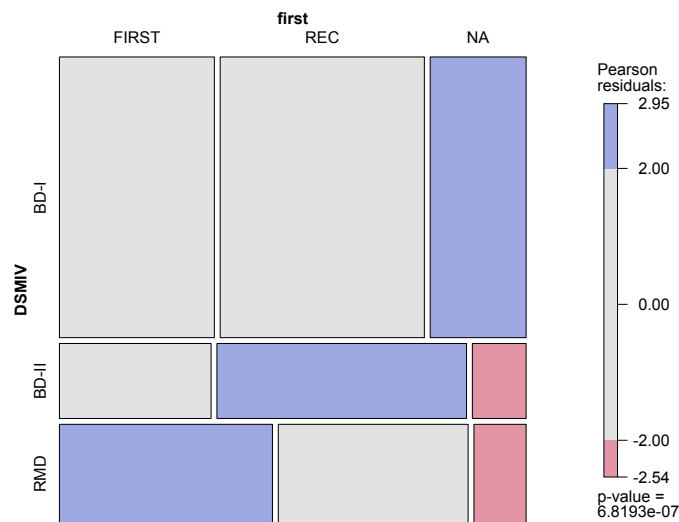
Figure 8.5: Association between lifetime diagnosis and first lifetime episode. Only women with a lifetime history of PNEs were included in the analyses (N=1438). The total area of the mosaic plot represent the total sample size. The plot is divided first into horizontal bars whose widths are proportional to the probabilities associated with the first categorical variable (in this case the DSM-IV diagnosis). Then each bar is split vertically into bars that are proportional to the conditional probabilities of the second categorical variable (*first* - whether the PNE was the the first lifetime episode of mood disorder or a recurrence).Abbreviations: BD-I: bipolar I disorder, BD-II:bipolar II disorder, RMD: recurrent major depression, FIRST:PNE as first lifetime episode of mood disorder, REC: PNE as a recurrence of a pre-existing mood disorder, NA information missing

The rates of missingness for each variable inputed are listed in table 8.1, while

graphical diagnostics to inspect the imputations are presented in figure 8.6 and 8.7.

Table 8.1: Fraction missing for individual variables in the analyses on first episode

VARIABLE NAME	FRACTION MISSING
ID	No missing
History of PNE	No missing
First episode in the perinatal period?	0.17
DSM-IV	No missing
Age at impairment	0.03
Age at first PNE	0.86
Age at first live birth	0.68
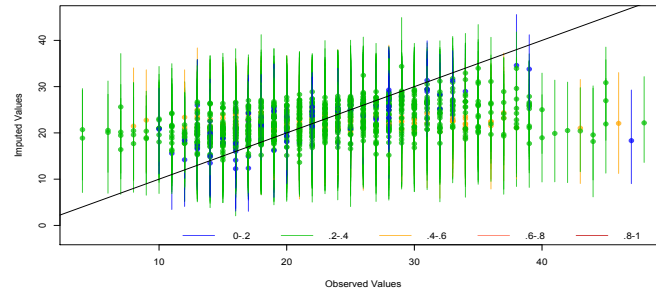
(a) Age at impairment
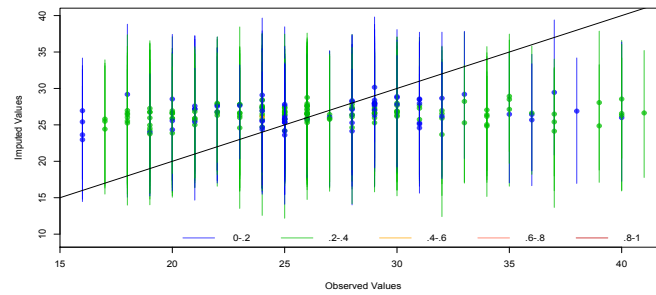
(b) Age at first perinatal episode
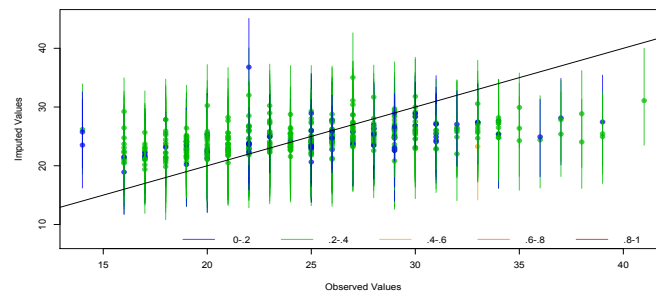
(c) Age at first pregnancy

Figure 8.6: Overimputation diagnostic graph for multiple imputations for life-time onset in relation to childbirth. The majority of confidence intervals fell on the regression line and there was less than 20-40% of covariates missing for each value imputed.

Overdispersed Start Values

(a)

Overdispersed Starting Values
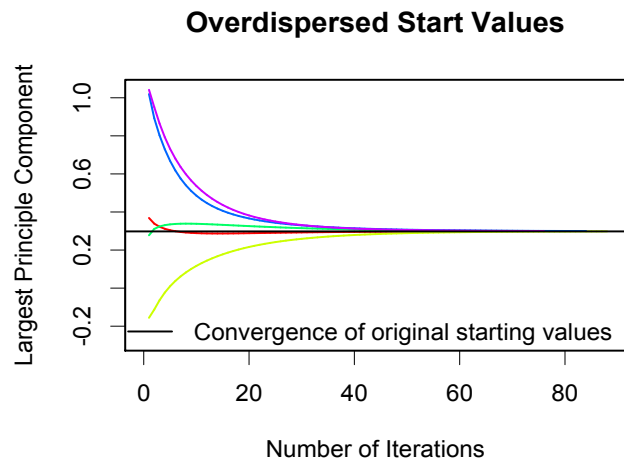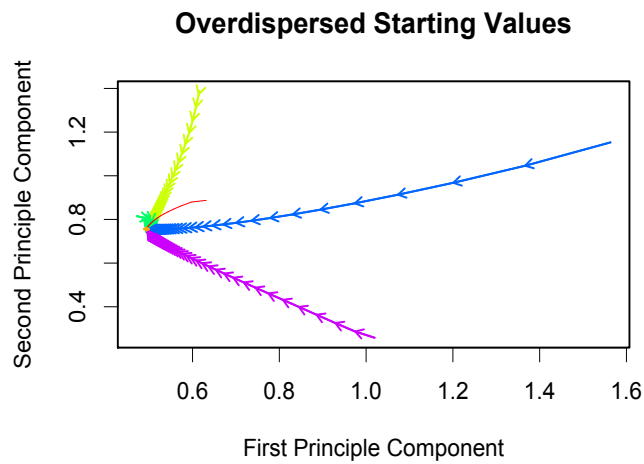
(b)

Figure 8.7: Overdispersion diagnostic for multiple imputations for lifetime onset in relation to childbirth. EM chains converged. A detailed explanation of overdispersion is provided in chapter 5.

I performed 4 independent tests, so the correct p value threshold for significance was $0.05/4 = 0.0125$. The first lifetime episode was temporally associated with childbirth in 43.1% (99%CI 38.3%-48.1%) of women with BD-I, in 37.7% (99% CI 29.2%-46.9%) of women with BD-II and in 52.9% (99%CI 45.0%-60.7%) of women with RMD. Postpartum depression within 6 weeks (49.3%, 99% CI 44.0%

-54.7%) and, to a lesser extent, postpartum mania/psychosis within 6 weeks (45.1%, 99% CI 39.3% -51.0%) were overrepresented in the group of women with onset in the postpartum period in comparison to episodes occurring in pregnancy or later than 6 weeks postpartum (34.8%, 99%CI 28.5%-41.6%) - for postpartum depression estimate= -0.60, SE 0.16, t= -3.67, p= 0.0006; for postpartum mania/psychosis estimate= -0.43, SE = 0.16, t= -2.67, p= 0.0090. I used logistic regression to model the association between perinatal onset and a set of explanatory variables, always including age at impairment as covariate. Women with RMD reported a significantly greater proportion of first PNEs representing the first lifetime episode (estimate: -0.41, SE: 0.13, z: -3.08, p=0.0020), than women with BD-I, while there were no differences across the bipolar spectrum (estimate:0.12, SE: 0.15, z=0.82, p= 0.4094). However, the difference across mood disorder spectrum was no longer significant in the multivariate model including age at first episode and age at first pregnancy as covariates.

If childbirth does not represent a specific trigger, the age at the first exposure (age at first full term delivery) should be similar in the group with a recurrence in the perinatal period and in the group with a first episode in the perinatal period. Women who have the first child later in their life have a longer period at risk of developing a mood disorder before becoming mothers than those who have their first child at a younger age. So, I expected that age at first pregnancy was inversely correlated with the probability of having a perinatal onset of illness. However, in the current sample older primiparae had a greater probability of a perinatal onset than younger primiparae. Age at first pregnancy was positively associated with the probability of having the first lifetime episode in relation to childbirth (estimate=0.02, SE= 0.01, t=3.17, p= 0.0017). The association between age and the probability of having a perinatal onset of illness was significant for postpartum mania or psychosis within 6 weeks (estimate= 0.05, SE= 0.02, t= 2.78, p=0.0054 - figure 8.8, part A) and there was a trend toward significance for depression within 6 weeks postpartum (estimate=0.02, SE=0.01, t= 2.28, p= 0.0228, figure 8.8, part B).

In summary, about 1 in 2 women with a history of mood episodes within 6 weeks postpartum, reported the onset of the mood disorder in the postpartum period. Women in which the first manifestation of the mood disorder was postpartum mania or psychosis were older than those in which postpartum mania or psychosis was a recurrence. This finding may support the hypothesis that childbirth acts as a specific trigger for mood disorders in a subgroup of women in which the first life-time episode occurred in the postpartum period.
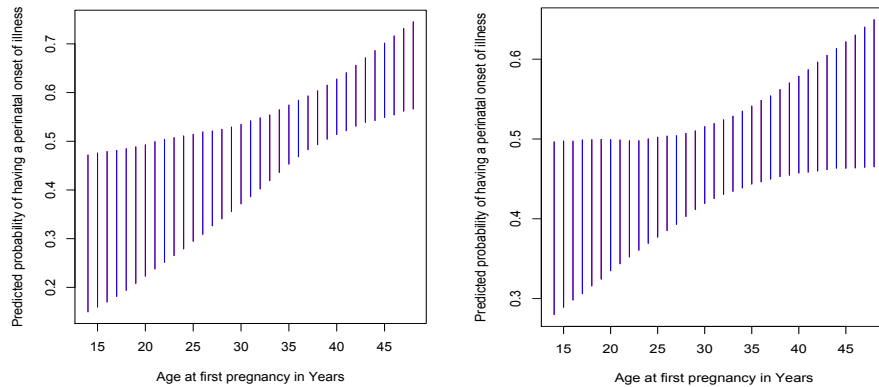
(a) Mania, mixed episode or psychosis within 6 weeks postpartum

(b) Depression within 6weeks postpartum

Figure 8.8: Probability of having a perinatal onset of illness as a function of age at first pregnancy resulting in a live birth. Part A. Probability of having a manic, mixed or psychotic episode within 6 weeks postpartum as first episode (estimate= 0.05, SE= 0.02, t= 2.78, p=0.0054) Part B. Probability of having a major depressive episode within 6 weeks postpartum as first episode (estimate=0.02, SE=0.01, t= 2.28, p= 0.0228). Vertical bars represent simulated confidence intervals for predicted probability of having a perinatal onset of illness over a specified range of one explanatory variable (age at first pregnancy resulting in a live birth between 14 and 50 years of age) [168]. I used the function `plot.ci` in the package`Zelig` to produce the graph.

8.2   Course

Analyses were performed separately for women with a lifetime history of post-partum psychosis or mania or mixed episodes within 6 weeks and BD-I and for those with non psychotic depression within 6 weeks of delivery. I excluded episodes occurring in pregnancy or later in the postpartum or psychotic episodes in BD-II and RMD because of the small samples in these subgroups. As I wanted to explore the longitudinal course of illness, I included in my analyses only women with at least 2 live births and who had the first mood episode at least 5 years before the assessment by the Mood Disorder Research Group. I used a very conservative approach and the Wilcoxon signed rank test to compare the rates of episodes that occurred within 6 weeks after delivery with the rates

of lifetime episodes/YEAR in a subsample of women who suffer with at least one postpartum episode of mania, psychosis or mixed or major depression. I conducted 2 independent tests for each diagnostic subgroup, so I used a p value threshold for significance of p=0.05/2=0.025.

8.2.1 Postpartum psychosis in bipolar I disorder

I use here the term postpartum psychosis to label episodes of DSM-IV mania or psychotic depression with onset within 6 weeks postpartum. 239 women met the inclusion criteria (BD-I, at least one episode of postpartum psychosis, at least two live births, and at least 5 years of observations after the first mood episode). The mean period of observation was 25.2 years (SD 11.82 years). The rates of missingness for each variable inputed are listed in table 8.2, while graphical diagnostics to inspect the imputations are presented on figures 8.9 and 8.10. Because the variable 'total number of lifetime episodes' was not normally distributed, I transformed it using the natural logarithm.

Table 8.2: Fraction missing for individual variables for the analyses on bipolar I postpartum psychosis and course of illness

VARIABLE	FRACTION MISSING
ID	no missing
First episode postpartum psychosis?	0.04
Age at first live birth	0.81
Total number of episodes lifetime	0.10
Total number of postpartum episodes	0.03
Deliveries	no missing
Age at impairment	no missing
Age at first postnatal episode	0.89
Age at interview	no missing
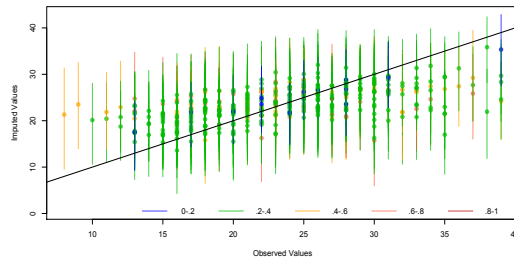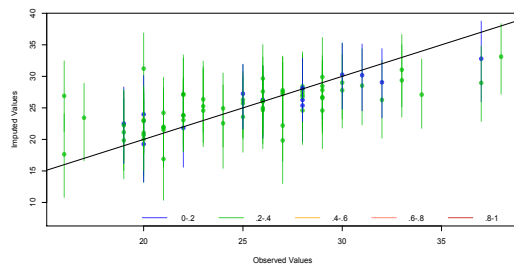
(a) Age at impairment

(b) Age at first pregnancy
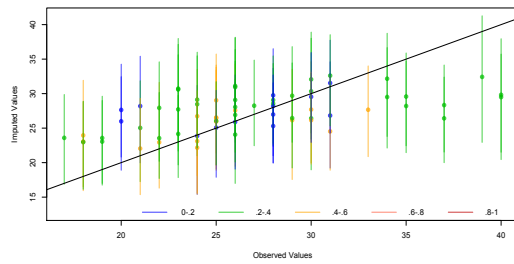
(c) Age at first postpartum episode
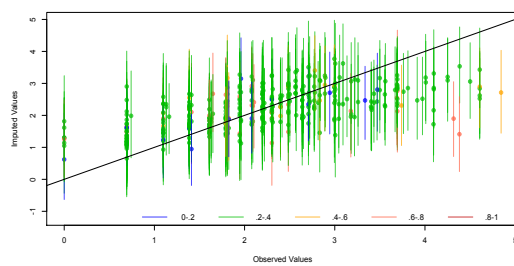
(d) Log(total number of lifetime episodes)

Figure 8.9: Overimputation diagnostic graphs for multiple imputations for bipolar I postpartum psychosis in relation to lifetime course. The majority of confidence intervals fell on the regression line and there was less than 20-40% of covariates missing for the majority of value imputed.

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Overdispersed Start Values

(a)

Overdispersed Starting Values
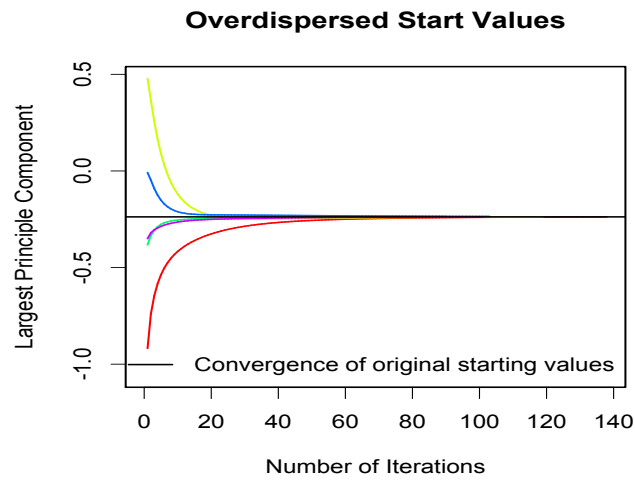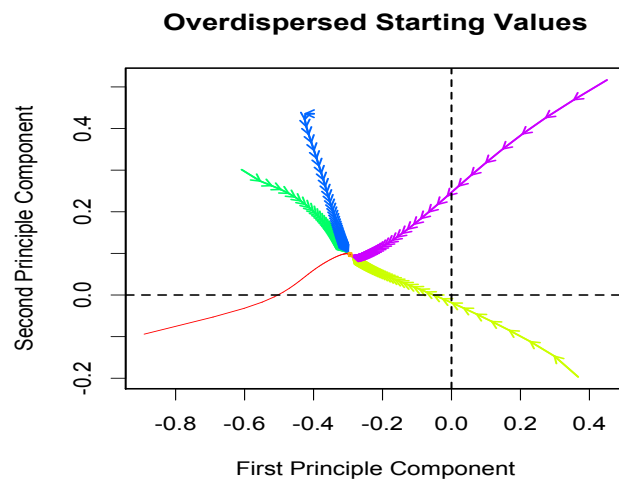
(b)

Figure 8.10: Overdispersion diagnostic plots for multiple imputations for bipolar I postpartum psychosis in relation to lifetime course. EM chains converged. A detailed explanation of overdispersion is provided in chapter 5.

Table 8.3 summarises the distribution of course of illness for each simulation. Although the majority of women (about 58% had a recurrent course with less than an episode every two year, a chronic/highly recurrent course was reported by more than 15% of women).

Table 8.3: Course of illness in women with postpartum mania or psychosis. Only women with BD-I, at least 2 live births and 5 years of observations were included. In each cell count (%). Y:year

Simulation	Chronic	>1 episode/y	1-2 episode/2 yr	< 1 episode/2y
1	3 (1.3)	40(16.9)	54 (22.8)	140 (59.1)
2	3 (1.3)	35 (14.8)	55 (23.2)	144 (60.7)
3	3 (1.3)	37 (15.6)	55 (23.2)	142 (59.9)
4	3 (1.3)	40 (16.9)	58 (24.5)	136 (57.4)
5	3 (1.3)	37 (15.6)	61(25.7)	136 (57.4)

The proportions of deliveries affected by postpartum psychosis or mania in women with a history of postpartum psychosis are listed in table 8.4.

Table 8.4: Proportion of live births affected by postpartum psychosis in women with BD-I and a history of postpartum psychosis

Proportion of deliveries affected	N	%	99%CI
1/6	1	< 0.1	< 0.1− < 0.1
1/4	8	3.3	1.1-7.6
1/3	20	8.4	4.4-14.1
2/5	13	0.7	< 0.1-3.2
1/2	92	38.5	30.1-46.5
3/5	1	< 0.1	< 0.1− < 0.1
2/3	10	4.2	1.6-8.7
3/4	1	< 0.1	< 0.1− < 0.1
4/5	1	< 0.1	< 0.1− < 0.1
1	101	42.3	34.4-51.2

Including any type of PNE (the concordance between PNEs occurring in the same woman is the subject of investigation in the next section) 19.7% of multiparae with a history of postpartum mania/psychosis had all deliveries affected and less than 1 recurrence every 2 years. I compared with the Wilcoxon test the proportion of live birth affected by mood episodes within 6 weeks postpartum with the episodes per YEAR of illness. This approach was highly conservative, because I used a 6 weeks denominator versus a one year denominator. However, episodes in the postpartum period were significantly overrepresented in comparison to episodes outside the perinatal period in multiparae with BD-I and a history of postpartum psychosis ($p < 0.0001$ in any stimulation).

8.2.2   Postpartum depression in bipolar I disorder

166 women met the inclusion criteria (BD-I, at least one episode of non psychotic within 6 weeks postpartum, at least two live births, and at least 5 years of observations after the first mood episode).The mean period of observation was 28.7 years (SD 11.49 years). The rates of missingness for each variable imputed are listed in table 8.5, while graphical diagnostics to inspect the imputations are presented on figure 8.11 and 8.12. Because the variable *total number of lifetime episodes* was not normally distributed, I transformed it using the natural logarithm.

Table 8.5: Fraction missing for individual variables for the analyses on bipolar I non psychotic depression and course of illness

VARIABLE	FRACTION MISSING
ID	no missing
First episode postpartum psychosis?	0.14
Age at first live birth	0.65
Total number of episodes lifetime	0.06
Total number of postpartum episodes	0.11
Deliveries	no missing
Age at impairment	no missing
Age at first postnatal episode	0.83
Age at interview	no missing
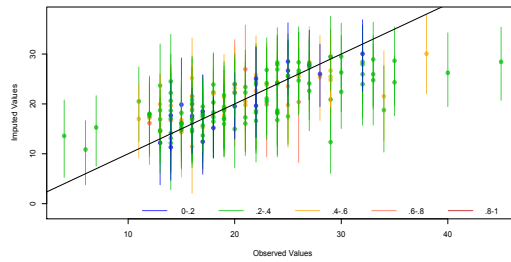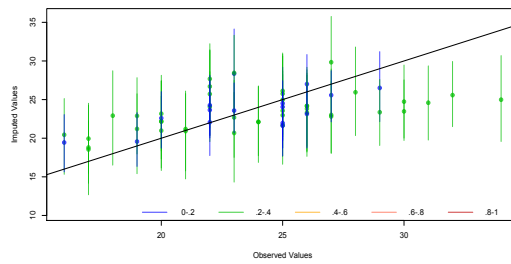
(a) Age at impairment

(b) Age at first pregnancy
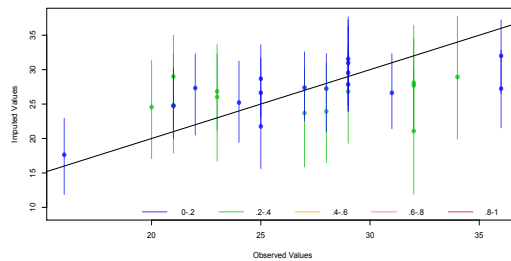
(c) Age at first postpartum episode
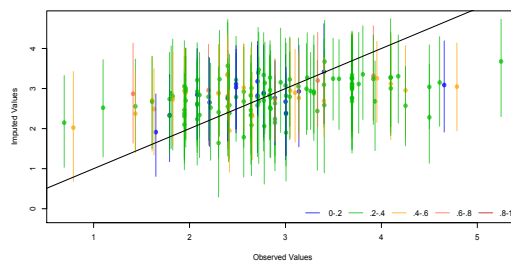
(d) Log(total number of lifetime episodes)

Figure 8.11: Overimputation diagnostic graphs for the analyses on bipolar I non psychotic depression and course of illness. The majority of confidence intervals fell on the regression line and there was less than 20-40% of covariates missing for the majority of value imputed.

(a)

(b)
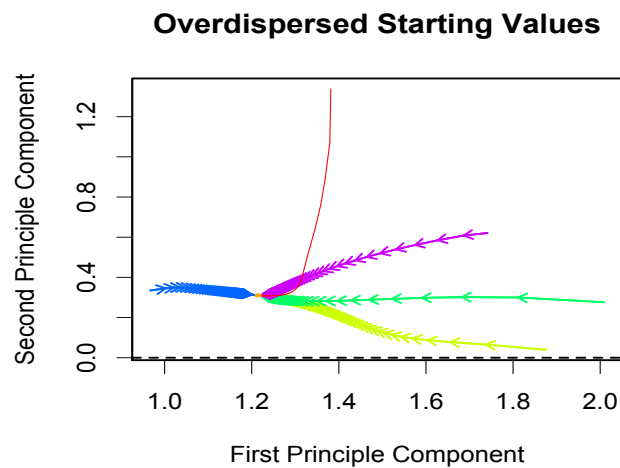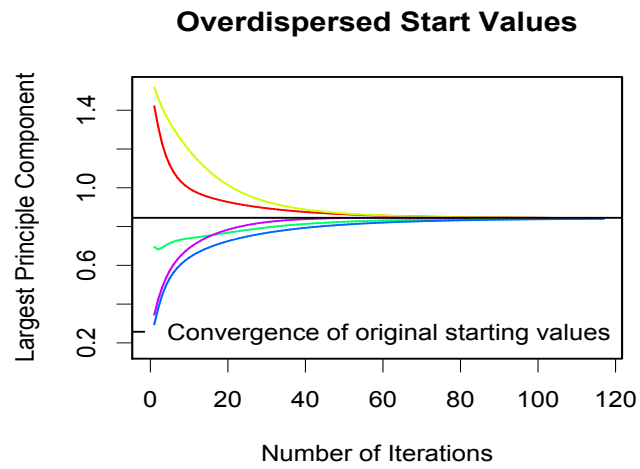
Figure 8.12: Overdispersion diagnostic plots for the analyses on bipolar I non psychotic depression and course of illness. EM chains converged.

Table 8.6 summarises the distribution of course of illness for each simulation. Compared to what I reported for postpartum mania/psychosis, a recurrent course with less than an episode in 2 years was reported by less than 40% of multiparae with a history of bipolar I non psychotic depression. On the contrary, about 1 in 4 women reported a chronic/highly recurrent course.

Table 8.6: Course of illness in women with postpartum bipolar I non psychotic depression. Only women with BD-I, a lifetime history of postpartum non psychotic depression, but not postpartum mania/psychosis, at least 2 live births and 5 years of observations were included. In each cell count (%), y:year

Simulation	chronic	>1 episode/y	1-2 episode/2y	< 1 episode/2y
1	4 (2.4)	41(24.7)	59 (35.5)	62(37.3)
2	4 (2.4)	40(24.1)	57 (34.3)	65 (39.1)
3	4 (2.4)	42 (25.3)	57 (34.3)	63 (37.9)
4	4 (2.4)	42 (25.3)	56 (33.7)	64 (38.5)
5	4 (2.4)	43 (25.9)	57 (34.3)	62 (37.3)

The proportions of deliveries affected by postpartum non psychotic bipolar I depression in multiparae with a history of postpartum non psychotic bipolar I depression are listed in table 8.7.

Table 8.7: Proportion of live births with postpartum non psychotic bipolar I depression in multiparae with a history of postpartum non psychotic bipolar I depression

Proportion of deliveries affected	N	%	99%CI
1/6	1	0.6	$< 0.1 - 6.4$
1/5	2	1.2	$< 0.1 - 7.9$
1/4	9	5.4	3.9-19.1
1/3	23	13.8	4.4-14.1
2/5	2	0.7	< 0.1-3.2
1/2	60	36.1	26.8-46.3
3/5	1	0.6	$< 0.1 - 6.4$
2/3	14	8.4	3.8-15.5
3/4	3	1.8	$< 0.1 - 6.5$
4/5	1	0.6	$< 0.1 - 6.4$
1	50	30.1	21.3-40.1

Only 15/166 (9.0%) of multiparae with a history of postpartum bipolar I non psychotic depression had all deliveries affected and less than 1 recurrence every 2 years. As above for postpartum psychosis, I compared with the Wilcoxon test the proportion of live birth affected by non psychotic depression within 6 weeks postpartum with the episodes per YEAR of illness. There were no differences between the rates of episodes occurring in the postpartum period and those of episodes outside the postpartum period in multiparae with BD-I and a history of

postpartum non psychotic depression, but not psychosis/mania ($W < 12394.5$, $p > 0.112$ in any stimulation).

8.2.3 Postpartum non psychotic bipolar II depression

88 women met the inclusion criteria (BD-II, at least one episode of postpartum depression within 6 weeks, at least two live births, and at least 5 years of observations after the first mood episode). The mean period of observation was 27.6 years (SD 11.32). The rates of missingness for each variable inputed are listed in table 8.8, while graphical diagnostics to inspect the imputations are presented on figure 8.13 and 8.14. Because the variable *total number of lifetime episodes* was not normally distributed, I transformed it using the natural logarithm.

Table 8.8: Fraction missing for individual variables for the analyses on postpartum bipolar II depression and course of illness

VARIABLE	FRACTION MISSING
ID	no missing
First episode postpartum psychosis?	0.06
Total number of episodes lifetime	0.09
Total number of postpartum episodes	0.06
Deliveries	no missing
Age at impairment	no missing
Age at interview	no missing
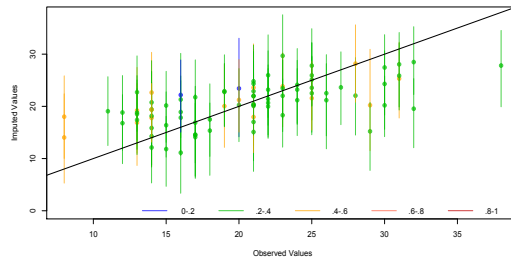
(a) Age at impairment
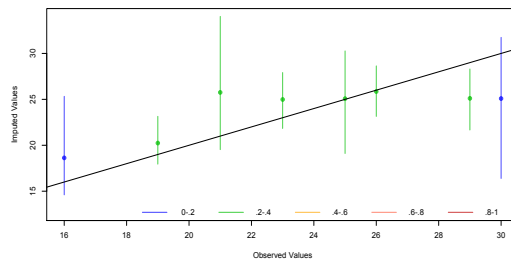
(b) Age at first pregnancy
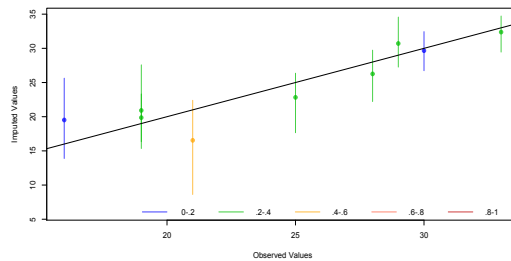
(c) Age at first postpartum episode
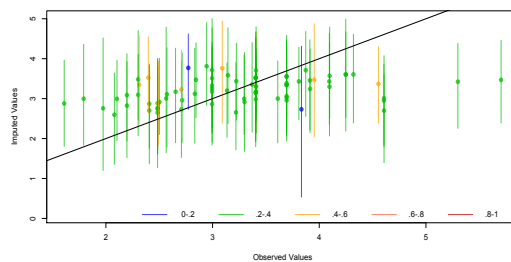
(d) Log(total number of lifetime episodes)

Figure 8.13: Overimputation diagnostic graphs for postpartum non psychotic bipolar II depression. Although I report here the graphs also for age at first live birth and age at first perinatal episode, these variables were dropped from the final model because of overdispersion (see figure 8.14)

146

Overdispersed Starting Values

(a)

Overdispersed Start Values

(b)

Overdispersed Starting Values
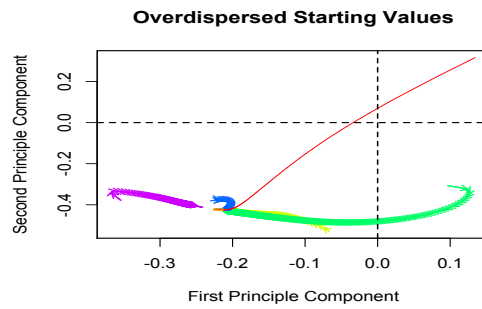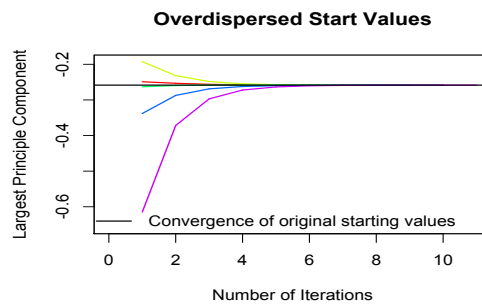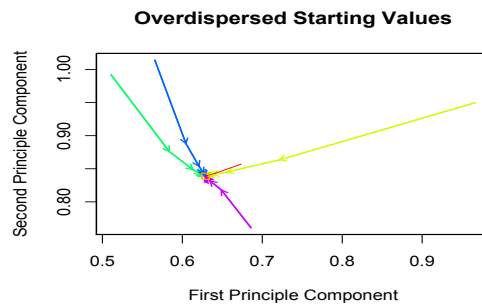
(c)

Figure 8.14: Overdispersion diagnostic plots for multiple imputations for bipolar II non psychotic depression. First I run multiple imputations on a model including age at first live birth and age at first perinatal episode. However, in one of the two overdispersion diagnostic plots the EM chains were not completely converging (part A), so I preferred to drop age at first birth and age at first perinatal episode from the model (part B and C).

Table 8.9 summarises the distribution of course of illness for each simulation.The

distribution of the course patterns was different from that observed for BD-I (especially for women who suffered with postpartum mania/psychosis). The majority of multiparae with BD-II (52.3%) had a chronic course and less than 1/5 (19.3%) reported less than 1 episode/ 2 years of illness.

Table 8.9: Course of illness in women with bipolar II depression within 6 weeks postpartum. Only women with BD-II, at least 2 live births and 5 years of observations were included. In each cell count (%), y:year

Simulation	Chronic	>1 episode/y	1-2 episode/2y	< 1 episode/2y
1	13 (14.8)	33(37.5)	25 (28.4)	17 (19.3)
2	13 (14.8)	33 (37.5)	25 (28.4)	17(19.3)
3	14 (15.9)	32 (36.4)	25 (28.4)	17 (19.3)
4	14 (15.9)	32 (36.4)	25 (28.4)	17 (19.3)
5	14 (15.9)	32 (36.4)	25 (28.4)	17 (19.3)

The proportions of deliveries affected by bipolar II depression within 6 weeks of delivery in multiparae with a history of bipolar II depression within 6 weeks are listed in table 8.10.

Table 8.10: Proportion of live births affected by bipolar II depression within 6 weeks of delivery in multiparae with a history of bipolar II depression within 6 weeks

Proportion of deliveries affected	N	%	99%CI
1/6	1	1.1	< 0.1-8.2
1/5	1	1.1	< 0.1-8.2
1/4	2	2.3	0.1-10.2
1/3	9	10.3	3.7-21.5
1/2	40	46.0	32.2-60.2
3/5	1	1.1	< 0.1-8.2
2/3	8	9.2	3.0-20.1
1	25	28.4	17.1-42.7

As for lifetime course, in multiparae with bipolar II postpartum depression the distribution of live birth delivery affected differed from that in postpartum mania/psychosis and postpartum bipolar I depression, with only 7.9% of women having all deliveries affected and less than 1 recurrence every 2 years. Episodes in the postpartum period were *under*represented in comparison to episodes outside the perinatal period ($W > 1994$ and $p < 0.0001$ in any stimulation).

8.2.4 Postpartum non psychotic depression in recurrent major depression

154 women met the inclusion criteria (RMD, at least one episode of postpartum depression within 6 weeks, at least two live births, and at least 5 years of observations after the first mood episode).The mean period of observation was 24.1 years (SD 11.73). The rates of missingness for each variable inputed are listed in table 8.11, while graphical diagnostics to inspect the imputations are presented on figure 8.15 and 8.16. Because the variable *total number of lifetime episodes* was not normally distributed, I transformed it using the natural logarithm.

Table 8.11: Fraction Missing for individual variables for the analyses on postpartum unipolar depression and course of illness

VARIABLE	FRACTION MISSING
ID	no missing
First episode postpartum psychosis?	0.03896104
Age at first delivery	0.08441558
Total number of episodes lifetime	0.02597403
Total number of postpartum episodes	0.03896104
Deliveries	no missing
Age at impairment	no missing
Age at interview	no missing
Age at first perinatal impairment	0.90909091
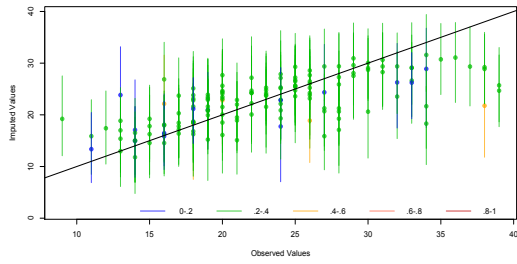
(a) Age at impairment
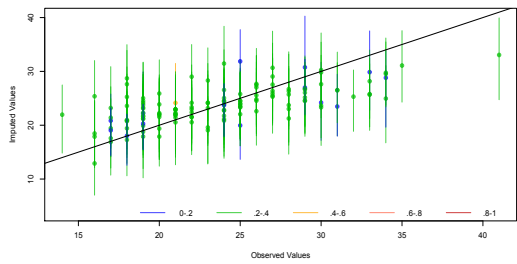
(b) Age at first pregnancy
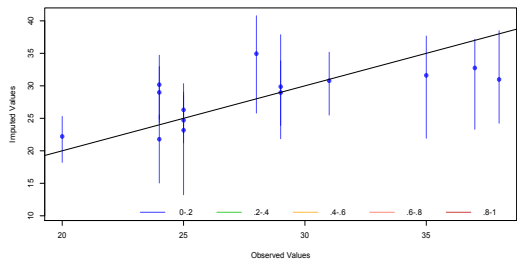
(c) Age at first postpartum episode
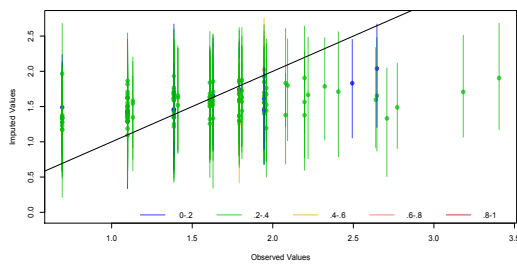
(d) Log(total number of lifetime episodes)

Figure 8.15: Overimputation diagnostic graphs for postpartum non psychotic depression in RMD. The majority of confidence intervals fell on the regression line and there was less than 20-40% of covariates missing for the majority of value imputed.

Overdispersed Start Values

(a)

Overdispersed Starting Values
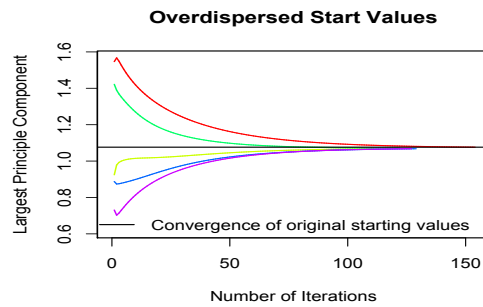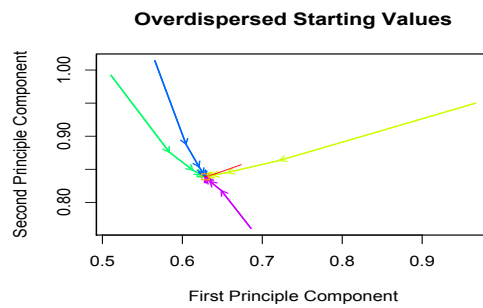
(b)

Figure 8.16: Overdispersion diagnostic plots for multiple imputations for non psychotic depression in RMD. EM chains converged. See chapter 5 for details

Table 8.12 summarises the distribution of course of illness for each simulation. There were no cases of chronic course and only one woman reported more than 1 episode/year of illness. The vast majority of multiparae with RMD (90%), reported less than 1 episode/ 2 years of illness.

Table 8.12: Course of illness in women with RMD and history of non psychotic postpartum depression. Only women with RMD, at least 2 live births and 5 years of observations were included. In each cell count (%), y:year

Simulation	Chronic	>1 episode/y	1-2 episode/2y	< 1 episode/2y
1	-	1	137 (89.5)	15 (9.8)
2	-	1	138 (90.2)	14(9.1)
3	-	1	138 (90.2)	14(9.1)
4	-	1	138 (90.2)	14(9.1)
5	-	1	138 (90.2)	14(9.1)

The proportions of deliveries affected by postpartum non psychotic depression

in women with a history of RMD and non psychotic postpartum depression are listed in table 8.12.

Table 8.13: Proportion of live birth affected by non psychotic depression within 6 weeks of delivery in multiparae with a history of bipolar II depression within 6 weeks

Proportion of deliveries affected	N	%	99%CI
1/6	2	1.3	< 0.1-5.9
1/5	2	1.3	< 0.1-5.9
1/4	9	5.8	2.1-12.5
1/3	24	15.6	8.9-24.5
2/5	2	1.3	< 0.1-5.9
1/2	55	35.7	26.0-46.3
2/3	12	7.8	3.3-15.1
3/4	2	1.3	< 0.1-5.9
1	46	30.0	20.8-40.2

(26%) of multiparae with RMD had all deliveries affected and less than 1 recurrence every 2 years. Episodes in the postpartum period were overrepresented in comparison to episodes outside the perinatal period ($W > 20895$ and $p < 0.0001$ in any stimulation).

8.2.5 Is the postpartum trigger specific for postpartum psychosis/mania?

In this final subsection I report the results on the analyses I conducted on a subsample of 146 women with BD-I, 2 live births, at least one of which affected by postpartum mania/psychosis within 6 weeks. I sought to estimate i) how many women had both deliveries affected and ii) how many of these women had both deliveries affected by psychosis/mania within 6 weeks postpartum.
I conducted 2 independent tests, so I considered a p value threshold for significance of p=0.05/2=0.025.
The rates of missingness for each variable inputed are listed in table 8.14, while graphical diagnostics to inspect the imputations are presented on figure 8.17. I did not perform overimputations because time to onset of episode was coded as a categorical variable (assuming values: in pregnancy, within 6 weeks postpartum, later in the postpartum).

Table 8.14: Fraction missing for individual variables for the analyses on recurrences of postpartum mania/psychosis. Unaffected births are included (and counted as missing for time to onsets)

VARIABLE	FRACTION MISSING
ID	no missing
Total number of postpartum episodes	0.02
Time to onset of first perinatal episodes	0.260
Time to onset of seconds perinatal episodes	0.34
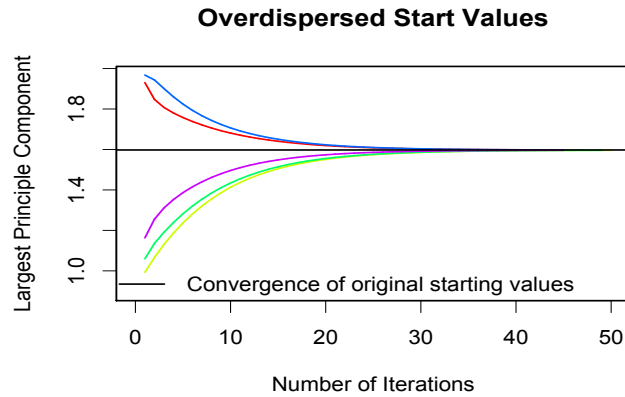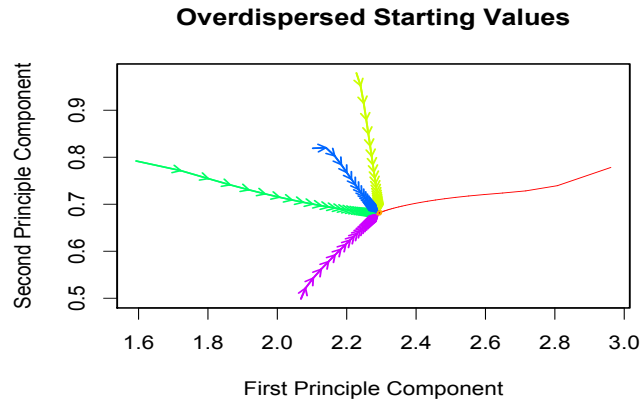
Figure 8.17: Overdispersion diagnostic plots for multiple imputations for the correlation between PNEs. EM chains converged.

68/128 women had both perinatal period affected by a mood episode. There were significantly more episodes of postpartum mania/psychosis following the first delivery (98/128-76.6%) than the second one(78/128-60.9%)- (McNemar's $\chi^2 = 20.45$, df $= 1$, p$= < 0.0001$, OR 2.1, 99%CI 1.00-4.47). 48 women (37.5% of the total 128 women and 70.6% of the 68 with both perinatal period affected by a mood episode) had both live births affected by postpartum mania/psychosis within 6 weeks. 20 women (20/128=15.6%, 20/68=29.4%) had one episodes of postpartum mania/psychosis and one episode of any other mood disorder in pregnancy or within 6 months postpartum. I used the test of proportion and found that the proportion of women of having both episodes affected by

mania and psychosis was significantly higher than the proportion of women who had one episode of postpartum mania/psychosis and one episode of any broadly defined perinatal disorder (70.6%, 99%CI 54.29 %-83.00%, $\chi^2 = 10.72$, df = 1, p = 0.0011,)

8.3   Summary

In this chapter I have reported the analyses I conducted on the childbirth trigger of mood episodes in relations to the lifetime course of illness.

Episodes of mania or psychosis within 6 weeks postpartum represented the first episode for about 45% of women who suffered from them. Women who experienced a first mania/psychotic episode within 6 weeks postpartum were significantly older than women who had a postpartum recurrence. The excess of episodes occurring within 6 weeks was not completely explained by the highly recurrent nature of BD-I. There was in particular a subgroup of 1 in 5 multiparae who reported all deliveries affected by a postpartum episodes despite a low number of lifetime recurrences. For 70% of multiparae with BD-I suffering with more than one postpartum recurrence the childbirth was a specific trigger for postpartum psychosis, while 30% of them suffered with an episode of postpartum psychosis after one pregnancy and an episode of postpartum depression after another pregnancy.

Bipolar I non psychotic depression within 6 weeks postpartum , on the contrary, was not overrepresented compared to episodes at other times. Women who reported non psychotic depression within 6 weeks postpartum had a more recurrent pattern on average that those who reported mania and psychosis within 6 weeks postpartum, with about 1 in 2 reporting at least one episode of illness/year. Less than 1 in 10 multiparae reported all deliveries affected despite a low number of lifetime recurrences. It seemed that in the majority of cases bipolar I non psychotic depression occurred in relation to childbirth just by chance and that the relationship childbirth-mood episode is just temporal, and not causal.

For bipolar II non psychotic depression within 6 weeks postpartum I found a similar, but even more pronounced, pattern. Over 50% of women with BD-II, in fact, had a chronic/highly recurrent course of illness with

more that 1 episode a year, while less than 8% reported all deliveries affected despite a low number of lifetime recurrences. There was no association between postpartum period and increased rates of recurrences.

Non psychotic unipolar depression within 6 weeks postpartum had a pattern similar to postpartum mania/psychosis in BD-I: about 1 in 2 women reported the onset of the depressive disorder in the postpartum period and postpartum episodes were overrepresented compared to episode outside the postpartum period.

Chapter 9

Parity: a clue to the aetiology of the postpartum trigger

"The study of the thing caused must precede the study of the cause of the thing."

Hughlings Jackson, in Brockington [77]

Understanding the childbirth triggering of severe mood episodes is of vital importance. An intriguing clue that may help in this task is the greater risk following first pregnancies that has been shown in a number of previous studies [93,169–172]. This has implications, not only for the identification of women at risk, but also for the aetiology of PNEs. The link to primiparity may suggest relationships with other pregnancy related disorders such as pre-eclampsia in which parity is known to play an important role and lead to specific hypotheses about the nature of the perinatal trigger.

In both register based [169,170] and clinical studies [80,93,171,172] postpartum psychosis has been shown to be more common after first deliveries. The link between first pregnancy and non-psychotic postpartum depression is more controversial. The majority of studies report no effect of parity [169,173], although one study did find an association with primiparity [174] and another found the opposite effect [113].

A number of methodological issues may influence the results of studies on parity. If women suffering a postpartum episode are less likely to go on to have further children, this will reduce rates in multiparae and may account for the association with first pregnancies. Similarly, other demographic and obstetric variables may also explain the excess of psychosis in primiparae. For example, first pregnancies occur at a younger age and delivery by caesarean section has been associated with both primiparity [175] and postpartum psychosis [169]. Another issue is the variability in methodology in studies of postpartum mood disorder. In particular this may account for the heterogeneous results with perinatal depression and parity. There is a lack of consensus on the definition of postpartum depression and it has been argued that parity itself influences the validity of rating scales for perinatal depression [176].

Despite the potential importance of this topic, there is a paucity of large-scale systematic studies on the effect of parity in women with severe mood disorders and with few exceptions [93], the research to date has not considered potential confounders. Moreover, although women with bipolar disorder experience both postnatal depression and postpartum psychosis, no data are available on parity and bipolar depression.

In this chapter I reported the analyses I conducted to explore the link between parity and PNEs. I tested the hypothesis that the risk of perinatal mood episodes is greater following first pregnancies and ask whether this association: (i) holds across the mood disorder spectrum (BD-I, BD-II and RMD); (ii) is found for both episodes of high and low mood; (iii) applies to all perinatal episodes or is limited to those with onset in the immediate postpartum; and finally (iv) I investigated the impact of possible confounders, such as decisions about having further children, age at pregnancy and method of delivery.

9.1 Methods

Recruitment and assessment of participants have been already described in chapter 5. Figure 9.1 summarised the sample selection and the relationship between samples.
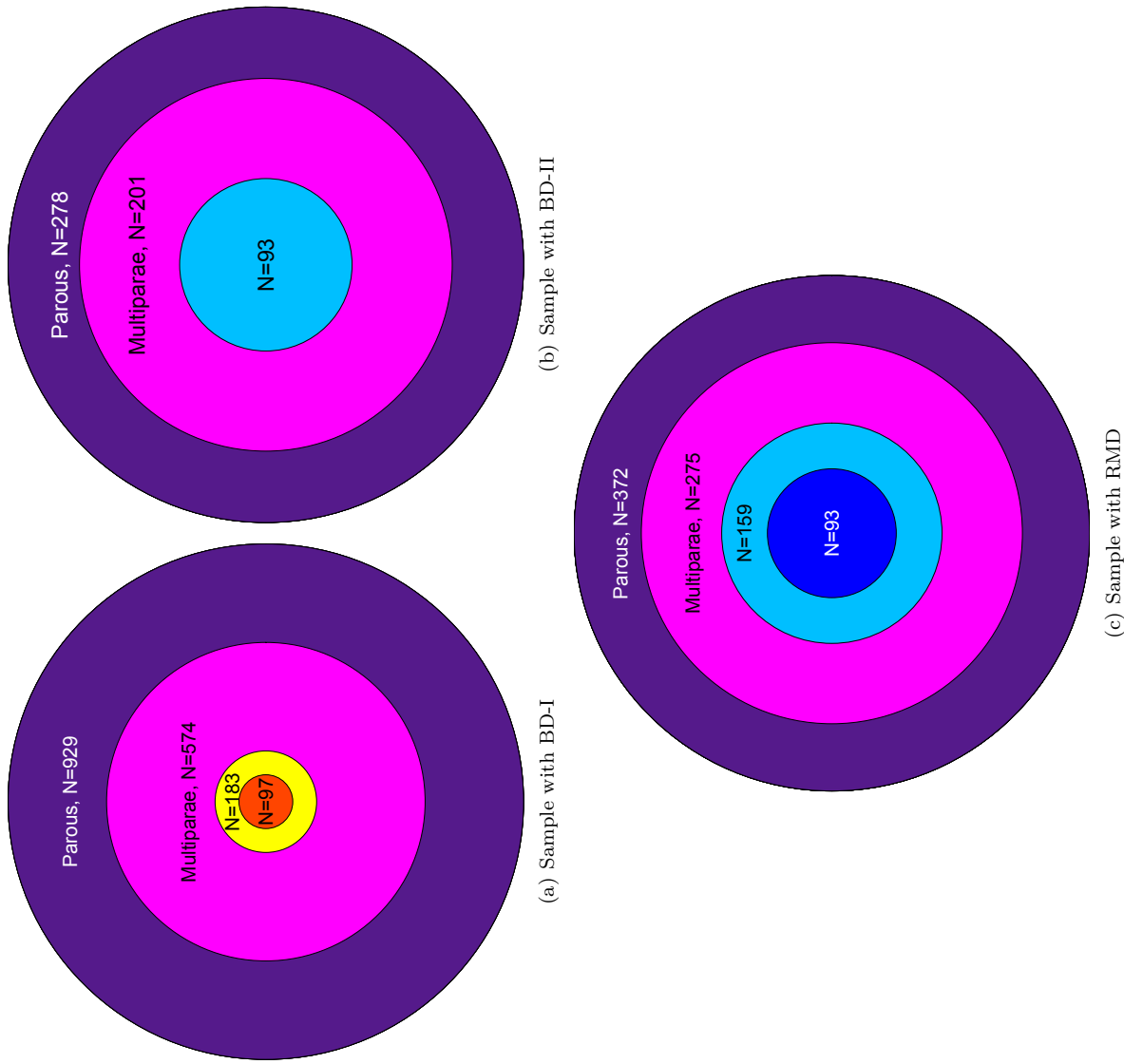
Figure 9.1: Samples selected for the different analytic stages. Parous women with pregnancy by pregnancy ratings were initially included (purple). Subsequent analyses were restricted to multiparous (magenta) with first or second pregnancy affected by mania/psychotic depression in the BD-I sample (yellow) or by non psychotic depression in BD-II and RMD (pale blues). Further analyses where conducted only in the subgroups of women with BD-I (orange) or RMD (blue) who had their first lifetime episode within 6 weeks postpartum. Women with BD-II were excluded from this stage of analysis, because episodes of bipolar II depression were not associated with parity (see result section)

9.1.1 Analytic plan

1. First, I conducted some exploratory data analyses on the entire sample.

   - I explored graphically the association between parity and mood disorders across lifetime diagnoses and phenomenology of PNEs (mania/psychotic depression and non psychotic depression).

   - I explored the influence of potential biases such as:

     - The association between psychiatric outcome of first pregnancies and the proportion of women going on to have further children. It was, in fact, possible that any association between PNEs and primiparity was due to women who suffer severe postpartum episodes deciding not to have further children;

     - Age at pregnancy;

     - Caesarean section

2. To exclude the potential effect of the psychiatric outcome of first pregnancies on reproductive decisions, I compared the rates of mood episodes in the first perinatal period with the rates of mood episodes in the second perinatal period in a subsample of women who were (a) multiparous and (b) had experienced at least one delivery affected by a mood episode. I performed the analyses on 3 mutually exclusive groups of onset: onset in pregnancy, onset within 6 weeks postpartum, onset between 6 weeks and 6 months postpartum. Information on time of onset of PNEs was available for 90% of deliveries affected, so I used the package `Amelia` to perform multiple imputations and the package `Zelig` [162] to analyse the multiple datasets (see chapter 5 for more details on dealing with missing values). Overdispersion diagnostic plots for multiple imputations are shown in figure 9.2.

3. Pregnant women with established mood disorder may be aware of the risk of recurrence and take medication to prevent or promptly treat an emerging postpartum episode. A reduced risk in multiparae may therefore be due to the effects of prophylactic medication or other strategies designed to help keep women well. I did not have detailed information on the drug
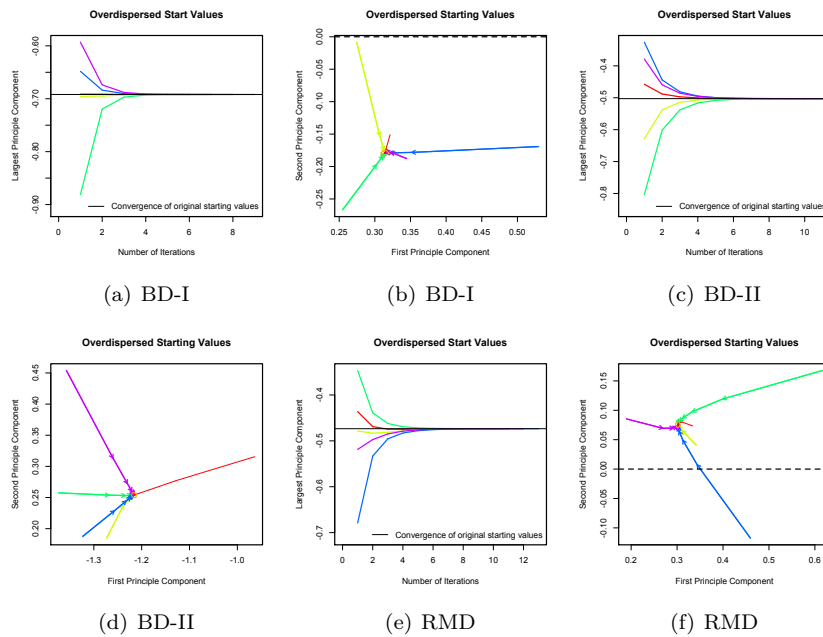
Figure 9.2: Overdispersion diagnostic plots in the analyses on parity. On the left: The x- axis represents the iteration number of the chain. The y-axis represents movement in the (very high dimensional) parameter space. On the right: Two dimensional parameter space using the first two principal components of the end points of the EM chains. The distance between iterations is marked by the distance between arrowheads on each chain. The EM chains converged

management of the women in subsequent pregnancies but to examine this bias I re-ran the significant analyses including only multiparae who reported their first lifetime episode in relation to childbirth. In fact, these women were drug naïve at the onset of the first postpartum episode by definition.

In this chapter I use the term postpartum psychosis to label episodes of DSM-IV mania, mixed episodes or psychotic depression occurring within 6 weeks after childbirth. I performed 4 sets of independent comparison, so I considered a p value threshold for significance of p=0.05/4=0.0125.

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9.2 Results

9.2.1 Sample characteristics

Detailed information was collected for 3174 full term deliveries from 1579 participants, 929 with BD-I, 278 with BD-II and 372 with RMD. Sample characteristics are summarised in table 9.1. The morbidity rates I report here exceeded to some extent the figures reported in chapter 6, which focused on the prevalence of PNEs and therefore excluded women recruited on the basis of a history of postnatal psychosis or depression. In the analyses I present in this chapter, instead, I included also women specifically recruited to the studies on postpartum psychosis and postnatal depression, where an inclusion criterion was a history of postnatal psychosis or depression and thus the rates of postnatal psychosis or depression were 100%.

9.2.2 Parity

Data were available for 1579 first and 1595 subsequent pregnancies. In the BD-I group, 304 (32.7%) women reported an episode of mania/psychotic depression in the first perinatal period. The proportion dropped to 19.3% (109/566) in the second perinatal period and to 14.7% (30/204) and 14.8% (12/81) in the subsequent pregnancies (figure 9.2A). Women with BD-I reported similar rates of perinatal depression across all perinatal periods (range 21.0%-23.5% - figure 9.2B).

Rates of perinatal depression in women with BD-II dropped between the first (45.0%, 125/278) and the second pregnancy (33.0%, 63/191). Large confidence intervals allowed less precise estimates for subsequent pregnancies (figure 9.2C).

An episode of perinatal depression occurred in 47.3% (176/372) primiparae with RMD. The proportion dropped to 38.1% (105/275) in the second perinatal period and to 37.1% (49/132) and 34.0% (16/47) in the following pregnancies (figure 9.2D). I do not report here the estimates on pregnancies affected by depressive psychosis in the BD-II group and in the RMD group because of the low incidence rates (table 9.1).
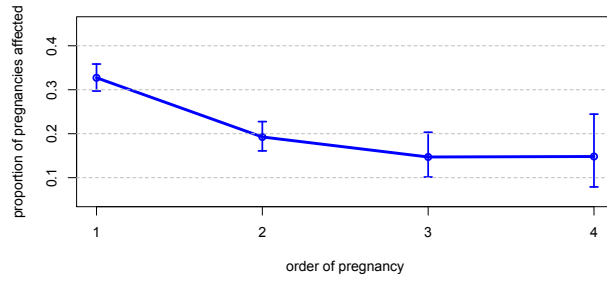
(a) Perinatal mania and psychotic depression in BD-I
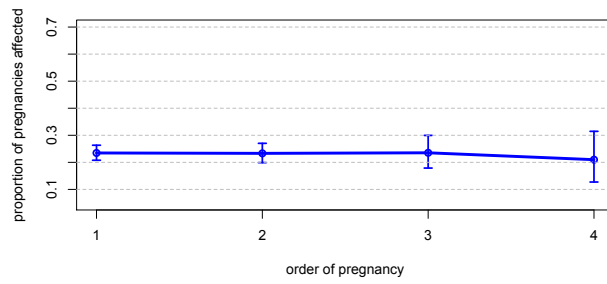
(b) Perinatal depression in BD-I
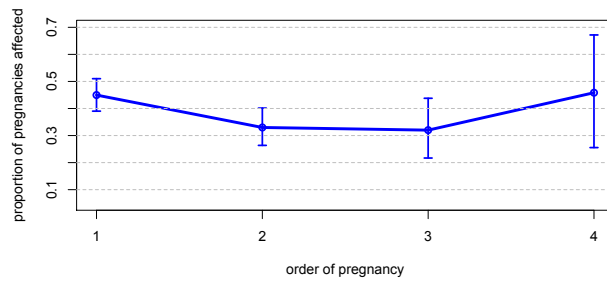
(c) Perinatal depression in BD-II
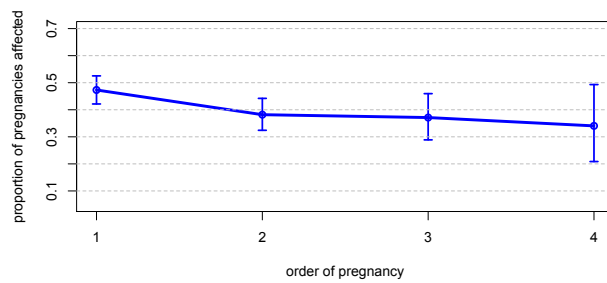
(d) Perinatal depression in RMD

Figure 9.3: Proportion of live births complicated by PNEs by order of delivery

9.2.3 Controlling for the influence of perinatal episodes on having further children

The psychiatric outcome of first pregnancies was significantly associated with the proportion of women going on to have further children (figure 9.3). In the BD-I group, only 56.6% of primiparae with a PNE had further children compared to 76.6% of those who didn't have any PNE (OR: 2.5, 99% CI 1.70-3.72, p< 0.0001). Similarly primiparae with either BD-II or RMD who suffered with a PNE were less likely to have further children (respectively 69.1% v 88.5%, OR: 3.44, 95% CI 1.46-8.81, p< 0.0001 and 70.9% v 87.4%, OR: 2.8, 95%CI 1.39-6.04, p< 0.0001).
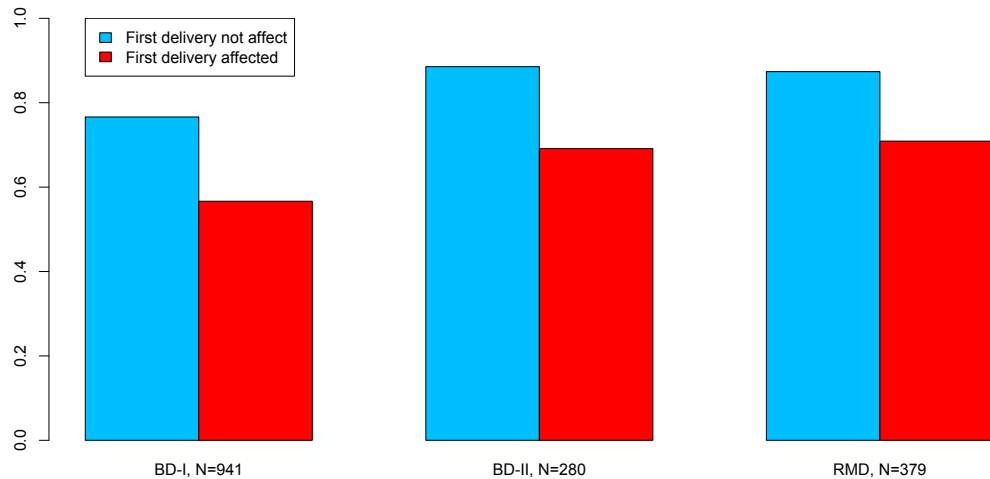
Figure 9.4: Proportion of primiparae going on to have further children according to whether they had a PNE in the first perinatal period or not. On the y axis: proportion

It is therefore possible that any association between perinatal mood episodes and primiparity is due to women who suffer severe postpartum episodes deciding not to have further children. To examine this potential bias, I compared the rates of mood episodes in the first perinatal period with the rates of mood episodes in the second perinatal period in a subsample of women who were (a) multiparous and (b) had experienced at least one delivery affected by a mood episode. Information on onset of episodes occurring in relation to pregnancy and childbirth was categorised into 3 groups: onset in pregnancy, onset within 6 weeks postpartum, onset between 6 weeks and 6 months postpartum.

There were 183 multiparae with BD-I and at least one episode of perinatal mania or psychotic depression. We focused our analysis on episodes occurring with onset within 6 weeks postpartum, as the vast majority (90%) of these episodes occurred within this time frame. Primiparity was significantly associated with mania/ psychotic depression occurring within 6 weeks of delivery (p=0.001, OR 2.1, 99%CI 1.15-3.69). Table 9.2 shows the results of logistic regression model for mania or psychosis within 6 weeks on each one of the 5 multiple data sets, while table 9.3 shows the results for the combined model.

Table 9.2: Separate results of logistic regression model for mania or psychosis within 6 weeks in BD-I on each one of the 5 imputed data sets

Coefficients	Estimate	Standard Error	z values	p value
Intercept	0.10	0.15	0.66	0.5060
Primiparae	0.72	0.22	3.30	0.0009
Intercept	0.10	0.15	0.66	0.5060
Primiparae	0.75	0.22	3.41	0.0006
Intercept	0.08	0.15	0.52	0.6049
Primiparae	0.72	0.22	3.29	0.001
Intercept	0.12	0.15	0.81	0.4164
Primiparae	0.65	0.22	2.98	0.0029
Intercept	0.05	0.15	0.37	0.7117
Primiparae	0.79	0.22	3.61	0.0003

Table 9.3: Combined results of logistic regression model for mania or psychosis within 6 weeks in BD-I on 5 imputed data sets

Coefficients	Value	Standard Error	t-stat	p value
Intercept	0.09	0.15	0.60	0.5513
Primiparae	0.72	0.22	3.21	0.0014

No association between parity and perinatal depression was found in the group of 93 multiparae with BD-II and at least one pregnancy affected by perinatal depression (p=0.137 for depression in pregnancy, p=0.473 for depression within 6 weeks postpartum, p=0.096 for depression occurring between 6 weeks and 6 months postpartum).

In the RMD group (N=159), primiparity was associated with depression with onset within 6 weeks of childbirth (p= 0.004, OR 1.9, 99% CI 1.06-3.52), but not with onset in depression in pregnancy (p=0.653) or later in the postpartum (p=0.447-Figure 9.4). Table 9.4 shows the results of logistic regression model for unipolar depression within 6 weeks on each one of the 5 multiple data sets, while table 9.5 shows the results for the combined model.

Table 9.4: Combined results of logistic regression model for unipolar depression within 6 weeks on 5 imputed data sets

Coefficients	Value	Standard Error	t-stat	p value
Intercept	-0.35	0.16	-2.15	0.0316
Primiparae	0.66	0.23	2.85	0.00443

Table 9.5: Separate results of logistic regression model for unipolar major depression within 6 weeks on each one of the 5 imputed data sets

Coefficients	Estimate	Standard Error	z values	p value
Intercept	0.39	0.16	-2.44	0.0146
Primiparae	0.71	0.23	3.12	0.0019
Intercept	-0.34	0.16	-2.13	0.0331
Primiparae	0.69	0.23	3.01	0.0026
Intercept	0.076	0.15	0.52	0.6049
Primiparae	0.63	0.23	2.79	0.0052
Intercept	-0.32	0.16	-1.97	0.0483
Primiparae	0.61	0.23	2.68	0.0073
Intercept	-0.37	0.16	-2.29	0.0222
Primiparae	0.66	0.23	2.90	0.0037
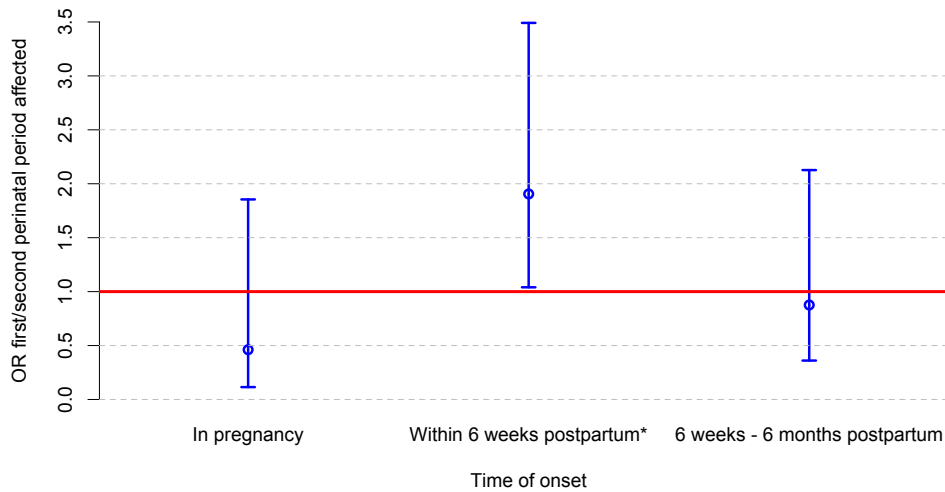
Figure 9.5: Time-to-onset of postpartum mania according to order of pregnancy. ∗ p=0.004

9.2.4   Controlling for the influence of age and Caesarean section

The association between primiparity and severe mood episodes could be mediated by age at pregnancy. If this were true, I would expect women to report a younger age at delivery for pregnancies complicated by psychiatric sequelae. However, there were no age differences between deliveries complicated by postnatal psychosis (mean age at delivery 26.0, sd 4.99), those complicated by postnatal depression (mean age at delivery 26.0, sd 4.94) and those with no psychiatric complications (mean age at delivery 26.0, sd 5.02).

In previous studies, deliveries by Caesarean section were associated with postpartum psychosis. However, in the Mood Disorder Research Project sample method of delivery was not associated with postpartum mania/psychosis in BD-I (p=0.626) or with postpartum non-psychotic depression (p= 0.443).

9.2.5   Controlling for the influence of medication

Another possible factor that could lead to an increased risk in first pregnancies is a history of previous mood episodes having an influence on further pregnancies. Pregnant women with established mood disorder may be aware of the risk of recurrence and take medication to prevent or promptly treat an emerging postpartum episode. A reduced risk in multiparae may therefore be due to the effects of prophylactic medication or other strategies designed to help keep women well. I did not have detailed information on the drug management of the women in subsequent pregnancies but to examine this bias I re-ran the analyses on only multiparae who reported their first lifetime episode in relation to childbirth. By definition, these women were drug naïve at the onset of the first postpartum episode. In both women with BD-I (N=97, p=0.0006, OR: 2.8, 99%CI 1.29-6.28) and RMD (N=93, p=0.005, OR: 2.3, 99%CI 1.08-5.08) I again found an association with first pregnancies. Moreover, I found an increased effect size compared to previous analyses conducted on the entire sample. The effect of parity is, therefore, not due to women taking prophylactic medication.

9.2.6 Are women with an onset in the postpartum a more homogeneous group?

The latter analysis suggest that it is possible that women with an onset of mood disorder in the perinatal period represent a more homogeneous group, especially in relation to the increased risk in first pregnancies. To explore this hypothesis I compared the effect of primiparity in the subgroup of women with an onset within 6 weeks postpartum with the effect in those in which the postnatal episode was a recurrence. I found that the effect of parity on postpartum episodes was driven by the group of women with an onset in the postpartum - for women with BD-I and a recurrence of postpartum psychosis (p=0.248, OR 1.5, 99%CI 0.61-5.08; for RMD and a postnatal recurrence p= 0.104, OR=1.9, 99%CI 0.69-4.98).
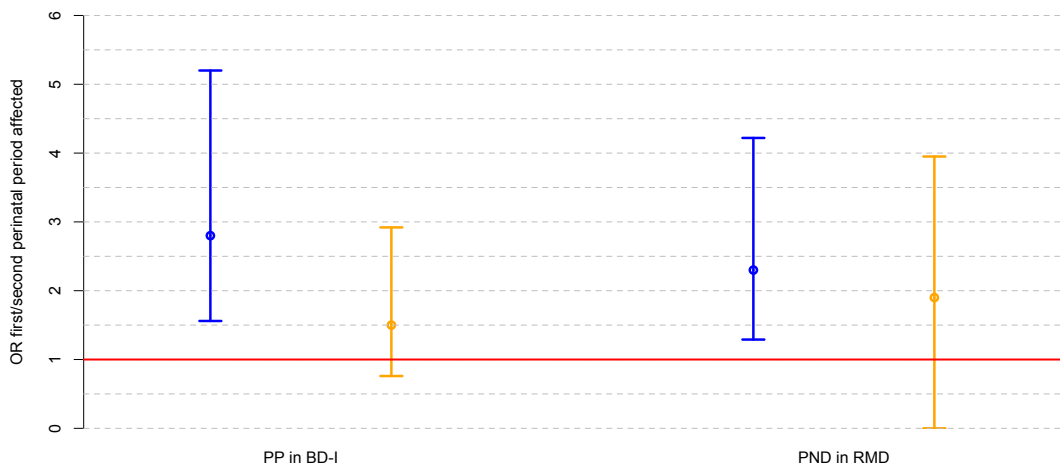
Figure 9.6: Primiparity effect according to lifetime course

To explore possible clinical characteristics that may differ between *first onset* postnatal episodes and *recurrences* in the postpartum, I compared the survival curves for postnatal episodes in women with BD-I and postpartum psychosis and in women with RMD and postnatal depression (figure 9.6). The time of onset of postnatal mania/psychosis did not differ between the two groups. The same analysis was performed including only first live births. Again there were not significant differences between women with postpartum psychosis as first

lifetime episode (N=119) and those in which postpartum psychosis did not represent the first lifetime episode (N=123, χ^2= 1.5 , df= 1, p= 0.217). The time of onset of postnatal psychosis did not differ between the two groups (χ^2= 2.2, df=1, p= 0.135). The same analysis was performed including only first live births. Again there were not significant differences between women with postpartum unipolar depression as first lifetime episode (N=51) and those in which postpartum unipolar depression was a recurrence (N=92, χ^2= 0.6, df=1, p= 0.432)
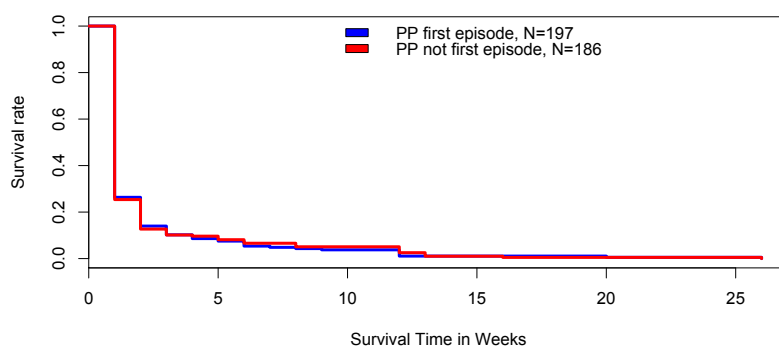
(a) Perinatal mania and psychotic depression in bipolar I disorder
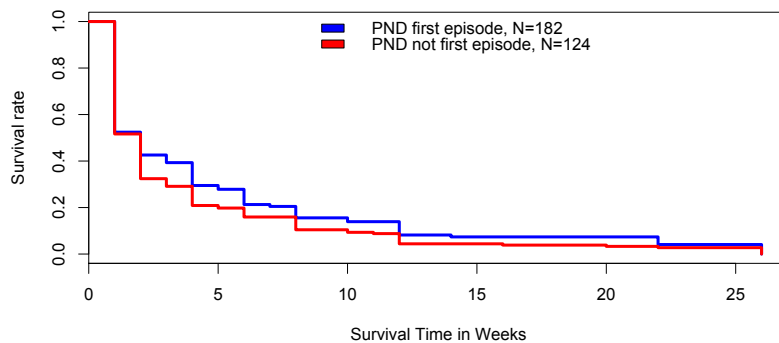
(b) Perinatal depression in bipolar I disorder

Figure 9.7: Survival curves for postpartum episodes according to lifetime course. Part A. Survival curves for postpartum psychosis in women with BD-I and the first lifetime episode in relation to childbirth (blue) and in women with BD-I in which the postpartum episode represented a recurrence (red). Part B. Survival curves for postpartum non-psychotic depression in women with RMD and the first lifetime episode in relation to childbirth (blue) and in women with RMD in which the postpartum episode represented a recurrence (red).

9.3 Summary

In this chapter I explored the link between parity and PNEs.

- The results support previous research findings of an association between primiparity and postpartum psychosis occurring soon after childbirth [93, 169–172].

- In women with BD-I, I found an excess of postpartum psychosis following first deliveries, but no similar link to primiparity for episodes of non-psychotic depression. In contrast I found that there was a greater risk of a postnatal depression following first deliveries in women with RMD. I did not find an effect of parity in women with a lifetime diagnosis of BD-II.

- The association between parity and mood episodes was significant only for episodes occurring within 6 weeks postpartum. Episodes occurring in pregnancy or later in the postpartum did not show a significant association with parity.

- The excess of mood episodes in primiparae was not explained by women with a perinatal episode not going on to have further children, by the age at pregnancy, by method of delivery, or by the use of prophylactic medication in subsequent pregnancies.

Part III

A pilot prospective study on bipolar disorder in pregnancy and the postpartum

Chapter 10

Study design

Prospective design is the gold standard for observational studies. A prospective study on bipolar disorder in pregnancy and postpartum would allow i) an estimation of the risk of perinatal recurrences i) to investigate the influence of a range of variables on the vulnerability to develop an episode of severe illness in pregnancy or the postpartum iii) a detailed description of the episodes occurring during the time of observation. I argued in the background section that there is a paucity of prospective studies on perinatal mood disorders. For these reasons, with the help of the Mood Disorder Research Project team, I set up a prospective study aimed at recruiting a large, well characterised sample of women with bipolar disorder preconception or in early pregnancy and to monitor them through pregnancy and the postpartum. The aims of the full blown prospective study were:

- to establish the proportion of women who suffer a severe episode of psychiatric illness

- to characterise the clinical features of episodes occurring in the postpartum

- to explore the influence of a range of variables on the vulnerability to develop an episode of severe illness in pregnancy or the postpartum

In this chapter I first describe the study design and the research protocol then the ethics procedures, finally I report the research outcomes of the pilot study I conducted between April 2011 and June 2012.

10.1 Study design

The study was designed in 2010 as part of the large Mood Disorder Research Project. When the prospective study of pregnancy was being designed, the Mood Disorder Research Project was committed to recruiting further 4000 individuals with bipolar disorder over a three years period as part of the Bipolar Disorder Research Network project (BDRN - see bdrn.org). I therefore design the study to fit the BDRN research protocol to optimise the resources available. The study had broad inclusion criteria. Women were included if i) they had a diagnosis of bipolar disorder (DSM-IV schizoaffective disorder bipolar-type, BD-I, BD-II, bipolar disorder not otherwise specified) and if ii) they were currently pregnant. Women with bipolar disorder planning a pregnancy were also approached and given information on the study, in case they wanted to take part once pregnant.

The algorithm followed by the study is presented on figure 10.1.

10.1.1 Recruitment

The BDRN project has been very successful in recruiting people with bipolar disorder. However, the proportion of participants who were pregnant at the interview was limited to sporadic cases. Moreover, recruitment of pregnant women with severe mental disorders such as bipolar disorder is particularly challenging [177]. So, additional recruitment strategies were developed specifically to enhance the chances of recruiting pregnant women.

BDRN Modified telephone screening Women below 45 years of age who were willing to take part in the BDRN study were asked whether they were pregnant or planning a pregnancy.

CUPS- Second Opinion Clinic at Cardiff University Dr Ian Jones provides second opinions in the form of single consultations including specialised information and counselling relating to the relationship of psychiatric illness to childbirth - see http://medicine.cf.ac.uk/psychological-medicine-neuroscience/cups/perinatal-psychiatry-service/. I assisted to Dr Jones visits and approached there suitable participants.

Perinatal mental health services throughout UK Through Dr Ian Jones, I contacted perinatal teams in Glasgow (Dr Roch Cantwell), Manchester
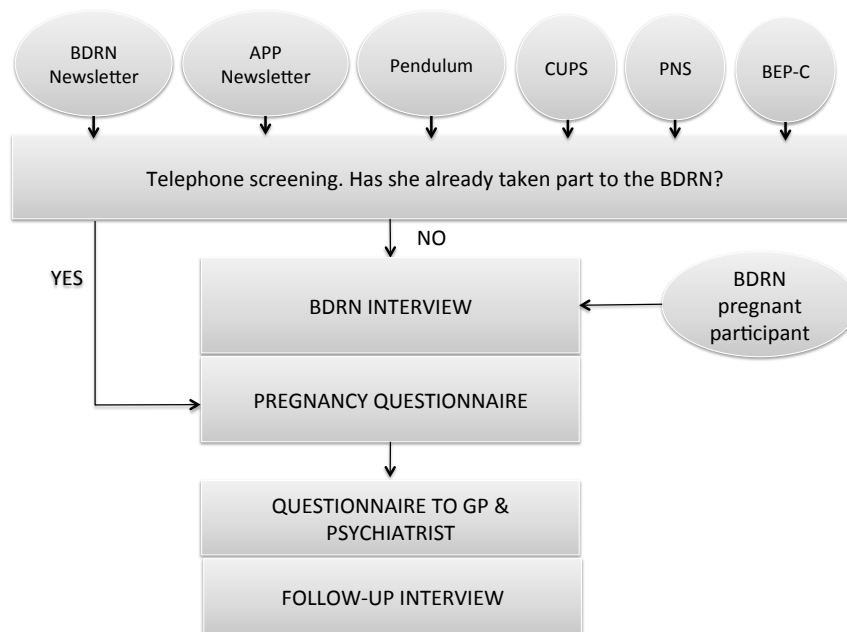
Figure 10.1: Algorithm for the recruitment and assessment of pregnant women with bipolar disorder. Women were assessed in pregnancy and 3 months after childbirth. Information on pregnancy and the postpartum period was gathered through face-to-face interview with the woman, questionnaires completed by the woman and by GPs and psychiatrists and case notes. The study was expressly designed to collect the same information for multiple sources. Abbreviations: CUPS: Second Opinion Clinic at Cardiff University, PNS: perinatal services across the UK, BEP-C: Bipolar educational programme - Cymru , more information at http://www.bep-c.org/

(Dr Angelika Weik), Newcastle (Dr Hamish McAlister-Williams and Dr Angela Walsh), Southampton (Dr Alain Gregoire), London (Dr Liz McDonald), Birmingham (Dr Floriana Coccia and Dr Giles Berrisford), Hull (Dr Deepak Garg), Sheffield (Dr Nusrat Mir), Derby(Dr Paula Brownsett), Edinburgh (Dr Fiona Murray), Nottingham (Dr Gopinath Narayan). All these services manage bipolar women in the perinatal period and screen antenatal populations for women at risk of postpartum psychosis.

Advertisements The study was advertised in the annual BDRN newsletters, in the annual APP magazine and in the Pendulum magazine. Moreover information on the study was available on the APP website (http://www.app-network.org/research/).

10.1.2 Assessment

Once recruited, women underwent the standard BRDN assessment and were asked to donate a blood sample for DNA extraction. To assess potential risk factors for perinatal recurrences not included in the BDRN assessment participants were asked to complete an additional questionnaire. It was given to pregnant women during the BDRN interview. Women who had already taken part in the BDRN project before getting pregnant and, once pregnant, wanted to take part in the prospective study, were sent the pregnancy questionnaire at home, along with the information sheet and two copies of an additional consent form to be signed (Appendix A and B).

The pregnancy questionnaire

Pregnant participants were asked to complete an additional self-rated questionnaire with information about their pregnancy, which took around 10 minutes to complete. The questionnaire was left with the other questionnaires that were part of the BDRN study and returned in the same pre-paid envelope. A copy of the questionnaire is available in appendix C. The questionnaire was designed in order to obtain additional information in relation to specific risk factors for perinatal recurrences. It had 5 parts and contained questions on :

Pregnancy Expected date of delivery and week of gestation in which the questionnaire was completed.

Psychosocial risk factors a modified version of the Pregnancy Risk Questionnaire [178]

Drug and alcohol use in pregnancy This section consists in both closed-ended and open questions on the use and amount of drug, alcohol and tobacco smoking.

Medications The participant was asked to indicate the daily doses of medications and when eventual changes in the prescriptions occurred from 6 months before pregnancy since the date in which the questionnaire was filled in. Information on medications would enable to replicate and extend to the postpartum period the findings by Viguera et al [64] (see background section).

Premenstrual symptoms screening tool [179] This questionnaire investigates the presence of DSM-IV premenstrual dysphoric disorder and clinically significant premenstrual syndrome. I modified it, by asking women to recollect the presence of premenstrual symptoms before pregnancy.

10.1.3 Follow-up

Information from physicians

For pregnant women who gave consent, two months after the expected date of delivery I contacted her GP and psychiatrist by letter (appendix D) to gather information on pregnancy and postnatal period. They were asked to complete a GP and psychiatrist questionnaire (appendix E and appendix F) respectively and were asked if there was any reason not to contact the woman. If the physicians did not reply, the form was sent a second time. GPs were asked about obstetric complications and whether the woman had any perinatal psychiatric complication. The psychiatrist questionnaire was more detailed and had both open and close-ended questions on episodes occurred in pregnancy and after childbirth and medications prescribed in the perinatal period.

Follow-up telephone interview

Following this contact with her GP and psychiatrist, the participant was contacted three months after the expected date of delivery to arrange an additional telephone interview asking about symptoms experienced in relationship to pregnancy and childbirth (appendix G). The interview took about 20 minutes and repeated the relevant sections of the SCAN interview [142], modified from the BDRN interview and the following additional features:

- Structured questions on obstetric variables, including pregnancy and delivery complications, method of delivery, hour of birth.

- Open question about psychological stressors in pregnancy and the postpartum period

- Closed-ended questions on breastfeeding and sleep

- Life chart of pregnancy and the postpartum period. Questions on stressors and medication during pregnancy included in the questionnaire were reviewed and women who did not completed the questionnaire were asked about medications at this stage.

The study was expressly designed to collect the same information from multiple sources in order to compare the consistency across sources and to minimise the chances of missing information. Table 10.1 summarises the principal variables investigated, the sources from which information was collected and the rationale behind the choice of each variable.

Table 10.1: **Potential risk factors for postpartum episodes**
1st column: potential risk factors (grouped by the bio-psycho-social paradigm), 2nd column: source from which data were gathered; 3^{dr} column: previous studies.

FACTOR	SOURCE	PREVIOUS STUDIES
FH	BDRN	Association with general family history of psychiatric disorders [77] and [180] Only a FH of perinatal episodes predicts PP [59, 87]
Age	BDRN	NS [77] [169]*; Postpartum mental illness patients are older [76]*
Current SUD	PQ	Differential diagnosis, + [180]
Medications	PQ, PsychQ, Follow-up interview, CN	Increased risk of pregnancy and postpartum recurrence after (rapid) lithium discontinuation [58, 64]*
Premenstrual syndrome	PSST [179]	+ [77]
Previous PP/PND	BDRN	57% PP recurrence [100]
1st episode puerperal	BDRN	NS [100]
Length of time since last delivery	BDRN	a gap of at least 5 years [181]*; 3y for psychotic mothers v 2.5y for controls [76]*
First pregnancy (nulliparity)	BDRN	+ [76, 93, 169, 170, 180, 182]*; Marce, Winter: NS [77]; confounding factors in the old studies: high parity, relative risk higher late in reproductive life [93, 170, 180]

Table 10.1 – *Continued from previous page*

FACTOR	SOURCE	PREVIOUS STUDIES
Obstetric complications	GPQ, follow-up interview, CN	pregnancy complication NS; caesarian section [93] [169]*, no birth complication [170]; induction, foetal distress, instrumental delivery, abnormalities [183]; hypertension, respiratory illness, cephalopelvic disproportion, uterine dysfunction [76]*; need for intensive medical care for the baby or death of the baby [180]
Short gestation	GPQ, follow-up interview, CN	++ [76]*, [170]
Low birth weight	Follow-up interview	'If episodes were more frequent after short gestation, the obstetric reasons for early delivery might provide a clue to the aetiology of the psychosis' [77]; NS [93]
Previous miscarriage rate	BDRN interview	[169]* : lower rate of miscarriage, higher rate of for termination
Sex	Follow-up interview	NS [93]; Excess of females [184], [169]*
Breastfeeding	Follow-up interview	NS PAFFENBARGER:1964mi*
Sleep loss during delivery	Follow-up interview	+ [185]
Sleep loss because of the baby	Follow-up interview	+ [185]

Table 10.1 – *Continued from previous page*

FACTOR	SOURCE	PREVIOUS STUDIES
Personality	Questionnaires	Marks: NS EPQ [186]
Polarity at the onset	BDRN, CN	NS [186], + time since last admission [186]
Illness severity (comorbidity, age at onset, course of disorder, deterioration from premorbid level of function)	BDRN, CN	[64]*
Predominance mixed	BDRN, CN	
Periodicity	BDRN, CN	
Affective vs psychotic features	BDRN, CN	
Time since last illness	BDRN, CN	
Time since last discharge	BDRN, CN	
Social Class	BDRN	'modern controlled studies have shown little social class difference' [77]; higher social class [187]; NS [186]
Interpersonal difficulties	BDRN , PQ	+ [186, 187]
Single	BDRN, PQ	Nguni, South Africa: 80% unmarried [188]* , Edinburgh: unmarried, widows , separated, divorced [169]* , [76]*: NS; interaction w/ primiparity [189]

Table 10.1 – *Continued from previous page*

FACTOR	SOURCE	PREVIOUS STUDIES
Material situational problems	BDRN interview, pregnancy questionnaire	- (more positive life situation) [187], NS (SPQ) [186]
Attitude toward the pregnancy	PRQ	[187]
Marital relationship	PRQ	+ (MAMA) [186] , [190]: NS
Support	PRQ	+ [186, 187]; [190]:NS
Life events	PRQ	No [186, 190, 191]
Stillbirth	GPQ	+ [77]

[0]Symbols and abbreviations *: not specific for puerperal psychosis, non psychotic postpartum episodes included; + positive association, - negative association, AFF: affective disorders; BDRN: BDRN interview; CN: case notes; FH: family history; GPQ: questionnaire for GP; LEDS: Life Events and Difficulties Schedule [192], MAMA:Maternal Adjustment and Maternal Attitudes [193]; NS:non significant, PN: perinatal episodes, PP puerperal psychosis, PND, postnatal depression; PQ: pregnancy questionnaire, PsychQ: questionnaire for psychiatrist, PSST: premenstrual symptoms screening tool [179], part of the pregnancy questionnaire, SPQ: Social Problem Questionnaire [194], SUD: substance use disorde

10.2 Ethics procedures

Part of the sample was recruited sistematically through NHS across UK, thus the study was subject to local and national level ethical review. The Mood Disorder Research Project had Local Research Ethics Committee approvals and held Multi-Centre Research Ethics Committee approval from the West Midlands Research Ethics Committee. However, for my research project it was necessary to obtain the MREC approval and my research passport.

10.2.1 MREC approval

The study required that the West Midlands Research Ethics Committee approved an amendment to the Mood Disorder Research protocol[1] in order to conduct the prospective assessment. The following amendments to the research protocol were proposed by the Mood Disorder Research Team and approved by the West Midlands Research Ethics Committee:

- Pregnancy questionnaire

- GP and psychiatry questionnaire

- Follow up interview (it was not necessary to submit the text of the follow-up interview.

- Modification to the participant information sheet (appendix B) and to the consent form (appendix A) in order to add information about the additional part of the study for pregnant women

10.2.2 NHS research passport

The research passport is a document issued (in my case) by Cardiff University that allowed me to obtain honorary research contracts in any NHS organisation, although I did not have any contractual arrangements with NHS. Although the

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[1]The full title of the study conducted by the Mood Disorder Research team is 'Molecular genetic investigation of bipolar disorder and related mood disorders', REC reference number MREC/97/7/0, commenced on 22 December 1997

research passport was design to simplify the administrative procedures, it took me more than 6 months to obtain it.

10.3   Summary

In this chapter I described the methodology of the research protocol of a longitudinal study on bipolar disorder in pregnancy and the postpartum period aimed to i) establish the proportion of women who suffer a severe episode of psychiatric illness, ii) characterise the clinical features of episodes occurring in the postpartum and iii) explore the influence of a range of variables on the vulnerability to develop an episode of severe illness in pregnancy or the postpartum.
The study was conducted as part of the Mood Disorder Research Project. Pregnant women with bipolar disorder were recruited through mental health services and by non-systematic means throughout UK.

In pregnancy participants were interviewed with a modified SCAN interview. A number of questionnaires were also completed that included measures of current mood, life events prior to onset, personality and temperament, alcohol and illicit drug use, childhood life events and information about the current pregnancy.

Two months after the expected date of delivery the woman's GP and psychiatrist were contacted to gather information on the pregnancy and post-natal period. They were asked to complete a short questionnaire, which took less than 5 minutes to complete, and if there was any reason not to contact the woman.

Three months after the expected date of delivery the woman was contacted to arrange an additional telephone interview asking about symptoms experienced in relationship to pregnancy and childbirth. The interview took about 20 minutes and repeated the relevant sections of the SCAN. Case notes were also reviewed by the research team.

Chapter 11

Pilot study

I report here the results of the pilot study, that was conducted between April 2011 and June 2012. The aims of the pilot study were:

- to establish the effectiveness of the recruitment methods

- to test the adequacy of the assessment tools

- to estimate the variability in the outcomes to calculate the sample size that would be needed in further studies

- to assess the feasibility of the large scale study and to modify the current research protocol in order to increase the chance of success in recruiting and following-up women

Over 15 months I was in contact with 66 women. Because it took about 10 months to finalise the protocol and obtain the necessary documentation, including my research passport (this was the longest step), 5 women assessed before the beginning of the study by Dr Jones at the CUPS clinic were also included. Figure 11.1 and table 11.1 show the flow-chart of the inclusion process.

Only $38/71(60.6\%)$ women met the inclusion criteria, gave their consent, were interviewed by the BDRN team and thus included in the prospective study. Women planning a pregnancy or in the postpartum period were included in the BDRN general study, but were excluded from the current research project.

Table 11.1: Number of contacts generated and number of participants by recruitment strategies. The participant recruited through BEP-C was given information about the study during the session on perinatal bipolar disorder included in the program.

	SCREENED	EXCLUDED-NOT BIPOLAR	EXCLUDED-PRE-CONCEPTION	EXCLUDED-POSTPARTUM	REFUSED/NOT AVAILABLE	EXCLUDED-MISCARRIAGE	INITIAL ASSESSMENT COMPLETED	DROP-OUT	FOLLOW-UP COMPLETED	FOLLOW-UP TO BE COMPLETED
BDRN newsletter	5	0	2	0	1	0	2	0	0	2
APP newsletter	8	0	2	1	2	0	3	0	1	2
Pendulum magazine	9	0	2	0	0	0	7	0	4	3
CUPS-Dr Jones	17	0	1	1	2	2	10	0	10	1
PNS	17	0	2	8	2	0	5	0	3	2
BDRN	14	0	3	1	1	0	10	2	1	6
BEP-C	1	0	0	0	0	0	1	0	0	1

Abbreviations and notes: CUPS: Second Opinion Clinic at Cardiff University, PNS: perinatal services across the UK, BEP-C: Bipolar educational programme - Cymru , more information at http;//www.bep-c.org/, [a]2 women initially accepted to be interview, but then declined and preferred to procrastinate the interview to the postpartum. However, while I am writing, they have not been in contact with the team for the interview, so I included them as 'dropped-out'[b] 1 woman did not undergo the follow-up telephone interview, because she left to live abroad. However, I had follow-up information through the postpartum assessment by the BDRN team and the psychiatrist; [c] including 5 women recruited in followed-up before the study was officially started
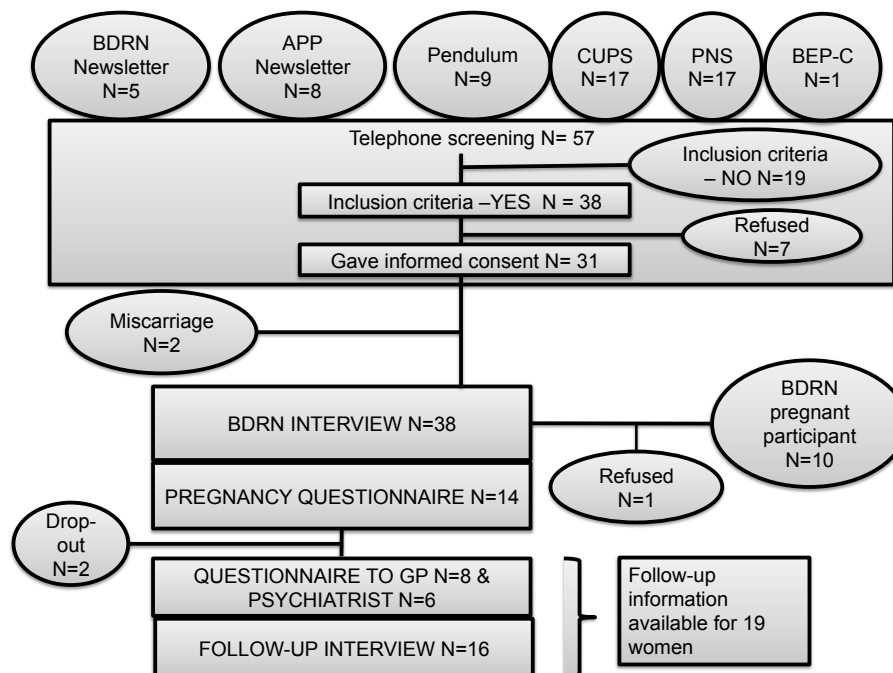
Figure 11.1: Flow chart including information on the sample sizes. Abbreviations and notes:CUPS: Second Opinion Clinic at Cardiff University, PNS: perinatal services across the UK, BEP-C: Bipolar educational programme - Cymru , more information at http://www.bep-c.org/. d from the current research project. To date16/38 (42.1%) women have already completed the follow-up, including the telephone interview, 1/38 woman was not available for the telephone in interview, because moved abroad, but she was interviewed by the BDRN team after delivery and the GP questionnaire was available, 19/38(50.0%) still need to complete the follow-up assessment (for 3 of them information through the GP and/or the psychiatrist is already available) and 2/38 (5.3%) dropped-out.

Overall 10 pregnant women initially contacted/ indicated refused or were not available for the initial BDRN interview:

- 1 woman contacted me via e-mail to have more information, saying she wanted to be contacted only via e-mail and never got back to me

- 1 woman, initially recruited through Manchester PNS in her 3rd trimester was not available for the telephone screening, despite 5 phone calls over 2 months

- 1 woman recruited through Manchester PNS in her 2rd trimester refused her consent at the initial telephone screening, without giving any explanation

- 1 women recruited though the BDRN, 2 recruited through the APP newsletter initially accepted to be interviewed, but then procrastinated the interview until the postpartum period. To date they have still not arranged the interview with the team

- 2 women recruited through the CUPS clinic were not interview, one because declined the interview in a second moment saying she was too stressed, another one did not turn up at the interview and was not available to arrange a further appointment.

- Despite giving their consent to the interview, additional 2 women were not interviewed because they had a miscarriage (1 women in the first trimester, one during the second trimester, both recruited through the CUPS) before the interview. For these women information are available through case notes.

To date 16/38 (42.1%) women have already completed the follow-up, including the telephone interview, 1/38 woman was not available for the telephone in interview, because moved abroad, but she was interviewed by the BDRN team after delivery and the GP questionnaire was available, 19/38(50.0%) still need to complete the follow-up assessment (for 3 of them information though the GP and/or the psychiatrist is already available) and 2/38 (5.3%) dropped-out. For the 2/38 women who dropped out information on the postpartum period was not available, either because they never sent back the consent to take part to the follow-up study, despite a written reminder (1 woman recruited though the BDRN), or because they were not available for the telephone follow-up interview and were not in contact with the services (1 woman recruited through the BDRN had the landline interrupted).

11.1   Effectiveness of the recruitment methods

The majority of women screened were recruited through the CUPS clinic and through the PNS. However, the ratio women recruited/women screened was the lowest for PNS with less than 30% of the initial contacts actually recruited, half of the proportion actually recruited thought the CUPS clinical. Moreover, the recruitment through the PNS, despite being effective in generating contacts on paper, required lot of effort in engaging the clinicians and, although I have been repeatedly in contact with 13 services, women were referred only by 5 services

and only 2 services referred women who met inclusion criteria and accepted to take part.

Considering the number of women who were interviewed for the initial assessment, the best recruitment methods were the CUPS clinic and BDRN. However, women recruited through CUPS were more likely to complete the follow-up than women recruited through BDRN. The entire cohort of women recruited through the CUPS clinic completed the follow-up versus 1/3 of those recruited through the BDRN. These statistics were drawn from a small sample and 1 in 2 participant was still in the follow-up stage of the study. However, beside statistics, it was my personal experience that it was much easier to remain in contact with women recruited through the CUPS clinic rather than through other methods. I think it was because the clinician recruiting through the CUPS clinic was Dr Jones, the supervisor of my research project, who was very committed to the research. Moreover, I assisted to all consultations and thus I met in person all participants recruited through the CUPS clinic.

Another effective method of recruitment was Bipolar UK through advertisements in the Pendulum magazine. It is worth to notice that within the group of 10 women recruited thorough the BDRN, 1 heard about the study at the Bipolar UK conference.

In summary, considering both the absolute number of women who completed the follow-up and the proportion of women initial contacted who completed the study, the recruitment through the CUPS clinic was the most effective method of recruitment, followed by the advertisements in the Pendulum magazine.

These findings overlapped to what was found in previous studies. Peindl and Wisner [177] reported on the effectiveness of recruitment strategies in two trials on prevention and treatment of postpartum depression and found that recruitment through physicians was difficult and time consuming, requiring more than one year to develop relationships and to establish a referral network.

11.2   Adequacy of the assessment tools

I present here the statistics including only the 19 women for whom I had information on the postpartum period. The pregnancy questionnaire was completed during the clinical interview with Dr Jones for 5 women recruited before the beginning of the study, 9/19 completed it in their own time during pregnancy and 5/19 did not return the questionnaire during pregnancy and were asked the questions during the postpartum telephone interview. Pregnancy questionnaires were completed in median 11 weeks before childbirth (range 2-25 weeks).

Contact details were available for 12 GPs and 12 psychiatrists. The follow-up questionnaires were sent back by 8/12 GPs (66.7%) and 6/12 (50%) psychiatrists. For 3/19 (15.8%) women the physicians questionnaires were the only source of follow-up information. The median time of follow-up was 15 weeks (range 2-174 weeks). In one case the GP reported a delivery affected by 'bipolar disorder', while the woman reported euthymia during pregnancy and the postpartum period. In another case the psychiatrist did not report any episode, while the woman reported a depressive episode (developed after the appointment with the psychiatrist). A woman reported that she discontinued the medications in the first trimester of pregnancy, despite the medical prescription.

For episodes occurring in pregnancy and in the postpartum period, diagnoses were made by Dr Jones and myself independently by DSM-IV criteria. We then met and reviewed the diagnoses. There was perfect agreement between Dr Jones and me on the perinatal diagnoses. Interestingly, women who were not available for the follow-up telephone interview were all reported to be affected by a manic/mixed episode after childbirth (in 2 cases a new onset episode, in 1 case the continuation of a previous episode).

11.2.1 Medications

A major limitation was that in my study I did not collect information on the drug concentration in blood. My approach had two major problems: i) the compliance to the prescribed treatment and ii) the physiological changes in drug metabolism during pregnancy. Alterations in the absorption, distribution, metabolism, and excretion can modify the necessary dose. It should be noticed that other physiological alterations, not related to the pharmacokinetics, can alter the efficacy of the drugs, for example lower protein binding, higher sensitivity to nausea and vomiting, altered glucose metabolism. The latter needs to be acknowledged in pregnant women who take drugs known to be associated with metabolic syndrome and glucose resistance, such as olanzapine and quetiapine. Although pharmacokinetics changes are often a major concern for clinicians, the most important issue is probably compliance. In fact, about one in two woman does not take the medications as prescribed [195]. In the pilot study there was only one woman who reported discontinuing medications while her doctor reported she continued the therapy.

11.2.2 Refusal and dropout mechanisms

It has been suggested that response rates of at least 70% are necessary to infer that the sample group is sufficiently representative of the target population from which it is drawn [196]. Excluding women who had a miscarriage, 10/46 (21.7%) women who met the inclusion criteria either refused of take part to the study (8/10) or were not available for the follow-up interview (2/10). Thus, a rate of completion of 78.3% is satisfactory. Unfortunately I did not have systematic information on women who refused to take part to the study. However, it is interesting to point out that all 3 women who were not available for the follow-up telephone interview were, according to their GP and psychiatrist, ill after childbirth with a manic or mixed episode. Considering that there were overall 4 women who had a manic or mixed episode after childbirth (in one case it was a continuation of a previous episode), 3/4 (75%) severe episodes were detected only thanks to the collaboration with the woman's GP and psychiatrist.

11.3 Preliminary data for sample size calculation

The selection of an appropriate sample size is a crucial aspect of any experimental design problem. However, before performing any sample size calculation it is vital to have a clear idea of the aim of the study. As I have already mentioned, the aims of the full-blown longitudinal study were to estimate the rates of perinatal recurrences and to explore the risk factors of a perinatal recurrence. I focussed my analyses on women who have already completed the follow-up. Sample characteristics are summarised on table 11.2.

Table 11.2: Sample characteristics. Only women who completed the follow-up were included.

	N	%
DSM-IV LIFETIME DIAGNOSIS		
BD-I	13	68.4
BD-II	5	26.3
SAD-BT	1	5.3
	MEDIAN	**RANGE**
PREGNANCIES	1	0-4
DELIVERIES	1	0-3

11.3.1 Selection of the response variable

In the next two pages I report the a schematic summary of the **PNEs** that were identified through i) the BDRN face-to-face interview in pregnancy, ii) the questionnaires for the physicians and ii) the telephone interview I conducted in the postpartum period. In 2 cases the diagnosis made by physicians differed from that obtained during the telephone interview. I recorded 14 DSM-IV episodes in 10 women, 2 cases of prodromal manic symptoms soon after childbirth (colour orange in figure 11.2) that were promptly treated, while 1 woman experienced mixed features after lithium discontinuation (colour yellow in figure 11.2), that did not meet the severity criterion for a DSM-IV mixed episode. The symptomatology reported varied across women and within a woman over the time of observation. Only 2 episodes met the DSM-IV criteria for a mixed episode (criteria for a manic episode and for a major depressive episode - except for duration). However, mixed features during depressive episodes (colour purple in figure 11.2) were present in 3/4 episodes of depression occurring in pregnancy. In 2 cases the onset of manic symptoms during the depressive episode followed the introduction/increased of an antidepressant. Interestingly, none of the 3 major depressive episodes reported in the postpartum had mixed features. One woman, however, reported a dissociative episode during postpartum depression. While depressive and mixed episodes were common across the entire perinatal period, all 3 manic episodes and 2 cases of prodromic manic symptoms occurred in the first week postpartum. One woman reporting mania after childbirth experienced transitory auditory and visual hallucinations (colour grey in figure 11.2) in pregnancy that become more prominent after childbirth with the onset of manic symptoms. Interestingly I did not identify any episodes of hypomania.

Main issues in selecting the response variable were:

large variability between subjects symptomatology varied largely between subjected, leading to a large variance. The larger the variance , the larger sample size is required. Which is a good compromise between detailed information and small variability?

within- subject, across- time variability there were women who experienced more than one episode during the period of observation. Is a single variable defining a single episode the best approach? If so, which episode should be rated?
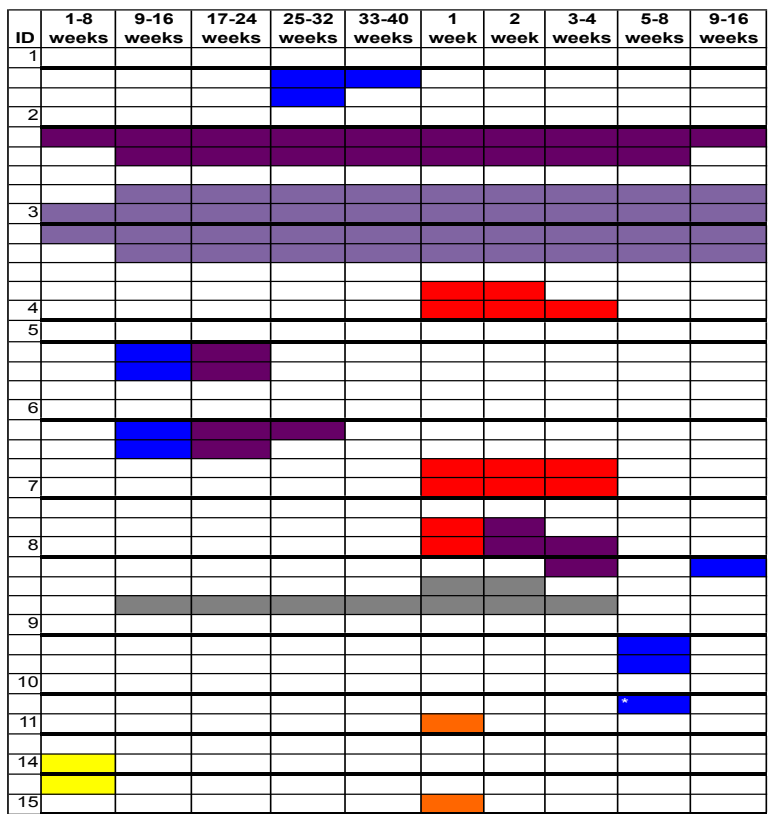
Figure 11.2: **Chart of perinatal period** for each woman who completed the follow-up and had manic (red), mixed (violet), major depressive episodes with (purple) or without (blue) manic symptoms, or prodromic symptoms (orange) or swings in relation to lithium discontinuation (yellow). Psychotic symptoms in grey. Euthymia is represented by the bold line. The high of the coloured bar symbolises the severity of the symptomatology: 2 rows: episode with severe impaired functioning, 1 row:episode with mild-moderate impaired functioning

definition of a mood episode in the cases in which women started a medication immediately after the onset of early symptoms of a severe episode and did not develop any full-blown severe episode, it is likely that the medications interfered with and modified the natural course of illness. How should these episodes be rated?

Table 11.3 shows how different definitions of PNE impacted on the estimates of recurrence rates. As discussed in the next paragraph on the choice of factors, levels and range, the definition of the outcome depends on the research question. To estimate the burden of bipolar disorder in the perinatal period, a broad definition, including all episodes occurring in pregnancy and in the postpartum period should be used. On the contrary, to assess the effect of medications on the risk of postpartum psychosis, a narrow definition of postpartum psychosis should be used, excluding those women with a postpartum episode that was the continuation of a previous episode.

Table 11.3: Rates of perinatal recurrences according to different definitions of the outcome variable

Outcome	Proportion
Proportion of deliveries affected by a DSM-IV manic or mixed episode or psychotic depression with onset within 6 weeks postpartum	3/19 = 15.8%
Proportion of deliveries affected by a DSM-IV manic or mixed episode or psychotic depression or hypomanic or prodromic symptoms of a manic or mixed episode or psychotic depression with onset within 6 weeks postpartum that required medications	4/19 = 21.0%
Proportion of deliveries affected by any DSM-IV episode with onset within 3 months postpartum	5/19 = 26.3%
Proportion of deliveries affected by any DSM-IV episode or prodromic symptoms that required medications with onset within 3 months postpartum	7/19=36.8%
Proportion of perinatal periods affected by any DSM-IV episode with onset in pregnancy or within 3 months after childbirth	9/19=47.4%
Proportion of perinatal periods affected by any DSM-IV episode or prodromic symptoms that required medications. Episodes could be the continuation of an episode	12/19=63.2%

11.3.2   Choice of factors, levels and range

As shown on table 10.1, there are many factors that can be explored and tested for an association with perinatal recurrences. However, the more independent variables are included in a model the larger sample size is required. I limited my

sample size calculation to the simplest case of one predictor. I ran the analyses for 2 predictors:

1. lifetime diagnosis, because it was associated with the type of perinatal recurrence in the retrospective study (see chapter 6 and figure 8.3);

2. pharmacological treatment, because it was the major source of complexity and variability (table 11.3).
   The questions I needed to answer were:

1. Which is the best definition of the independent variable/s?

2. How large a shift in the parameter I wish to detect in the full-blown longitudinal study?

3. How much variability is present in the population - i.e. how much variability did I find in the pilot study?

4. What size errors am I willing to take in the full-blown longitudinal study?

In order to deal with the complex data structure, the formulation of clear specific research hypotheses is vital. Table 11.4 shows the sample size needed according to different research questions. In each analysis I set α=0.05, β=0.20 and power=$1 - \beta$=0.8. I assumed that χ^2 test would be run to test any association between PNEs and categorical independent variables such as lifetime diagnosis and medications. Calculations were performed using the functions `ES.w2` and `pwr.chisq.test` in the package `pwr` [197]. `ES.w2` computed effect size w for a two-way probability table corresponding to the alternative hypothesis in the χ^2 test of association in two-way contingency tables. The effect size w is the square root of the standardised χ^2 statistic. The formula in terms of population values π_0 and π_1 is:

$$w = \sqrt{\sum \frac{(\pi_0 - \pi_1)^2}{\pi_0}} \tag{11.1}$$

with $w = 0.1$, $w = 0.3$ and $w = 0.5$ suggesting respectively a small, a medium and a large effect size. To calculate the effect size I used the data from the pilot study. However, when cell counts were $\leqslant 1$, I assumed $w = 0.1$. Table 11.4 reported also the sample size I calculated from the data of Viguera et al. [64] and that I report in the table as a reference.

As a reference book for power calculations I used [198]

Table 11.4: Sample size calculation according to different research hypotheses

Research question	Dependent variable	Independent variable	H_0	w	N
Are women with a narrowly defined bipolar disorder at higher risk of a postpartum recurrence?	any DSM-IV postpartum episode or prodromic symptoms requiring medications. Values: yes or no[a]	Narrowly defined bipolar disorder: yes if DSM-IV BD-I, no if DSM-IV BD-II or SAD-BT	BD-I is not associated with postpartum recurrence	0.29	94
Are women with broadly defined bipolar disorder at higher risk of being ill in pregnancy or later than 6 weeks after childbirth?	any DSM-IV or prodromic symptoms requiring medications with onset in pregnancy or later than 6 weeks after childbirth. Values: yes or no.	Broadly defined bipolar disorder: yes if DSM-IV BD-II or SAD-BT, no if DSM-IV BD-I	Broadly defined bipolar disorder is not associated with recurrences in pregnancy or later than 6 weeks after childbirth	0.37	59
Is a mood stabilising therapy before childbirth a protective factor against postpartum psychosis?	DSM-IV/prodromic symptoms requiring medications of a manic or hypomanic or mixed episode or psychotic depression within 6 weeks after childbirth. Values: yes or no.[a]	Mood stabilising therapy the week before delivery [b] Values: yes or no	Use of mood stabilisers before delivery is not associated with the onset of postpartum psychosis	0.05[c]	196
Is a mood stabilising therapy a protective factor against a perinatal recurrence?	At least one perinatal DSM-IV recurrence or prodromic symptoms of a recurrence requiring medications Values: yes or no.[a]	Prophylactic mood stabilizing therapy[d] Values: yes or no	Use of prophylactic mood stabilisers is not associated with a recurrence	0.17	280
Is mood stabiliser discontinuation in pregnancy a risk factor for a recurrence in pregnancy?[b]	Any DSM-IV recurrence in pregnancy	Mood stabilising therapy [b]. Values: continued, discontinued.	Discontinuation of mood stabilisers in pregnancy is not associated with any recurrence	0.49	89 [64]
Is mood stabiliser discontinuation in pregnancy a risk factor for a recurrence in pregnancy?	At least one perinatal DSM-IV recurrence or prodromic symptoms requiring medications. Values: yes or no. Women in which the postpartum episode was a continuation of the episode in pregnancy were excluded	Mood stabilising therapy[b]. Values: continued, discontinued. Women who did not take any mood stabiliser in the year before pregnancy were excluded	Discontinuation of mood stabilisers preconception or in early pregnancy is not associated with any recurrence	0.16[c]	196

[a]

195

[a]If the postpartum episode was a continuation of the episode in pregnancy,the woman was excluded [b] Lithium, valproic acid, lamotrigine, carbamazepine, gabapentin, olanzapine,quetiapine [c] As cell count $\leqslant$ 1, I assumed $w = 0.1$

Which is the best definition of the independent variable 'medications'?

The variable 'medications' presented:

1. great variability between subjects, and

2. within- subject, across- time variability

4/19 (21.0%) were treated with more than one drug and 4/19 (21.0%) changed the therapy at least once during pregnancy. Interestingly only 7/19 (36.8%) women did not take any medications during pregnancy and even less 4/18 (22.2%) in the postpartum period. However, when only mood stabilising drugs were taken into account, only 1 woman took lithium during pregnancy, 1 aripiprazole, 1 quetiapine and 1 olanzapine (only in the second part of the pregnancy), while 2 started quetiapine soon before childbirth. I did not consider chlorpromazine a mood stabiliser. In summary, only 3 women (15.8%) reported a mood-stabilising therapy all through pregnancy, while 6 women (31.6%) took an antidepressant alone, without any mood stabiliser, for at least 8 weeks during pregnancy. Despite recent reports (reviewed in [199]) challenged the safety of tricyclic antidepressants in pregnancy, 2/6 women on antidepressants (33.3%) were treated with dosulepin. To summarise, with the exception of 4 women who did not take any medication in pregnancy and in the postpartum period, there were 15 different therapeutic regimens, one for each woman and only 2 women maintain the same therapy all through pregnancy and the postpartum period.

Table 11.5: List of medications taken in the perinatal period by each woman

ID	PRECONC	1-8 weeks	9-16 weeks	17-24 weeks	25-32 weeks	33-40weeks	1week	2week	3-4weeks	5-8 weeks	9-16 weeks
1	Lithium CLPRZ 50 mg	CLPRZ 50 mg	CLPRZ 50 mg	CLPRZ 50 mg	Citalopram (non effec-tive¿stop) Venlafaxine 150 mg+ Quetiapine 100 mg	Venlafaxine 150 mg+ Quetiapine 200 mg Stop Ven-lafaxine 1 week before delivery	Quetiapine 500 mg	Quetiapine 500 mg	Quetiapine 300 mg, Lithium 600 mg	Quetiapine 100 mg, Lithium 800 mg	Quetiapine 100 mg, Lithium 800 mg
2 3	Venlafaxine 150 mg Quetiapine 800 mg Citalopram 40 mg Lamotrigine 100mg	Venlafaxine 150 mg ∅	Venlafaxine 150 mg ∅	Venlafaxine 150 mg Olanzapine 20 mg Fluoxetine 20 mg	Venlafaxine 185 mg Olanzapine 20 mg Fluoxetine 20 mg	Venlafaxine 150 mg Olanzapine 20 mg Fluoxetine 40 mg Lamotrigine 25 mg	Venlafaxine 150 mg Olanzapine 20 mg Fluoxetine 40 mg Lamotrigine 50 mg	Venlafaxine 150 mg Olanzapine 20 mg Fluoxetine 40 mg Lamotrigine 50 mg	Venlafaxine 150 mg Olanzapine 20 mg Fluoxetine 40 mg Lamotrigine 50 mg	Venlafaxine 150 mg Olanzapine 20 mg Fluoxetine 40 mg Lamotrigine 50 mg	Venlafaxine 150 mg Olanzapine 20 mg Fluoxetine 40 mg Lamotrigine 50 mg

Table 11.5 – *Continued from previous page*

ID	PRECON	1-8 weeks	9-16 weeks	17-24 weeks	25-32 weeks	33-40weeks	1week	2week	3-4weeks	5-8 weeks	9-16 weeks
4	Quetiapine 200mg	Quetiapine 200mg	Quetiapine 200mg	Quetiapine 200mg	Quetiapine 200mg	PRETERM DELIV-ERY 31/40	Quetiapine 400 mg, Sertraline 50 mg	Quetiapine 1200 mg, Sertraline 50 mg	Quetiapine 1200 mg, Sertraline 50 mg	Quetiapine 150 mg, Sertraline 50 mg	NA
5	∅	∅	Sertraline	Sertraline	Sertraline	Sertraline	Sertraline	Sertraline	Sertraline	Sertraline	Sertraline
6	Fluoxetine 40 mg	Fluoxetine 40 mg	Fluoxetine 40 mg	Fluoxetine 60 mg, briefly on Olanzap-ine 10mg, briefly on haloperi-dol 5 mg	Flouxetine 60 mg	NA	NA	NA	NA	NA	
7	Quetiapine 200 mg	∅	∅	∅	∅	∅	Quetiapine 200 mg VLP 500	Quetiapine 600 mg VLP 1000	Quetiapine 600 mg	Quetiapine 600 mg	

Table 11.5 – *Continued from previous page*

ID	PRECON	1-8 weeks	9-16 weeks	17-24 weeks	25-32 weeks	33-40weeks	1week	2week	3-4weeks	5-8 weeks	9-16 weeks
8	∅	∅	∅	∅	∅	∅	Quetiapine 100-300 mg	Quetiapine 300 mg	Quetiapine 300 mg	Quetiapine 300 mg	Quetiapine 300 mg
9	Aripiprazole 15 mg	Aripiprazole 15 mg	Aripiprazole 15 mg	Aripiprazole 15 mg	Aripiprazole 15 mg	Aripiprazole 15 mg	Aripiprazole 15 mg	Aripiprazole 15 mg	Aripiprazole 15 mg	Aripiprazole 20 mg Citalopram 20 mg	Aripiprazole 20 mg Citalopram 20 mg
10	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅
11	Dosulepin 75mg	Dosulepin 75mg	Dosulepin 75mg	Dosulepin 75mg	Dosulepin 75mg	Dosulepin 75mg	Quetiapine 600 mg Dosulepin 75mg	Quetiapine 600 mg Dosulepin 75mg	Quetiapine 600 mg Dosulepin 75mg	NA	NA
12	NA	Thyroxine	Thyroxine	Thyroxine	Thyroxine	Thyroxine	Thyroxine	Thyroxine	Thyroxine	Thyroxine	Thyroxine
13	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅
14	Stop lithium	∅	∅	∅	∅	∅	∅	∅	∅	∅	∅
15	Citalopram 20mg	Citalopram 20mg	Citalopram 20mg	Citalopram 20mg	Citalopram 20mg	Quetiapine 200 mg	Quetiapine 200 mg	Quetiapine 200 mg	Quetiapine 200 mg	Quetiapine 200 mg	Quetiapine 200 mg

Continued on next page

Table 11.5 – *Continued from previous page*

ID	PRECON	1-8 weeks	9-16 weeks	17-24 weeks	25-32 weeks	33-40weeks	1week	2week	3-4weeks	5-8 weeks	9-16 weeks
16	Dosulepin 150mg + Lithium	Dosulepin 150mg	Dosulepin 150mg	Dosulepin 150mg	Dosulepin 150mg	Citalopram 20mg Dosulepin 150mg	Citalopram 20mg Dosulepin 150mg	Citalopram 20mg Dosulepin 150mg	Citalopram 20mg Dosulepin 150mg	Citalopram 20mg Dosulepin 150mg	Citalopram 20mg Dosulepin 150mg
17	Lithium 800mg	Lithium 800mg	Lithium 800mg	Lithium 800mg	Lithium 800mg	Lithium 800mg	Lithium 800mg	Lithium 800mg	Lithium 800mg	Lithium 800mg	Lithium 800mg
18	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$	Sertraline 75mg	Sertraline 75mg	Sertraline 75mg	Sertraline 75mg	Sertraline 75mg
19	Quetiapine 75 mg	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$	$\varnothing$

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[1] Abbreviations and symbols:$\varnothing$:no medications, CLPRZ: chlorpromazine, NA: information non available

11.4 Feasibility of a large scale study and modifications to the current research protocol

> "If we want more evidence-based practice, we need more practice-based evidence."
> Lawrence W. Green @ http://www.lgreen.net/

The analyses of the data collected in the pilot showed a great variability, especially in the pharmacological treatment. A study aimed to investigate the effect of pharmacological treatment on the risk of perinatal recurrences would need a large sample size of at least 280 women. However, to replicate the findings of my retrospective analyses in a longitudinal study a much smaller sample size of about 60-100 women would be required. Over 14 months of recruitment 19 women completed the longitudinal study (16 with, 3 without telephone interview) and other 16 completed the initial assessment and are due to be interviewed in the next couple of months. Assuming a conservative drop-out rate of 50% , 8 women would complete the follow-up within 4 months. Therefore, assuming a constant rate of recruitment and follow-up completion, it would require about 3 years to recruit and follow-up other 60 women.

The major finding of this pilot study is that the **collaboration with GPs and psychiatrists is essential**. In the pilot study I would have missed 75% of severe episodes occurring after childbirth without the information gathered through physicians. Moreover, the response rate of GPs and psychiatrists was better than that I had expected, with 12/14 participants (excluding women recruited before I had ethical approval to contact physicians- 85.7%) having information from at least one of the two.

- I would suggest that a larger amount of resources should be put in establishing effective collaborations not only with PNS, but also with GPs and general adult psychiatrists. Although I did not have any element to justify the involvement of obstetricians, it would be interesting to explore it.

  Although the difficulties in recruiting women systematically through PNS (in addition to the difficulties in establishing effective contacts with the services, there were the efforts to obtain honorary contracts in the health boards involved), this method should not be dismissed and has got a great potential. Not only it would assure a large number of potential participants entering in the study, but it would also allow to have a more repre-

sentative sample of women with bipolar disorder who are pregnant in the general community. As observed by Peindl and Wisner [177], it may required time to establish an effective network and my discouraging findings may be due to the short period of time. The commitment of time and energy involved in the recruitment in the two studies reported by Peindl and Wisner [177] was greater than my commitment. For me, coming from a clinical background (but I suspect also because of my temperament), asking potential participants/potential collaborators for help with the study was the major challenge of the PhD. In my clinical experience, in fact, I was used to be contacted and to be asked for help and not vice versa. So, perhaps, future recruitment and follow-up could benefit from the help of more perseverant researchers. Peindl and Wisner [177] suggested monthly contacts with physicians in order to 'keep the studies fresh in the minds of health professionals', weekly meetings with specialists and their staff, giving informative talks to service users, carers and the general public, also after office hours. The talks should be not only about perinatal mental health, but also about the importance of research in improving the care.

- Another suggestion can be drawn from the high rates of missing interviews among women with postpartum psychosis: it is likely that women were still ill/recovering three months after childbirth and probably 6 months to 1 year follow-up for these women would be a more sensible option (especially because for the majority of women earlier information would be provided by physicians 2 months after childbirth).

- A third suggestion coming from the high rates of non response among women with postnatal psychosis is that it may be useful to make sure that case notes for the postpartum period are provided. At the moment, in fact, case notes are requested by the BDRN team after the face-to-face interview in pregnancy to assess lifetime course and severity of the illness. I would suggest that case notes could also be used to integrate detailed information on the postpartum period.

- Psychiatrists are currently asked about mania, without any reference to psychotic features[2]. Given that the psychiatrist questionnaire is vital for the assessment of episodes occurring in the postpartum period, I would

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[2]In the questionnaire for psychiatrists, on page 2: *Did she experience an episode of mania, hypomania or a mixed affective episode following this delivery?*

propose the additional question: *Were psychotic symptoms present?*

In summary, I would not make any major modifications to the current research protocol, but I would focus the resources in engaging the services involved in the care of the woman during pregnancy and postpartum.

Part IV

General discussion

Chapter 12

12.1 Summary of the findings

In the first part of my PhD I explored the link between childbirth and mood disorders in a large retrospective sample of women with mood disorders. Because it is likely that unipolar and bipolar disorder are on a continuum, without points of rarity, I investigated the childbirth trigger across the entire mood disorder spectrum (BD-I, BD-II, RMD). The main findings of my PhD are:

- Around two thirds of all diagnostic groups reported at least one episode of illness during pregnancy or the postpartum.

- Women with BD-I reported an approximately 50% risk of a perinatal major affective episode. Risks were lower in RMD and BD-II at around 40%.

- Mood episodes were significantly more common in the postpartum than outside the postpartum period in both BD-I and RMD, but not in BD-II.

- The majority of PNEs in women with BD-I and RMD occurred within 4 weeks of childbirth. In BD-I episodes of mania or psychosis had an earlier onset than those of depression. For BD-II, onsets of psychiatric episodes were more spread out over the perinatal period with more onsets in pregnancy and later in the postpartum.

- In women with BD-I, episodes of mania/psychosis within 6 weeks postpartum were associated with first live delivery. Episodes of depression in

the postpartum were associated with primiparity only in mothers suffering from RMD and I did not find any effect of parity on perinatal bipolar II depression. The primiparity effect was not due solely to women with postpartum episodes not going on to have further children or driven by the use of prophylactic medication in subsequent pregnancies.

- The effect of parity on postpartum mania/psychosis and unipolar postpartum depression was driven by women who experienced their first lifetime episode within 6 weeks postpartum.

In the second part of my PhD I designed and piloted a prospective study. I sought to test the feasibility and the validity of a study that aimed to recruit a large, well characterised sample of women with bipolar disorder in early pregnancy and to monitor them through pregnancy and the postpartum. The full-scale study aimed i) to replicate and ii) to extend the findings on the retrospective sample, exploring the influence of a range of variables on the vulnerability to develop an episode of severe illness in pregnancy or the postpartum. The main findings of the pilot phase of the study were:

- Over 14 months of recruitment 19 women completed the follow-up assessment. Excluding women who had a miscarriage, the rate of completion was 78%, with 8/10 women who met the inclusion criteria refusing to take part to the study and 2/10 not available for the follow-up interview.

- The recruitment through PNS, despite the high number of contacts generated, was not effective. Considering the number of women who were interviewed for the initial assessment, the best recruitment methods were the CUPS clinic and BDRN.

- The analyses of the data collected in the pilot showed a great variability, especially in the pharmacological treatment.

- The response rate by GPs and psychiatrists was better than that I had expected, with 85.7% participants having information from at least one of the two. The collaboration with physicians was essential. Without the information gathered through them, I would have missed 75% of severe episodes occurring after childbirth.

12.2 Previous research

12.2.1 Rates of perinatal episodes in women with mood disorders

Despite differences in inclusion criteria, assessment and phenotypic definitions that make direct comparisons of studies difficult, findings of the current study corroborate and extend previous research that has reported high rates of perinatal mood disturbances in relation to childbirth (chapter 3, table 3.1).

Robust evidence of an association between a history of bipolar disorder and increased risk of severe postpartum episodes has been previously reported. In the Danish population-based cohort study the cumulative incidence of readmission 0 to 3 months postpartum was 22% for first time mothers with bipolar disorder [65]. Similar rates were reported in a previous analysis of smaller numbers of bipolar women from the Mood Disorder Research Project sample, where 26% of deliveries in familiar bipolar disorder were affected by a severe episode [59]. Consistent with previous research, in the present study I found that in women with BD-I more than 1 in 5 pregnancies was complicated by psychosis or mania with onset within 6 weeks of delivery - episodes that correspond to the concept of postpartum psychosis.

Munk-Olsen [65] reported that less than 5% of first time mothers with a history of unipolar affective disorders were admitted with an episode within 6 months of childbirth. I found low rates (1.4%) of psychotic postpartum depression in women with RMD but these rates are considerably lower than the rates of non psychotic depression that complicated about 40% of pregnancies of women with RMD .

In these analyses I excluded women recruited on the basis of being recruited because of a perinatal episode and a proportion was recruited systematically. Thus, the sample was representative of women with mood disorders in contact with psychiatric services and there was no selection on the basis of having an episode in relation to childbirth. This represents an advantage over previous studies [6], where participants were drawn from perinatal psychiatry programs and subject to selection bias potentially raising the rates of PNEs.

12.2.2 Time of onset of perinatal episodes

Consistent with previous reports, in the current analyses the incidence of mood episodes was considerably lower in pregnancy than in the postpartum. My findings also corroborated the evidence of a strong link between mania or affective psychosis and the first postpartum weeks.

Contrary to expectation, however, I didn't find any differences between the BD-I and RMD groups in the time of onset of postpartum non psychotic depression. In the Danish population-based cohort study [65], the risk of admission for unipolar depression was spread out over 5 months, while first time mothers with bipolar disorder had the highest risk of readmission within the first three weeks postpartum. However, there are important methodological differences between the Danish study and the current report. The Danish study was based on hospital admissions and did not discriminate between bipolar depression and mania. My results on mothers with BD-I showed that the onset of bipolar depressive episodes is more spread out in the postpartum than manic episodes. This finding suggests that rather than a difference between lifetime unipolar or bipolar diagnosis, the latency of onset after childbirth is associated with the phenomenology of the puerperal episode itself. This hypothesis may explain differences with the Danish study.

There is a paucity of studies that discriminate between bipolar depression and mania in relation to childbirth. Bergink et al [80] [1] found that psychotic depression had a significantly later onset than psychotic mania. This contrasts with my findings of an overlapping survival distribution between mania and psychotic depression. Differences in the methodology and sample characteristics may account for this discrepancy.

In the Mood Disorders Project dataset, BD-II showed a pattern of onset surprisingly different from BD-I and RMD. As I analysed episodes of different polarity separately, it is unlikely that the different proportion of perinatal manic and depressive across mood disorders can be an explanation for this difference. However, there is a lack of studies on the differences between BD-II and other mood disorders in the perinatal period and my findings need to be replicated.

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[1] I discussed this study in the background section

12.2.3 Childbirth as a trigger for episodes of mood disorder

The registry studies that I largely discussed in the background section used either women as their own control or the general population as control to test the hypothesis that childbirth is a period of increased risk of mood episodes (table 12.1). In my research I selected women with at least 5 years of illness and compare the rates of postpartum periods affected by postpartum psychosis or postpartum depression with the rates of episodes per years of illness. Compared to registry studies, my approach gave a more general picture of the childbirth trigger in relation to bipolar disorder, because it considered a broader period of observation: from the onset of the mood disorder to the interview. Again, comparisons with registry studies are difficult because of the differences in the methodology. However, my findings replicated previous findings of an association between childbirth and BD-I and extend the findings to episodes of RMD, that probably do not require admission and thus were not included in the registry studies.

12.2.4 Primiparity

In table 12.2 I summarise the results of previous studies on parity and mood disorders. For each pertinent analysis reported in previous studies I calculated the effect size ES using the arcsin transformation of the probabilities [198].
[2] My finding of an association between first delivery and postpartum psychosis replicated previous findings of both register based and clinical studies. A number of methodological issues may influence the results of studies on parity. If women suffering a postpartum episode are less likely to go on to have further children, this will reduce rates in multiparae and may account for the association with first pregnancies. Similarly, other demographic and obstetric variables may also explain the excess of psychosis in primiparae. For example, first pregnancies occur at a younger age and delivery by caesarean section has been associated with both primiparity [175] and postpartum psychosis [169]. Only one previous study took into account the possible effect of postpartum psychosis on further pregnancies [93] and was conducted on a subsample of women that I included in my analyses.

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[2]I compute effect size h for two proportions using the function `ES.h` in the package `pwr`

$$h = 2 \arcsin \sqrt{p_1} - 2 \arcsin \sqrt{p_2} \tag{12.1}$$

where p_1 is the first proportion and p_2 the second proportion

Table 12.1: Studies investigating the risk of mood episodes in the postpartum compared to other times

Study	Subject	Comparison group	Outcome	Risk
Munk Olsen et al 2009 [65]	Primiparae with history of psychiatric admission who had given birth 0 to 6 months previously	Primiparae with psychiatric admission who had given birth 6 to 11 months previously	Readmission	↑ Mania
Munk Olsen et al 2009 [65]	Primiparae with history of psychiatric admission who had given birth 0 to 6 months previously	Nulliparae with mood disorder	Readmission	↑ Mania
Munk Olsen et al 2006 [68]	Primiparae without previous admission who had given birth 0 to 11 months previously	Primiparae without previous admission who had given birth 11 to 12 months previously	1st admission	↑ Mania
Munk Olsen et al 2006 [68]	Primiparae without previous admission who had given birth 0 to 11 months previously	Nulliparae without previous admission of the same age	1st admission	↑ Mania in age groups < 26 and > 30
Terp & Mortensen 1998 [67]	Parous women 0-3 months after delivery	General Danish female population	Admission	↑ 1st admission, but not readmission mania
Kendell et al 1987 [52]	Parous women 0-90 days after delivery	2 y before and the 2 y after delivery aged 15-44	Average monthly admissions	↑
Current study	Women with mood disorders and history of PNE	Episodes/year	PNE 6 weeks postpartum/delivery	**retrospective** ↑ in BD-I and RMD, but not BD-II

I also found an effect, although of smaller magnitude, for non-psychotic unipolar postpartum depression. Differences in the definition and assessment criteria could account for the differences between my results and those of previous studies, that did not report any effect of parity [169, 186], or even found the opposite effect [113]. Moreover, it has been argued that parity itself influences the validity of rating scales for perinatal depression [176].

Table 12.2: Studies investigating the association between parity and postpartum mood disorders. Positive associations in bold, negative associations in italics.

FIRST AUTHOR, YEAR	SAMPLE	COMPARISON GROUP	OUTCOME	ES	N
Bergink 2011 [80]	Inpatient admissions for DSM-IV-TR depressive disorder with psychotic features, mania with psychotic features, mixed episode with psychotic features, psychotic disorder not otherwise specified, or brief psychotic disorder within 4 weeks postpartum	General population N=6969	Primiparity	**0.49**	51
Bergink 2011 [80]	As above	As above	Primigravidity	**0.49**	51
Glavin 2009 [174]	EPDS score > 11	EPDS score < 12 (N=1968)	Primiparae v multiparae	**0.11**	121
Milgrom 2008 [113]	EPDS score > 12	EPDS score < 13 (N=11436)	0 v ¿2 children	*0.3*	925
Roberson Blackmore 2006 [93]	Multiparae with one delivery affected by mania or affective psychosis within 4 weeks postpartum and one delivery which was unaffected by any major affective disturbance	NA	Primiparae v multiparae	**1.34**	54
Kirpinar 1999 [171]	First time inpatient admissions with psychotic postpartum disorder	NA	Primiparae v multiparae	**0.61**	83
Videbech 1995 [170]					
Marks 1992 [186]	RDC schizoaffective sisorder,(manic or depressed type), manic or hypomanic disorder, bipolar depression with mania or hypomania, psychotic major depressive disorder, unspecified functional psychosis.	Not ill (N=21)	Primiparity	0.02	10
Marks 1992 [186]	any other RDC diagnosis but schizophrenia	Not ill (N=21)	Primiparity	0.06	12
Kendell 1981 [169]	RDC major depressive, manic or schizoaffective, disorder, schizophrenia or unspecified, functional psychosis	Control population (N = 35729)	Primigravidity	**0.51**	51
Kendell 1981 [169]	As above	As above	Living children	**0.36**	51
Kendell 1981 [169]	RDC major and minor depressive disorder	As above	Primigravidity	**0.44**	49
Kendell 1981 [169]	As above	As above	Living children	0.29	49
Paffengerger 1966 [76]	Any psychiatric admission six months following delivery	General population	Primiparae v multiparae	0.03	83
Current study	Multiparae with BD-I and ≥ mania or psychotic depression within 6 weeks postpartum	NA	Primiparity	0.36	183
Current study	Multiparae with RMD and ≥ major depression within 6 weeks postpartum	NA	Primiparity	0.34	159

12.3 Limitations

12.3.1 Retrospective study on mood disorders in pregnancy and the postpartum period

My results need to be interpreted in the light of several limitations:

- Information on PNEs was collected retrospectively and therefore the rates I reported may not equate exactly with the risk of PNEs to women with an existing mood disorder who become pregnant. This is for two reasons:

  - A small number of pregnant women with a previous diagnosis of BD-II or RMD may go on to develop a postpartum episode of mania and therefore switch diagnosis to BD-I. As I pointed out in the introduction, it has recently been reported that about 14% of women having a first psychiatric admission soon after childbirth developed bipolar disorder during a 15-year follow-up period [7]. In my analyses these women would be included in the BD-I group.

  - Some pregnancies may have been prior to the first episode of mood disorder. It is possible that having non-postpartum episodes of mood disorder raise the risk of an episode following childbirth.

  For these reasons, prospective longitudinal studies of women with a range of mood disorder diagnoses are necessary. They would allow to quantify the risk of developing PNEs. However, the retrospective design allowed a greater insight into the overall lifetime course and is, in general, a more cost effective method than the longitudinal design.
  It is also worth noting that these limitations are likely to mean that the high rates of PNEs I reported are likely to underestimate, to some extent, the true risk to women with mood disorders, particularly those with BD-II and RMD. Moreover, this represented a conservative bias also in the parity analyses, making it less likely that I would find an effect of primiparity.

- Individuals in the RMD group were excluded from the study if they had ever experienced mood incongruent psychosis or psychosis outside of mood episodes, thus the rates of postpartum psychotic illness in women with RMD may be underestimated.

- A further issue is the reliability of the women's recollections of PNEs. It should be noted, however, that the reporting of episodes at interview was in agreement with the medical records and the recollection of episodes of illness in relation to childbirth has been shown to be excellent [200].

- In the analyses on the course of illness in relation to the childbirth trigger, information on age at first pregnancy and age at first PNE was missing for the majority of women. Data for first episode in relation to childbirth were also missing for more than 10% of the sample. Despite the good performances of multiple imputed datasets, the analyses including these variables need to be interpreted with caution.

- It is possible that women with mood episodes only in relation to childbirth represent a separate nosological entity from those who experience recurrences both in the perinatal period and outside it. In the Mood Disorder Research Project dataset there were 16 women who had only episodes in relation to childbirth: 5 with unipolar postpartum depression, 1 with bipolar II postpartum psychosis and 10 with bipolar I postpartum psychosis. I did not conduct any analyses to estimate the rates of women who had only PNEs nor I explored the differences between this subgroup and women with episodes both in the perinatal period and at other times. Because of the methods of recruitment, it is likely that the Mood Disorder Research Project dataset underestimated the actual prevalence of women with only postpartum recurrences. Women who suffered with mania only after childbirth could in fact have a diagnosis of postpartum psychosis and not be aware of the link between postpartum psychosis and bipolar disorder. These women were very likely to be missed by the BDRN study.

- I did not provide an accurate description of symptoms. In the Mood Disorder Research Project dataset episodes of postpartum mania were recorded without any specification for psychotic features, so I was not able to perform separate analyses for psychotic mania and mania without psychotic features. Moreover, given that survival curves for postpartum mania and for postpartum psychotic depression overlapped, I merged mania with and without psychosis with psychotic depression in a unique category (postpartum psychosis), including also cycloid psychosis.

12.4 Implications for nosology

12.4.1 Bipolar II disorder

In the retrospective sample, the patten of findings for BD-II was surprisingly different from the patterns for BD-I and RMD:

- The onsets of PNEs in the BD-II group significantly differed from those in the BD-I and RMD groups. In women with BD-II episodes were more spread over the pregnancy and 12 months postpartum period.

- I did not find any relationship between parity and PNEs of any type in women with BD-II. In this regard, BD-II appeared to have a different relationship to childbirth than BDÐI and RMD.

- Although PNEs occurred in relation to 40% of pregnancies in women with BD-II and approximately 70% of parous women with BD-II experienced at least one PNE, childbirth did not seem to be a specific trigger for DSM-IV mood episodes. Over 50% of women with BD-II, in fact, had a chronic/highly recurrent course of illness with more than 1 episode a year. In this group of women it is likely that perinatal recurrences happen in concomitance with puerperium only by chance and are not causally related to it. On the opposite side, less than 8% reported all deliveries affected by PNE and a low number of lifetime recurrences. This small sub-group, with the majority of lifetime recurrences occurring in the perinatal period can represent a more homogeneous sub-group of women in which childbirth represents a specific trigger for mood episodes. However, considering the overall group of women with BD-II, there was no association between postpartum period and increased rates of recurrences.

My interpretation is that women with BD-II had many recurrences in the perinatal period because they suffered from a highly recurrent disorder and thus many episodes may not be causally related to childbirth but happen in concomitance with puerperium by chance.

There is a lack of studies on the differences between BD-II and other mood disorders in the perinatal period and my findings need to be replicated. Further work is needed to clarify the relationship of episodes of BD-II to childbirth. In general, the construct of BD-II is controversial. On one hand, there is the view that bipolar features/bipolar disorder are under-diagnosed and that at least 1

in 5 patients in primary care in the UK suffers with unrecognised bipolar disorder [201]. On the other hand, there is a paucity of evidence on the validity of the BD-II construct and clinicians have criticised its utility [202]. [3]

12.4.2 Possible bipolar features in women with postpartum major depression

I demonstrated an influence of parity on postpartum mood episodes in women with both BD-I and RMD - the effect was not found only in the former condition. In women with BD-I, however, the effect was limited to episodes of manic/mixed polarity. In RMD, in which by definition episodes of high mood have not occurred, there was an influence on episodes of depression with early onset following delivery. An interesting question for further work is whether these early onset depressive episodes in RMD, while not meeting criteria for hypomania, show evidence of bipolar features. Indeed previous work by Munk-Olsen et al found that episodes of depression with onset within 4 weeks of delivery are a marker of underlying bipolarity with a higher risk of subsequent conversion to a bipolar diagnosis [7].

The rates of hypomania in the perinatal period were surprisingly low (2.6% in the BD-I group and 4.0% in the BD-II group). It may be due to the difficulties in recollecting minor episodes and in differentiating hypomania from the extreme happiness following motherhood. In addition, mixed states may be common in the postpartum and it is possible that women focused on depressive symptoms when asked retrospectively about postpartum episodes. As discussed in the background section, mood swings are highly prevalent after childbirth in the general population. It is possible that childbirth is more likely to trigger a full-blown mood episode in women with a vulnerability to mood disorder, whereas in the general population, who do not have an underlying diathesis for major psychiatric illness, more minor mood symptoms are triggered.

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[3]For example, Spence [202] argued that there are economical implications and perhaps there is an economical interest in widening the spectrum of bipolar disorder to BD-II. He focused its claims on the BOLDER studies on the efficacy of quetiapine on bipolar depression, that were supported by AstraZeneca Pharmaceuticals and reported the data from the NHS Business Services Authority that the prescription of quetiapine has increased by 160% since 2005

12.4.3   Postpartum onset criterion

The decision about where to set the postpartum onset criteria is difficult. On one hand a broader definition may be of benefit in clinical practice, where the treatment of mothers who experience an onset within a few months of delivery should be informed by the postpartum context. On the other hand, onsets later in the postpartum are likely to be less related to childbirth as a trigger and a broad definition may be a problem for studies examining the aetiology of postpartum triggering. In my analyses over 90% of episodes of postpartum psychosis met the DSM-IV diagnostic criterion of 4 weeks, while it was the case for less than $\frac{3}{4}$ of episodes of postpartum depression.

Despite previous work suggesting differences between bipolar and unipolar disorders, I found that in BD-I and RMD, episodes of depression had a very similar pattern of onset following childbirth. When postpartum episodes in women with BD-I were analysed according to episode type, postnatal depression with psychotic features and mania had an overlapping pattern of onset, while the onset of non psychotic depression was later in the postpartum. Together, these findings suggest that if different postpartum onset criteria are to be employed this may be more appropriate according to the phenomenology of the episode rather than according to the lifetime diagnosis. There is no justification here for separate onset criteria for bipolar and unipolar disorders.

In the analyses on primiparity I refined the definition of PNE to better establish the relationship between parity and mood disorders. In women with both BD-I and RMD, the relationship with parity was only significant for episodes with onset within 6 weeks of delivery. Episodes with onset in pregnancy or later in the postpartum did not show any relationship with parity. My study therefore, provides empirical support for an onset specifier for research limited to the first few weeks following delivery. My findings are in agreement with previous studies that have found that the risk of mania is highest within 4 weeks of childbirth [65,68] and that an onset of any psychiatric symptoms but manic within 2 weeks after delivery predicts subsequent conversion to bipolar disorder (relative risk = 4.26; 95% CI =3.11-5.85) [7]. Similarly, Forty et al [84] found evidence for familial aggregation of unipolar PND only for episodes with onset within 4 weeks of delivery but not for those occurring within 6 months of delivery. In this study, however, the familiarity for postpartum unipolar depression maximised when a postpartum definition of 6-8 weeks was applied, suggesting that a 4-week postpartum onset specifier may be too narrow in the study of postpartum unipolar depression. In summary, in clinical practice there may be good reasons for extending the definition of postpartum episode but research

aimed at uncovering the aetiology of postpartum triggering should be focused on episodes with early onset.

12.5 Clinical implications

12.5.1 Burden of perinatal episodes

The present findings emphasise the high rates of PNEs for women with a broad range of mood disorders. My results indicated that more than 70% of parous women with mood disorders will experience at least one perinatal episode in relationship to pregnancy and childbirth. The importance of pregnancy and childbirth for women with mood disorders should therefore not be underestimated.

For women with BD-I, approximately 20% of deliveries were associated with a postpartum episode of mania or psychosis, a further 25% of deliveries were associated with an episode of non psychotic major depression and almost 50% of deliveries were associated with a PNE of major mood disorder of some description. Women with a lifetime diagnosis of BD-II or RMD by definition will not have suffered an episode of mania in relation to childbirth. It would be wrong, however, to underestimate the importance of PNEs to women in these diagnostic groups. Although showing lower rates of broadly defined PNE than women with BD-I, still approximately 40% of deliveries are associated with a PNE of major mood disorder.

In discussing the risk of a PNE in women with BD-I, it is therefore important to consider the risk of a postpartum depression in addition to the risk of postpartum psychosis. For these women there is a 1 in 2 risk of an episode of major mood disorder in relationship to pregnancy and childbirth.

The risk of PNEs, while highest in BD-I disorder, extends also to women with BD-II and RMD. The high rates of perinatal mood disorder across the mood disorder spectrum should be recognised and discussed with women and their partners.

It has been estimated that more than 40% of the approximately 23 million pregnancies occurring each year in high-income countries are unplanned. Thus, the risk of illness in the puerperium should be discussed with all women of childbearing age who have a personal history of mood disorders, even with those who are not currently planning a pregnancy. Given that women might not be in contact with mental heath services it is important that all healthcare pro-

fessional that look after pregnant women including midwifes, family physicians and obstetricians are aware of this increased risk.

In summary, for research into aetiology all evidence points to early onset, more severe and manic / mixed episodes being of primary importance and research strategies may be better focussing on these episodes. However, the clinical burden of PNEs is extended to include other less severe episodes of mania and non psychotic depressive episodes occurring in pregnancy and in the postnatal period. All these episodes in relation to childbirth are clinically important.

12.5.2 Parity

For women with mood disorders, particularly for those with bipolar disorder, difficult decisions need to be made in relation to pregnancy and childbirth. Any information that can help to individualise the risk of illness may be useful. For women with BD-I, the odds of postpartum psychosis following a first pregnancy are double those for further deliveries. If a woman has remained well after her first baby, this provides some reassurance in subsequent pregnancies. However, it is important to remember that the risk of postpartum recurrence is very high (> 60%) in women who have already experienced an episode of postpartum psychosis [100].

12.6 Implications for further research

Brockington defined postpartum psychosis as a 'relatively sharply phenomenon' that offers an 'exceptional opportunity for clinical observation' [77]. Moreover, the study of postpartum episodes could have implications for mood disorders in general. However, my research found that it is likely that postpartum mood disorders are complex entities and that research into the causes of these episodes should take into account this complexity.

12.6.1 Longitudinal studies

Although my analyses provided some insight in the complexity of the childbirth trigger of mood disorders, only large longitudinal studies could capture the great variability between subjects and provide detailed information on risk factors

and clinical features of PNEs. My findings on the lack of specificity of the childbirth trigger in BD-II particularly need to be replicated, as there have been no previous studies on BD-II in the perinatal period.

The pilot longitudinal study I conducted showed a great complexity in the course of illness during pregnancy and the postpartum period, with women suffering from multiple episodes and becoming ill at many different stages in the perinatal period. The major source of variability was medications that included poly-pharmacy and changing of medications and dosage at different occasions during the perinatal period.

The main finding on the feasibility of a longitudinal study was the importance of the collaboration with the NHS, that is vital not only to provide generalizable results, but also to get information about the most severe cases. A large-scale longitudinal study (¿200 women) that captures at least part of the complexity of the clinical course of bipolar disorder in pregnancy and after childbirth would be feasible only with the collaboration of PNS, GPs and general adult psychiatrists. However, establishing an effective network of collaborators in the NHS requires lot of time and resources.

12.6.2   Clinical phenotypes for biological studies

A consistent conclusion from all my analyses was that the current classification systems may not provide adequate definitions of postpartum episodes for biological studies, because they are too general. I propose the following suggestions for future biological studies on postpartum mood disorders:

- Postnatal episodes in women with BD-II should be excluded, because it is likely that in this subgroup most episodes occurred only by chance in the postpartum period, with no specific association with the childbirth trigger.

- Women with BD-I who experienced their first manic/psychotic episode within 6 weeks after the first delivery are likely to be a more homogeneous group.

- Studies on postnatal depression should be conducted separately for unipolar and bipolar depression. Although episodes of bipolar I depression and unipolar depression had overlapping survival curves, only episodes of unipolar depression were overrepresented after childbirth and associ-

ated with primiparity. However, more clinical studies on bipolarity and postpartum depression are needed.

- Although in my research there were not many women who had only episodes in relation to childbirth, attention should be paid on the longitudinal course of recurrences. Women with few recurrences and the majority of recurrences occurring soon after deliveries are likely to be more vulnerable to the childbirth trigger than those who have the same number of postpartum episodes, but in the context of a highly recurrent/rapid cycling disorder. Interestingly, the association between bipolar postpartum psychosis and the VNTR polymorphism of the serotonin-transporter gene, found by Coyle et al [88] on a sub-sample of women that was included also in my analyses, was stronger when the phenotype was narrowed to women who had experienced multiple postpartum episodes (OR=9.2, 95%CI=1.2-73.1).

12.6.3   What accounts for the influence of parity?

There are both psychosocial and biological differences between first and subsequent pregnancies that might underpin the association with parity. Women having their first child experience higher levels of stress and the concerns of motherhood are different for first and subsequent deliveries [203]. However, while undoubtedly important for postpartum mood disorders in general, in the case of severe postpartum episodes, there is a lack of evidence implicating psychosocial factors [173, 190, 191]. This suggests the potential importance of biological differences, immunological or hormonal for example, between first and subsequent pregnancies.

My findings raise the possibility of a relationship between postpartum mood disorders and other disorders influenced by parity. Pre-eclampsia has robustly been associated with primiparity [204], while more controversial findings have reported that autoimmune disorders [205–207] and gestational diabetes [208] are overrepresented in multiparous women.

There are a number of important overlaps in the clinical presentation and epidemiology of pre-eclampsia and postpartum psychosis and this relationship has been recognised for over 160 years [209] (figure 12.1) . Associations between pre-eclampsia and mood episodes have been described [210], and psychosis can be a dramatic feature of eclampsia [211]. It is of interest that psychotic symptoms occurring in this condition are not merely a post-ictal phenomenon but

rather occur prior to this end stage and are therefore thought to be part of the systemic effects of pre-eclampsia on the central nervous system [211]. It is also worth noticing that, although eclampsia is considered a disorder of the late stage of pregnancy, a multicenter study found that 33% of women with eclampsia had onset in the postpartum period [212].

Molecular studies have also shown possible similarities between the pathogenesis of eclampsia and that of postpartum psychosis. The isoprenoid pathway synthesizes from the acetil-coenzimA metabolites such as digoxin, dolichol, ubiquinone, and cholesterol. Alterations in the isoprenoid pathway have been reported in both pre-eclampsia and postpartum psychosis [213]. Magnesium sulfate, a drug commonly used to prevent and treat eclamptic seizures, has antimanic-like effects in this animal model [214].

PRE-ECLAMPSIA   POSTPARTUM PSYCHOSIS

Primiparity

Eclamptic psychosis sine convulsions [210]

Efficacy of magnesium sulphate (for mania in animal models [213])

Isoprenoid pathway and hypothalamic digoxin [212]

Immunological dysfunction [214, 215]

Usually in pregnancy, but 33%of eclampsia postpartum [211]

Usually within days after delivery [78]
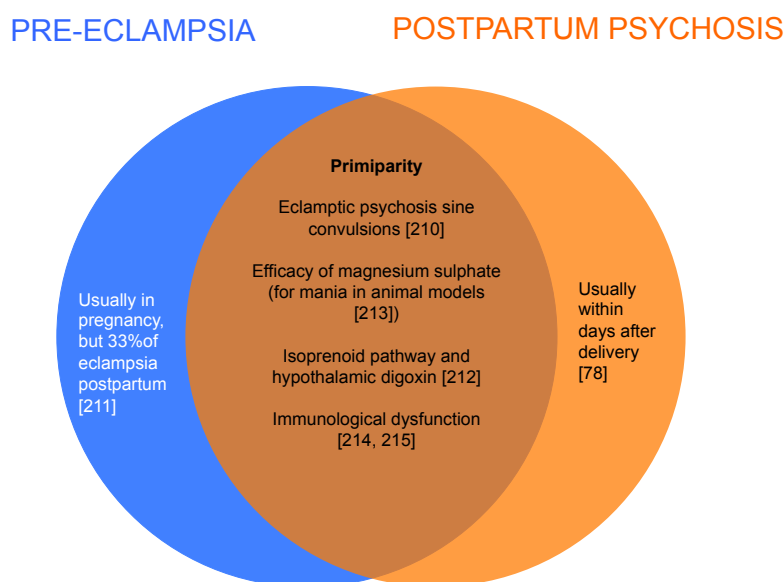
Figure 12.1: Overlap between preeclampsia and postpartum psychosis

The primiparity effect in pre-eclampsia supports an immunological aetiology of this complex condition [215], and my findings suggest immunological factors may similarly play a role in postpartum triggering of mood episodes. Interestingly, Bergink et al [216] reported a 4 fold increase in the rates of autoimmune thyroid disease in primiparae with de novo postpartum mania/psychosis compared to new mothers without psychiatric complications.

The primiparity effect in unipolar depression within 6 weeks postpartum needs to be investigated further. Studies on unipolar postpartum depression have

shown great heterogeneity. The aetio-pathology of postnatal depression is probably complex and multifactorial, including biological and psycho-social factors (I briefly overviewed them in chapter 2). However, it is of interest that immunity has been implicated in the pathogenesis of major depression [217]. Maes et al [218] comparing non-pregnant healthy women with healthy pregnant women found that plasma tryptophan and the tryptophan/CAAs[4] ratio were significantly lower at the end of term and even lower 1-3 days after childbirth and that women with an history of major depression had an enhanced inflammatory response 1 and 3 days postpartum compared to women without a history of major depression [219]. It is therefore possible that immune activation close to delivery increases tryptophan metabolism to kynurine, reducing tryptophan availability. However, the decreased availability of plasma tryptophan was not related with psychometric measures of depression or anxiety [219].

My findings give clues, therefore, to the pathogenesis of the postpartum trigger and, perhaps, to the causation of mood disorders more generally. Future studies are needed to clarify the role that biological and psychosocial differences between first and subsequent pregnancies on the postpartum triggering of mood episodes. Studies exploring the relationship of perinatal mood disorders and other conditions associated with parity such as pre-eclampsia may also prove fruitful.

12.7 Conclusion

The research on perinatal mood disorders relies mostly on arbitrary definitions of postpartum disorders, while more evidence-based criteria are needed. Confusion in the nosology has probably prevented firm and consistent conclusions on the nature of the postpartum trigger. My PhD project sought to address these deficiencies.

In the first part of this thesis I explored the link between childbirth and mood disorders in a retrospective sample of over parous 1500 women with mood disorders, recruited as part of ongoing molecular generic studies. Because it is likely that unipolar and bipolar disorder are on a continuum I included a sample of women with RMD as a comparison group. I found that PNEs are highly prevalent across the mood disorder spectrum. Primiparity is associated with bipolar I mania and psychosis and unipolar major depression within 6 weeks postpartum. Childbirth does not seem to be a specific trigger for episodes of BD-II.

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[4]CCAs are the amino acids valine, leucine, tyrosine, phenylalanine and isoleucine that are known to compete with tryptophan for the same cerebral uptake mechanism

In the second part I designed and piloted a prospective study to follow-up women with bipolar disorder in pregnancy and the postpartum period. From the pilot study a great variability emerged , especially in the course of illness and in medications, between women and within the same woman over time.

To conclude, the association between childbirth and mood episodes may be specific only for mania/psychosis and unipolar depression occurring soon after childbirth. These episodes are associated with first deliveries and are important candidates for further biological studies. To capture the clinical complexity of bipolar disorder in pregnancy and the postpartum period very large scale longitudinal studies are needed. These studies must be based on a strong collaboration with the NHS.

Appendices

Appendix A

Consent form for the longitudinal study

UNIVERSITY OF BIRMINGHAM

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

AGREEMENT TO TAKE PART IN THE STUDY OF MOOD DISORDERS

Please initial box

1. I have read the attached information sheet **(version 5, dated 12.12.10)** on the above project and have been given a copy to keep. I have had the opportunity to ask questions about the project and understand why the research is being done.

2. I agree to give a sample of blood for research in the above project.

3. I agree to part of the interview being audio recorded.

4. I understand that participation in this project is voluntary and that I am free to withdraw from the study without giving a reason and without my medical treatment being affected.

5. I give permission for my medical records to be looked at in strict confidence by responsible people from the Mood Disorders Research Group, Birmingham University.

6. I understand that the tests done as part of this research are not clinically diagnostic and I will not be informed of any specific results.

7. I understand that I will not benefit personally from taking part in this research.

8. I understand that the information and blood sample I have donated for this study will be held in a confidential and anonymised form by the research team and may be made available to researchers at other centres who are carrying out similar work.

9. I agree that I may be contacted again, in connection with the research, in the future.

10. I know how to contact the research team if I need to.

If you are pregnant:

11. **I give permission for my GP and psychiatrist to be contacted 2 months after my expected delivery date to request information about the pregnancy and postnatal period.**

12. **I agree to be contacted 3 months following my expected delivery date to be invited to take part in a telephone interview about my pregnancy and the postnatal period. I understand that I am free to decline this invitation.**

NAME _____   SIGNED _____   DATE _____

WITNESSED _____   SIGNED _____   DATE _____

THANK YOU FOR PARTICIPATING IN OUR RESEARCH
YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP

Department of Psychiatry, University of Birmingham, The Barberry, 25 Vincent Drive, Birmingham B15 2FG
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Version 5 – 12.12.10

Appendix B

Information sheet

INFORMATION ABOUT RESEARCH INTO MOOD DISORDERS

INTRODUCTION

We are a team of psychiatrists and psychologists who work in the Department of Psychiatry at the University of Birmingham and the Department of Psychological Medicine at Cardiff University. We are conducting research (funded by the Wellcome Trust) into the causes of mood disorders and work closely with other research groups both in Europe and the United States. We would like to ask you if you would be willing to take part in our research. Before you decide whether or not you would like to take part, please take the time to read the following information carefully.

WHAT IS THE PURPOSE OF THE RESEARCH?

Mood disorders sometimes run in families but in other cases only one member of a family is affected. Unfortunately no-one understands enough about the illnesses to know what causes particular individuals to become unwell. The main aim of our research is to look for genes and other factors, such as stressful life events, which make some people more likely than others to become ill. We hope that our study will improve understanding of mood disorders and help other workers find better treatments in the future.

WHO IS BEING ASKED TO TAKE PART IN THE STUDY?

Over 3000 individuals have already taken part in our ongoing research into mood disorders. It is important for us to see many more people in order that we can get the best possible understanding of the causes of mood disorders. We are hoping to recruit individuals who have experienced one or more episodes of high mood (often called mania, hypomania or bipolar disorder) at some point in their lives and would be extremely grateful if you would be kind enough to help with this study.

WHERE DOES THE STUDY TAKE PLACE?

If you agree to take part, a member of our research team will arrange a suitable time to visit you in your home or at another place convenient for you.

WHAT DOES TAKING PART INVOLVE?

Taking part involves:
- An interview by a trained member of our research team who will spend around an hour and a half asking you about your experiences and the kinds of symptoms you have had in the past. If you are willing we would like to audio record part of the interview for consistency and training purposes.
- Completing a set of questionnaires (which will take around half an hour).
- Giving a blood sample from your arm (2 standard blood tubes).

With your permission, we would like to look at your medical records in strict confidence in order to gain further information about the kinds of symptoms you have experienced. We only need to see you once but may contact you again in the future if we need to collect more information for the research. However, you will be free to decline if you do not want to participate further. Once you have agreed to take part in the study we will ask you to sign a consent form and will give you a copy to keep along with this information sheet.

If you are pregnant, we will also ask you to complete an additional questionnaire about your pregnancy (which will take around 10 minutes). With your permission, two months after your expected date of delivery we would like to contact your GP and psychiatrist to request information about the pregnancy and postnatal period. Unless your doctors advise us otherwise, will then

arrange an additional telephone interview with you (which will take about 20 minutes) to ask about any symptoms you may have experienced in relationship to pregnancy and childbirth.
You can decline to participate in this part of the study. You do not have to take part when contacted after the delivery and this will not affect the care you receive.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART? ARE THERE ANY RISKS?
- By taking part in the study you will not gain any direct benefit. However, your help will be of great value in allowing us to learn more about the causes of mood disorders and we hope this will lead to important advances in the treatment and prevention of mood disorders.
- This study does not include any treatment changes or invasive techniques. Some people experience mild discomfort when giving a blood sample and sometimes there is mild bruising afterwards.
- Most people find talking about their illness beneficial, but some may find it distressing. If at any time during the interview you feel distressed, you can ask the interviewer to move onto another question, take a break or end the interview.
- If you have a concern about any aspect of this study, please speak to Katherine Gordon-Smith. Her contact details are provided at the end of this information sheet.

DECLINING AND WITHDRAWING FROM THE STUDY
- You do not have to take part in this study. If you do decide to take part you are still free to withdraw at any time and without giving a reason.
- A decision to withdraw at any time, or a decision not to take part, will not alter the care you receive.
- If you decide to withdraw from this study, all information and samples you have provided will be destroyed and not used further in the research.

DATA CONFIDENTIALITY
- All interviews and results will be strictly confidential.
- The interview data, audio recordings of interviews **and blood samples** will be stored in accordance with the Data Protection Act. The data will be stored for a minimum of 10 years, but probably for longer as this is an ongoing long-term programme of research.
- The blood sample you provide will be coded and stored safely in a laboratory. It will be analysed to identify genetic variations that might cause some people to develop mood disorders. The results of your blood test are for research purposes only and will not be available to anybody on an individual basis.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?
- It is our intention to publish the results of this study in academic journals. Participants will not be identifiable in any report or publication.
- We will keep in touch with you by sending a regular newsletter to let you know how our research is progressing and to ask you to let us know about any important changes in your health since we last saw you.

FURTHER INFORMATION AND CONTACT DETAILS
If you have any further questions about this research, please contact the Mood Disorders Research Team and ask for Dr Katherine Gordon-Smith (Research Psychologist). Our address appears below, our telephone number is 0121 301 2361, and our e-mail address is moodresearch@contacts.bham.ac.uk

This study was given a favourable ethical opinion for conduct in the NHS (or other) by the West Midlands Multi-centre Research Ethics Committee (MREC/97/7/01).

Department of Psychiatry, University of Birmingham, The Barberry, 25 Vincent Drive, Birmingham B15 2FG
Tel: +44(0) 121 301 2361   Fax: +44(0) 121 301 2351   Email: moodresearch@contacts.bham.ac.uk

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Appendix C

Pregnancy questionnaire

PART D
QUESTIONNAIRE 8. PREGNANCY QUESTIONNAIRE

Date of Completion

☐☐ / ☐☐☐ / ☐☐
D D   M M M   Y Y

Part A Questions about your pregnancy:

What date is your baby due? ☐☐ / ☐☐☐ / ☐☐   How many weeks pregnant are you? ☐☐
　　　　　　　　　　　　　　　 D D   M M M   Y Y

Part B Questions about your feelings about your pregnancy and the support you are receiving
Please only answer the items in this section if you are past 24 weeks pregnant. If you are up to 24 weeks pregnant, please go to Part E on page 4 and we will ask you about this when we contact you again in the future.

1. Overall, has this pregnancy been a positive experience for you? (please cross one)

☐   ☐   ☐   ☐   ☐
1   2   3   4   5
Not at all   Somewhat   Very much

2. Do you feel you will have people you can depend on for emotional support when you go home with your baby? (please cross one)

☐   ☐   ☐   ☐   ☐
1   2   3   4   5
Not at all   Somewhat   Very much

3. Have you a partner in this pregnancy? (please cross one)   Yes ☐   No ☐

If yes, is your relationship with your partner an emotionally supportive one? (please cross one)

☐   ☐   ☐   ☐   ☐
1   2   3   4   5
Not at all   Somewhat   Very much

4. Have you had any major stresses, changes or losses in the course of this pregnancy (e.g. separation, moving house, domestic violence, bereavement)? (please cross one)   Yes ☐   No ☐

If YES, please describe briefly:

_____

Part C Questions about smoking, drugs and alcohol in pregnancy

1. In this pregnancy have you smoked cigarettes?   Yes ☐   No ☐
 (please cross one)

If YES, on average, how many cigarettes a day have you smoked?

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2. In this pregnancy, have you drunk alcohol regularly?   Yes ☐   No ☐

If YES, how many units of alcohol have you consumed on average per week? (1 unit of alcohol is equal to one small glass of wine, a single measure of spirits or half a pint of beer/lager/cider)

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3. During this pregnancy have you used any of the following substances when they have not been prescribed by a doctor?

	Yes	No
Sedatives	☐	☐
Cannabis	☐	☐
Speed	☐	☐
Ecstasy	☐	☐
Glue	☐	☐
Solvents	☐	☐
Cocaine	☐	☐
Heroin	☐	☐
Methadone	☐	☐
Other non prescription/over the counter drugs	☐	☐

If yes please give brief details

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Part D Questions about medications

1. What drug treatments (medications) as prescribed by your doctor did you take in the 6 months before you became pregnant?
(If you can, please indicate daily doses and say when any changes were made)

2. What drug treatments (medications) as prescribed by your doctor have you been taking during your pregnancy?
(If you can, please indicate daily doses and say when any changes were made)

Part E Questions about your periods

These questions refer to your periods (menstrual cycle) before your pregnancy.

Please mark an X in the appropriate box (mark one for each symptom)

1. Do you experience some or any of the following premenstrual symptoms which start before your period and stop within a few days of bleeding?

	Not at all	Mild	Moderate	Severe
1. Anger/irritability	☐	☐	☐	☐
2. Anxiety/tension	☐	☐	☐	☐
3. Tearful/increased sensitivity to rejection	☐	☐	☐	☐
4. Depressed mood/hopelessness	☐	☐	☐	☐
5. Decreased interest in work activities	☐	☐	☐	☐
6. Decreased interest in home activities	☐	☐	☐	☐
7. Decreased interest in social activities	☐	☐	☐	☐
8. Difficulty concentrating	☐	☐	☐	☐
9. Fatigue/lack of energy	☐	☐	☐	☐
10. Overeating/food cravings	☐	☐	☐	☐
11. Insomnia	☐	☐	☐	☐
12. Hypersomnia (needing more sleep)	☐	☐	☐	☐
13. Feeling overwhelmed or out of control	☐	☐	☐	☐
14. Physical symptoms: breast tenderness, headaches, joint/muscle pain, bloating, weight gain	☐	☐	☐	☐

2. Have your symptoms, as listed above, interfered with:

	Not at all	Mild	Moderate	Severe
15. Your work efficiency or productivity	☐	☐	☐	☐
16. Your relationships with coworkers	☐	☐	☐	☐
17. Your relationships with your family	☐	☐	☐	☐
18. Your social life activities	☐	☐	☐	☐
19. Your home responsibilities	☐	☐	☐	☐

Thank you very much for completing this questionnaire. Arianna Di Florio will arrange to contact you again by telephone following your delivery.

Appendix D

Letter to GPs and psychiatrists

Dear

Re: Participation in Mood Disorders Research Study (Name and DOB)

The above named woman has very kindly taken part in our research study into the causes of mood disorders, based at the University of Birmingham and Cardiff University. She has given us permission to write to you as her doctor to request information about her recent pregnancy and post natal period.

Please find enclosed with this letter an information sheet with further details about the study which has been approved by the West Midlands Multi-centre Research Ethics Committee and a copy of your patient's signed consent form.

We would be very grateful if you would be kind enough to complete the attached questionnaire, with questions about her pregnancy and post partum period, and return it in the free post envelope provided.

We plan to re-contact your patient with the next few weeks by telephone or by e-mail to arrange a brief telephone interview, which will take about 20 minutes. **If you know any reason why we should not re-contact her**, or require any further information about the research please do not hesitate to contact us, our contact details appear below.

Yours sincerely

Mood Disorders Research Team

Appendix E

Postpartum General Practitioner Questionnaire-to be sent with postpartum letter 2 months after due date

Pregnancy and Childbirth Questionnaire

Q 1. Date of delivery

Q 2. Pregnancy outcome

Live birth

Stillbirth

Termination

Miscarriage

Q 3. Delivery modality

Normal vaginal delivery

Elective caesarean section

Emergency caesarean section

Forceps / Ventouse

Q. 4 Baby heath status:

Healthy

Minor problem

Major problem

Please give brief details of any problems:

Q 5. Has she suffered an episode of psychiatric illness in this pregnancy or post-partum period?

Yes   No

If yes please give brief details:

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Completed by:

Name

Position

Date

Address

E-mail address

Telephone number

Please send completed questionnaire in the pre-paid envelope provided

Thank you for your time

Appendix F

Postpartum Psychiatrist Questionnaire- to be sent with postpartum letter 2 months after due date

Pregnancy and Childbirth Questionnaire

Q1. Episodes of psychiatric illness <u>during pregnancy</u>

Did she experience an episode of depression during the pregnancy?

Yes ☐   No ☐   Unknown ☐

Did she experience an episode of mania, hypomania or a mixed affective episode during the pregnancy?

Yes ☐   No ☐   Unknown ☐

Did she experience another form of psychiatric episode during the pregnancy?

Yes ☐   No ☐   Unknown ☐

If yes please give brief details:

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If yes to any of the above, was the onset of the episode;

In the first trimester of pregnancy	Yes ☐	No ☐
In the second trimester of pregnancy	Yes ☐	No ☐
In the third trimester of pregnancy	Yes ☐	No ☐
A continuation of an episode from before pregnancy	Yes ☐	No ☐

Was she admitted to hospital?
Yes ☐   No ☐

Q 2.   Episodes of psychiatric illness in the <u>postpartum period</u>

Did she experience an episode of depression following this delivery?

Yes ☐   No ☐

Did she experience an episode of mania, hypomania or a mixed affective episode following this delivery?

Yes ☐   No ☐

Did she experience another form of psychiatric episode following this delivery?

Yes ☐   No ☐

If yes please give brief details:

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If yes to any of the above, was the onset of the episode:

    the continuation of an episode from pregnancy   Yes ☐   No ☐
    an onset following delivery   Yes ☐   No ☐

If a postpartum onset, when was the onset in relationship to delivery?

☐ days   **Or**   ☐ weeks   following delivery

Was she admitted to hospital?
Yes ☐   No ☐

Q 3. Medication in relationship to the pregnancy

What prescribed medication did she take in the 6 months before pregnancy?
(Please indicate daily doses and say when any changes were made)

What prescribed mediation did she take during the pregnancy?
(Please indicate daily doses and say when any changes were made)

What prescribed medication did she take in the postpartum period?
(Please include daily doses and say when any changes made)

Completed by:

Name

Position

Date

Address

E-mail address

Telephone number

Please send completed form in the pre-paid envelope provided

Thank you for your time

Appendix G

Postpartum telephone interview with the participant - 3 months after due date

TIMELINE

BDRN interview _____

Questionnaire _____

Consent to the follow-up interview _____

Follow-up interview _____

IF THE QUESTIONNAIRE HAS NOT BEEN COMPLETED, FILL IT

OBSTETRIC RISK FACTORS

Expected date of delivery _____

Date of delivery _____ Time_____

Length of gestation (weeks) _____

Parity and gender_____

Birth status
- O Stillbirth (a birth after a gestation period of 24 weeks (168 days) where the baby shows no sign of life when delivered)
- O Alive

Method of delivery
- O Spontaneous –Spontaneous cephalic vaginal delivery, Normal delivery and Other breech delivery
- O Instrumental –Forceps cephalic delivery, Vacuum delivery and Breech extraction delivery
- O Caesarean –Elective caesarean delivery and Other caesarean delivery (includes emergency caesarean delivery)
- O Other – Caesarean hysterectomy
- O Unknown

Method of onset of labour
- O Spontaneous – includes spontaneous onset only
- O Induced – includes surgical induction, medical induction and combination of surgical and medical induction
- O Caesarean – includes caesarean section only
- O Method of onset not applicable or not known

Normal delivery (without induction, without the use of instruments, not by caesarean section and without general, spinal or epidural anesthetic before or during delivery. Procedures related to assisted deliveries are excluded, except repair of laceration)
- O Yes
- O No

Length of labour (in hours)_____
Postnatal days of stay _____

Complication during pregnancy (maternal or fetal medical condition severe enough to warrant treatment by the antenatal healthcare provider, either as an outpatient or through hospital admission - antepartum hemorrhage, gestational diabetes and pre-eclampsia)
- O Yes
- O No

Delivery complications (breech presentation, fetal distress and cord accidents)
- O Yes
- O No

APGAR 1   /10

APGAR 5   /10

COMMENTS:

Edema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium:

- O   NO
- O   Pre-existing hypertension
- O   Pre-existing hypertension with pre-eclampsia/eclampsia (please, rate also one of the following)
- O   Gestational edema and proteinuria without hypertension (Development of significant proteinuria (>=0.3 g/l) after 20 weeks of gestation or during labor and/or within 48 hours of delivery)
- O   Gestational hypertension without significant proteinuria (Hypertension without the development of significant proteinuria (<0.3 g/l), after 20 weeks of gestation or during labor and/or within 48 hours of delivery)
- O   Pre-eclampsia (Development of gestational hypertension and significant proteinuria after 20 weeks of gestation or during labor and/or within 48 hours of delivery)
- O   Eclampsia (Convulsions ante, intra- or postpartum)
- O   Unspecified maternal hypertension (Hypertension found when blood pressure is recorded for the first time after 20 weeks of gestation or during labor and/or within 48 hours of delivery)

PSYCHOLOGICAL STRESSORS

BREASTFEEDING and SLEEP

Length of breastfeeding (weeks) _____

Frequency of breastfeeding_____

Sleep pattern_____

Comments

ID

INITIALS

LIFE CHARTING

Severity

ID

INITIALS

EPISODES OF ILLNESS

SCID – MAJOR DEPRESSION
SCID – MANIA
SCID- PSYCHOSIS

LENGTH

OUTPATIENT TREATMENT

INPATIENT TREATMENT
O   General adult psychiatric unit without baby
O   General adult psychiatric unit with baby
O   M&B unit

Medications

COMPULSORY TREATMENT
O   Yes
O   No

COMMENTS

BRIEF HISTORY OF ILLNESS IN PREGNANCY AND POSTPARTUM

Have you experienced during pregnancy or after childbirth periods of depression when you may have felt sad, been unable to positively enjoy things, had less energy than usual or had thoughts that life was not worth living?

If yes

- Approximately when did these episodes occur?

- Were you able to take care of your child?

- Did you receive treatment for these periods of low mood? (such as counselling, antidepressants by GP or psychiatrist, ECT or admission to hospital)

Have you experienced during pregnancy or after childbirth periods of high or irritable mood when you may have experienced your thoughts racing through your mind, been more active and energetic than usual or felt especially efficient at work or in your daily activities?

If yes

- Approximately when did these episodes occur?

- Were you able to take care of your child?

- Have you received treatment for these periods of high mood (such as Lithium, Depakote, Olanzapine, Haloperidol by GP or psychiatrist or admission to hospital)?

DEPRESSION

Since pregnant..

- 6.001 Depressed mood

Have you ever felt sad, downcast, gloomy, despairing or deeply depressed?

- 7.004 Loss of interests

Have you lost interest in work, your recreations, and appearance?
Check this was a definite loss compared from normal

- 6.004 Capacity for enjoyment

Have you ever lost the ability to positively enjoy things like working at your hobbies or interests, having a nice meal with friends?

- 6.012 Tedium vitae

Have you ever thought that life was not worth living, or you didn't care if you wake up?
Have you ever wished you had a fatal disease?

- 6.011 Suicide or self-harm

Have you ever thought about harming yourself or even made an attempt at suicide?

- 6.009 Morning depression

At what time of the day *does* the depression feel worse?

- 6.017 Loss of self-esteem

Have you felt less competent, inferior or worthless compared to other people?

- 6.013 Pathological guilt

Have you tended to blame yourself for things you had done? Or have you felt guilty or ashamed of yourself?

- 6.015 Loss of self confidence with other people

How confident have you felt in yourself- in talking to others and managing relationships with others?

- 6.016 Social withdrawal

Have you ever wanted to stay away from other people? Have you answered the door or telephone? Or have you tried to avoid company of others?

- 7.002 Loss of concentration

Has your concentration been as good as usual or has your attention wandered?

- 7.003 Subjectively inefficient thinking

Have simple decisions been hard to make? Have you found your thoughts have been much slower?

- 7.005 Subjective feeling of retardation

Have you felt as though you are slowed down in your movements, as though everyone and everything is moving much faster?

- 7.006 Loss of energy

Have you ever felt as though you have lost energy or vigour?
Check this was a definite loss compared from normal

- Agitated anxiety (in the context of depression)

Were you so fidgety and restless that you couldn't sit still?

- Mixed episodes

During episodes of depression, have you also experienced (even for brief periods) manic-type symptoms such as elevated mood, increased energy, racing thoughts and increased self esteem?

MANIA

Since pregnancy….

- 10.001 Expansive (elevated) mood

Have you ever felt intensely happy or elated?

- 10.002 Irritable mood

Have you found that you were easily irritated?

- 10.004 Pressing and racing thoughts

Have you ever found your thoughts crowded into and raced through your mind- as though they were speeded up?

- 10.005 Over-talkativeness

Have people said that you talked too fast and too much so that they couldn't understand you? Did you feel a pressure to keep talking?

- 10.006 Distractibility

Have you found that you could not keep your attention on one subject long enough to deal with it properly?

- 10.007 Self-reported over activity

Have you ever been more active than usual- so active that you or other people thought something was wrong?

- 10.010 Exaggerated self esteem

Have you ever felt especially efficient at work or in your daily activities- as though you had super powers or talents?

- 10.012 Actions based on expansive mood

Have you ever done anything that you wouldn't normally do, like spend a lot of money, gamble, give inappropriate gifts, drive recklessly?

- 10.013 Decreased need for sleep

Are you able to manage with far less sleep than usual without seeming to get tired?

- 10.014 Socially embarrassing behaviour

Have you been more sociable than usual? Were you ever over-familiar or inappropriate?

- 10.015 Increased sexual drive or activity

Have you found that your sex drive or interest in sex increased?

- Dysphoric Mania

During episodes of high mood, did you ever also experience (even for brief periods) depressive-type symptoms such as low mood, loss of energy, hopelessness or suicidal feelings?

HALLUCINATIONS, THOUGHT DISORDER, REPLACEMENT OF WILL &

DELUSIONS

..Since pregnancy

- **Probe question: Hearing noises/voices**

Have you ever heard noises or voices when there was nobody around and no ordinary explanation seemed possible?

IF YES

17.009 Third person Auditory Hallucinations
Did you ever hear voices talking about you between themselves or did you ever hear a single voice talking about you?

17.008 Voice(s) commenting on thoughts or actions
Did a voice comment on your thoughts or actions?

- **Probe question: Visual Hallucinations**

Have you ever had visions or seen things other people couldn't see?

- Other hallucinations (17.022, 17.026, 17.028)
Have you ever noticed any unusual smells that you couldn't account for or any unusual sexual sensations or noticed any other strange or inexplicable sensations of touch, taste, or temperature, or pain, or floating? Or like a crawling sensation under the skin?

- **Probe Question: Interference with thoughts**

Have you ever felt some outside force or person was interfering with or controlling your thoughts or felt that your thoughts were being read?

- **Probe Question: Experience of Replacement of Will**

Have you ever felt some outside force or person was controlling your actions?

19.004 Delusions of reference
Have you ever felt the TV, radio or newspaper were talking about you? or giving messages to you? Have people ever seemed to drop hints meant for you, or say things with double meanings?

- 19.003 Delusions of being spied upon

Have people seemed to talk about you, check up on you, or follow you about, or record your movements?

- 19.012 Delusions of persecution

Have you ever experienced the feeling that someone or some organisation was trying to harm you?

- 19.021 Religious delusions

Have you ever been unusually preoccupied with religious ideas for example thoughts about God or the Devil?

- 10.016/19.029 Delusions of grandiose ability or 10.017/19.030 identity

Have you ever felt that you or your baby have had special powers? or thought you were somebody special?

- Delusions of guilt or worthlessness (6.018/19.025)

Have you ever felt responsible for a crime, evil or harm to others?

- (OPCRIT item 57) Delusions of poverty

Have you ever believed that you have lost all of your money or property?

- (OPCRIT item 58) Nihilistic delusions

Have you ever felt that part of your body had disappeared or was rotting away or was affected by some devastating or malignant disorder or did you ever believe that you were dead?

General probe question
Have you ever had any other unusual or abnormal experiences when your mind has played tricks on you that looking back now seems strange or unusual?

DURING: Mania   Depression   At other times   UK

MATERNITY RELATED SYMPTOMS

Have you ever had any unwanted thoughts about the baby?

Have you ever had any excessive worries about the baby?

Bibliography

[1] A. Diflorio and I. Jones, "Is sex important? gender differences in bipolar disorder," *International Review of Psychiatry*, vol. 22, no. 5, pp. 437–452, 2010.

[2] WHO — World Health Organization, "Burden of disease: Dalys," 2008.

[3] I. Jones and R. Cantwell, "The classification of perinatal mood disorders–suggestions for dsmv and icd11.," *Arch Womens Ment Health*, vol. 13, no. 1, pp. 33–36, 2010.

[4] V. Sharma, V. K. Burt, and H. L. Ritchie, "Bipolar ii postpartum depression: Detection, diagnosis, and treatment.," *Am J Psychiatry*, vol. 166, no. 11, pp. 1217–1221, 2009.

[5] American Psychiatric Association, "Dsm-iv: Diagnostic and statistical manual of mental disorders."

[6] A. C. Viguera, L. Tondo, A. E. Koukopoulos, D. Reginaldi, B. Lepri, and R. J. Baldessarini, "Episodes of mood disorders in 2,252 pregnancies and postpartum periods.," *Am J Psychiatry*, vol. 168, no. 11, pp. 1179–1185, 2011.

[7] T. Munk-Olsen, T. M. Laursen, S. Meltzer-Brody, P. B. Mortensen, and I. Jones, "Psychiatric disorders with postpartum onset: possible early manifestations of bipolar affective disorders.," *Arch Gen Psychiatry*, vol. 69, no. 4, pp. 428–434, 2012.

[8] R. E. Kendell, "Clinical validity.," *Psychol Med*, vol. 19, no. 1, pp. 45–55, 1989.

[9] D. Suzuki, "The basis of buddhist philosophy," 1980.

[10] J. Scadding, "The clinician and the computer," January 1968.

[11] T. Kuhn, *The Structure of Scientific Revolutions*, vol. II. University of Chicago Press, second ed., 1970.

[12] K. Popper, *Science: conjectures and refutations*. London: Routledge and Keagan Paul, 1963.

[13] W. James, *What is an emotion?* Wilder Publications, 2007.

[14] G. E. Berrios, "The psychopathology of affectivity: conceptual and historical aspects.," *Psychol Med*, vol. 15, no. 4, pp. 745–758, 1985.

[15] J. Phillips, A. Frances, M. A. Cerullo, J. Chardavoyne, H. S. Decker, M. B. First, N. Ghaemi, G. Greenberg, A. C. Hinderliter, W. A. Kinghorn, S. G. LoBello, E. B. Martin, A. L. Mishara, J. Paris, J. M. Pierre, R. W. Pies, H. A. Pincus, D. Porter, C. Pouncey, M. A. Schwartz, T. Szasz, J. C. Wakefield, G. S. Waterman, O. Whooley, and P. Zachar, "The six most essential questions in psychiatric diagnosis: a pluralogue part 3: issues of utility and alternative approaches in psychiatric diagnosis.," *Philos Ethics Humanit Med*, vol. 7, p. 9, 2012.

[16] S. Varga, "Defining mental disorder. exploring the 'natural function' approach.," *Philos Ethics Humanit Med*, vol. 6, p. 1, 2011.

[17] R. Kendell and A. Jablensky, "Distinguishing between the validity and utility of psychiatric diagnoses.," *Am J Psychiatry*, vol. 160, no. 1, pp. 4–12, 2003.

[18] R. M. Albert DA, Munson R., *Reasoning in medicine*. Baltimore: The Johns Hopkins University Press, 1988.

[19] T. Szasz, *The Myth of Mental Illness*. Harmondsworth: Penguin, 1970.

[20] I. Brockington, "Postpartum psychiatric disorders.," *Lancet*, vol. 363, no. 9405, pp. 303–310, 2004.

[21] W. H. Organization, *The ICD-10 classification of mental and behavioural*

disorders: diagnostic criteria for research. World Health Organization, 1993.

[22] K. Jasper, *Allgemeine Psychopathologie: Ein Leitfaden für Studierende, Ärzte und Psychologen.* Springer-Verlag Berlin and Heidelberg GmbH and Co, 8th edition ed., 1973.

[23] E. Robins and S. B. Guze, "Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia.," *Am J Psychiatry*, vol. 126, no. 7, pp. 983–987, 1970.

[24] K. S. Kendler, "The nosologic validity of paranoia (simple delusional disorder). a review.," *Arch Gen Psychiatry*, vol. 37, no. 6, pp. 699–706, 1980.

[25] S. N. Stefanis CN, *Depressive Disorders*, vol. 1, ch. Diagnosis of Depressive Disorders: A Review,. John Wiley and Sons, Ltd, 2001.

[26] M. Fink and M. A. Taylor, "Resurrecting melancholia.," *Acta Psychiatr Scand Suppl*, no. 433, pp. 14–20, 2007.

[27] J. Angst and A. Marneros, "Bipolarity from ancient to modern times: conception, birth and rebirth.," *J Affect Disord*, vol. 67, no. 1-3, pp. 3–19, 2001.

[28] J.-P. Falret, "Mémoire sur la folie circulaire," *Bulletin de l'Académie Imperiale de Médecine*, vol. 19, 1854.

[29] S. K. Kahlbaum, *Die Gruppierung der psychischen Krankheiten und die Eintheilung der Seelenstörungen.* Kafemann, 1863.

[30] E. Kraepelin, *Psychiatrie. Ein Lehrbuch für Studirende und Aerzte.* J. A. Barth , Liepzig, 1899.

[31] C. Wernicke, *Grundriss der Psychiatrie in klinischen Vorlesungen: Psycho-physiologische. Theil II. Die paranoischen Zustände.* Thieme, 1900.

[32] A. Marneros, "Expanding the group of bipolar disorders.," *J Affect Disord*, vol. 62, no. 1-2, pp. 39–44, 2001.

[33] D. J. Smith and N. Craddock, "Unipolar and bipolar depression: different of the same?," *Br J Psychiatry*, vol. 199, no. 4, pp. 272–274, 2011.

[34] L. Forty, D. Smith, L. Jones, I. Jones, S. Caesar, C. Fraser, K. Gordon-Smith, and N. Craddock, "Identifying hypomanic features in major depressive disorder using the hypomania checklist (hcl-32).," *J Affect Disord*, vol. 114, no. 1-3, pp. 68–73, 2009.

[35] H. S. Akiskal and O. Pinto, "The evolving bipolar spectrum. prototypes i, ii, iii, and iv.," *Psychiatr Clin North Am*, vol. 22, no. 3, pp. 517–534, 1999.

[36] S. K. Kahlbaum, "Über cyklisches irresein," *Breslauer ärztliche Zeitschrift*, no. 19, 1882.

[37] E. Kraepelin, *Manic-depressive insanity and paranoia.* Livingstone, 1921.

[38] M. E. Kretschmer E, *Physique and character: an investigation of the nature of constitution and of the theory of temperament.* Humanities Press, 1951.

[39] K. Schneider, *Psychopathic personalities.* Cassell, 1958.

[40] H. S. Akiskal, K. K. Akiskal, G. Perugi, C. Toni, G. Ruffolo, and G. Tusini, "Bipolar ii and anxious reactive "comorbidity": toward better phenotypic characterization suitable for genotyping.," *J Affect Disord*, vol. 96, no. 3, pp. 239–247, 2006.

[41] J. T. R. Walters and M. J. Owen, "Endophenotypes in psychiatric genetics.," *Mol Psychiatry*, vol. 12, no. 10, pp. 886–890, 2007.

[42] H. S. Akiskal, A. M. Djenderedjian, R. H. Rosenthal, and M. K. Khani, "Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group.," *Am J Psychiatry*, vol. 134, no. 11, pp. 1227–1233, 1977.

[43] N. Craddock and M. J. Owen, "The kraepelinian dichotomy - going, going... but still not gone.," *Br J Psychiatry*, vol. 196, no. 2, pp. 92–95, 2010.

[44] A. Marneros, "The schizoaffective phenomenon: the state of the art.,"

Acta Psychiatr Scand Suppl, no. 418, pp. 29–33, 2003.

[45] E. K. Green, D. Grozeva, V. Moskvina, M. L. Hamshere, I. R. Jones, L. Jones, L. Forty, S. Caesar, K. Gordon-Smith, C. Fraser, E. Russell, D. St Clair, A. H. Young, N. Ferrier, A. Farmer, P. McGuffin, P. A. Holmans, M. J. Owen, M. C. O'Donovan, and N. Craddock, "Variation at the gabaa receptor gene, rho 1 (gabrr1) associated with susceptibility to bipolar schizoaffective disorder.," *Am J Med Genet B Neuropsychiatr Genet*, vol. 153B, no. 7, pp. 1347–1349, 2010.

[46] N. Craddock, L. Jones, I. R. Jones, G. Kirov, E. K. Green, D. Grozeva, V. Moskvina, I. Nikolov, M. L. Hamshere, D. Vukcevic, S. Caesar, K. Gordon-Smith, C. Fraser, E. Russell, N. Norton, G. Breen, D. St Clair, D. A. Collier, A. H. Young, I. N. Ferrier, A. Farmer, P. McGuffin, P. A. Holmans, P. Donnelly, M. J. Owen, and M. C. O'Donovan, "Strong genetic evidence for a selective influence of gabaa receptors on a component of the bipolar disorder phenotype.," *Mol Psychiatry*, vol. 15, no. 2, pp. 146–153, 2010.

[47] N. Craddock, M. J. Owen, and M. C. O'Donovan, "The catechol-o-methyl transferase (comt) gene as a candidate for psychiatric phenotypes: evidence and lessons.," *Mol Psychiatry*, vol. 11, no. 5, pp. 446–458, 2006.

[48] B. Pfuhlmann, G. Stober, E. Franzek, and H. Beckmann, "Cycloid psychoses predominate in severe postpartum psychiatric disorders.," *J Affect Disord*, vol. 50, no. 2-3, pp. 125–134, 1998.

[49] P. B. Jabs B, Stöber G, "Cycloid psychoses: Clinical symptomatology, prognosis, and heredity," *Revista do Serviço de Psiquiatria do Hospital Fernando Fonseca*, pp. 10–16, 1998.

[50] B. H. Leonhard K, *Classification of Endogenous Psychoses and Their Differential Etiology*. Springer, 1999.

[51] C. Perris and I. Brockington, *Biological Psychiatry*, ch. Cycloid psychoses and their relation to the major psychoses. Elsevier, 1981.

[52] R. E. Kendell, J. C. Chalmers, and C. Platz, "Epidemiology of puerperal psychoses.," *Br J Psychiatry*, vol. 150, pp. 662–673, 1987.

[53] C. Henshaw, "Mood disturbance in the early puerperium: a review.," *Arch Womens Ment Health*, vol. 6 Suppl 2, pp. S33–42, 2003.

[54] I. Brockington, "Diagnosis and management of post-partum disorders: a review," *World Psychiatry*, vol. 3, pp. 89–95, Jun 2004.

[55] WHO — World Health Organization, "International statistical classification of diseases and related health problems 10th revision," 2008.

[56] L. S. Cohen, L. L. Altshuler, B. L. Harlow, R. Nonacs, D. J. Newport, A. C. Viguera, R. Suri, V. K. Burt, V. Hendrick, A. M. Reminick, A. Loughead, A. F. Vitonis, and Z. N. Stowe, "Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment.," *JAMA*, vol. 295, no. 5, pp. 499–507, 2006.

[57] M. C. Blehar, J. R. J. DePaulo, E. S. Gershon, T. Reich, S. G. Simpson, and J. I. J. Nurnberger, "Women with bipolar disorder: findings from the nimh genetics initiative sample.," *Psychopharmacol Bull*, vol. 34, no. 3, pp. 239–243, 1998.

[58] A. C. Viguera, R. Nonacs, L. S. Cohen, L. Tondo, A. Murray, and R. J. Baldessarini, "Risk of recurrence of bipolar disorder in pregnant and non-pregnant women after discontinuing lithium maintenance.," *Am J Psychiatry*, vol. 157, no. 2, pp. 179–184, 2000.

[59] I. Jones and N. Craddock, "Familiality of the puerperal trigger in bipolar disorder: results of a family study.," *Am J Psychiatry*, vol. 158, no. 6, pp. 913–917, 2001.

[60] M. P. Freeman, K. W. Smith, S. A. Freeman, S. L. McElroy, G. E. Kmetz, R. Wright, and P. E. J. Keck, "The impact of reproductive events on the course of bipolar disorder in women.," *J Clin Psychiatry*, vol. 63, no. 4, pp. 284–287, 2002.

[61] M. Eberhard-Gran, K. Tambs, S. Opjordsmoen, A. Skrondal, and A. Eskild, "Depression during pregnancy and after delivery: a repeated measurement study.," *J Psychosom Obstet Gynaecol*, vol. 25, no. 1, pp. 15–21, 2004.

[62] J. L. Payne, P. S. Roy, K. Murphy-Eberenz, M. M. Weismann, K. L.

Swartz, M. G. McInnis, E. Nwulia, F. M. Mondimore, D. F. MacKinnon, E. B. Miller, J. I. Nurnberger, D. F. Levinson, J. R. J. DePaulo, and J. B. Potash, "Reproductive cycle-associated mood symptoms in women with major depression and bipolar disorder.," *J Affect Disord*, vol. 99, no. 1-3, pp. 221–229, 2007.

[63] B. L. Harlow, A. F. Vitonis, P. Sparen, S. Cnattingius, H. Joffe, and C. M. Hultman, "Incidence of hospitalization for postpartum psychotic and bipolar episodes in women with and without prior prepregnancy or prenatal psychiatric hospitalizations.," *Arch Gen Psychiatry*, vol. 64, no. 1, pp. 42–48, 2007.

[64] A. C. Viguera, T. Whitfield, R. J. Baldessarini, D. J. Newport, Z. Stowe, A. Reminick, A. Zurick, and L. S. Cohen, "Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation.," *Am J Psychiatry*, vol. 164, no. 12, pp. 1817–1824, 2007.

[65] T. Munk-Olsen, T. M. Laursen, T. Mendelson, C. B. Pedersen, O. Mors, and P. B. Mortensen, "Risks and predictors of readmission for a mental disorder during the postpartum period.," *Arch Gen Psychiatry*, vol. 66, no. 2, pp. 189–195, 2009.

[66] F. Colom, N. Cruz, I. Pacchiarotti, L. Mazzarini, J. M. Goikolea, E. Popova, C. Torrent, and E. Vieta, "Postpartum bipolar episodes are not distinct from spontaneous episodes: implications for dsm-v.," *J Affect Disord*, vol. 126, no. 1-2, pp. 61–64, 2010.

[67] I. M. Terp and P. B. Mortensen, "Post-partum psychoses. clinical diagnoses and relative risk of admission after parturition.," *Br J Psychiatry*, vol. 172, pp. 521–526, 1998.

[68] T. Munk-Olsen, T. M. Laursen, C. B. Pedersen, O. Mors, and P. B. Mortensen, "New parents and mental disorders: a population-based register study.," *JAMA*, vol. 296, no. 21, pp. 2582–2589, 2006.

[69] T. M. Laursen and T. Munk-Olsen, "Reproductive patterns in psychotic patients.," *Schizophr Res*, vol. 121, no. 1-3, pp. 234–240, 2010.

[70] L. Kessing, "A comparison of icd-8 and icd-10 diagnoses of affective disor-

der -a case register study from denmark.," *Eur Psychiatry*, vol. 13, no. 7, pp. 342–345, 1998.

[71] S. O. Hoffmann, "Neurotic depression–a disease without a diagnosis or a diagnosis without a glossary?].," *Z Psychosom Med Psychother*, vol. 49, no. 4, pp. 346–362, 2003.

[72] I. Jones, J. Heron, E. R. Blackmore, and N. Craddock, "Incidence of hospitalization for postpartum psychotic and bipolar episodes.," *Arch Gen Psychiatry*, vol. 65, no. 3, p. 356, 2008.

[73] H. J. Freyberger and H. Dilling, "Recent aspects in psychiatric diagnosis with special reference to depression and anxiety disorders].," *Internist (Berl)*, vol. 35, no. 9, pp. 814–822, 1994.

[74] V. Sharma and M. Khan, "Identification of bipolar disorder in women with postpartum depression.," *Bipolar Disord*, vol. 12, no. 3, pp. 335–340, 2010.

[75] C. Tetlow, "Psychoses of childbearing.," *J Ment Sci*, vol. 101, no. 424, pp. 629–639, 1955.

[76] R. S. J. Paffenbarger, "Epidemiological aspects of parapartum mental illness.," *Br J Prev Soc Med*, vol. 18, pp. 189–195, 1964.

[77] I. Brockington, G. Winokur, and C. Dean, *Motherhood and Mental Illness*, ch. Puerperal psychosis, pp. 37–59. Academic Press, 1982.

[78] J. Heron, E. Robertson Blackmore, M. McGuinness, N. Craddock, and I. Jones, "No 'latent period' in the onset of bipolar affective puerperal psychosis.," *Arch Womens Ment Health*, vol. 10, no. 2, pp. 79–81, 2007.

[79] L. H. Chaudron and R. W. Pies, "The relationship between postpartum psychosis and bipolar disorder: a review.," *J Clin Psychiatry*, vol. 64, no. 11, pp. 1284–1292, 2003.

[80] V. Bergink, M. P. Lambregtse-van den Berg, K. M. Koorengevel, R. Kupka, and S. A. Kushner, "First-onset psychosis occurring in the postpartum period: a prospective cohort study.," *J Clin Psychiatry*, vol. 72, no. 11, pp. 1531–1537, 2011.

[81] C. Dean and R. E. Kendell, "The symptomatology of puerperal illnesses.," *Br J Psychiatry*, vol. 139, pp. 128–133, 1981.

[82] E. S. Meltzer and R. Kumar, "Puerperal mental illness, clinical features and classification: a study of 142 mother-and-baby admissions.," *Br J Psychiatry*, vol. 147, pp. 647–654, 1985.

[83] T. Okano, J. Nomura, R. Kumar, E. Kaneko, R. Tamaki, I. Hanafusa, M. Hayashi, and A. Matsuyama, "An epidemiological and clinical investigation of postpartum psychiatric illness in japanese mothers.," *J Affect Disord*, vol. 48, no. 2-3, pp. 233–240, 1998.

[84] L. Forty, L. Jones, S. Macgregor, S. Caesar, C. Cooper, A. Hough, L. Dean, S. Dave, A. Farmer, P. McGuffin, S. Brewster, N. Craddock, and I. Jones, "Familiality of postpartum depression in unipolar disorder: results of a family study.," *Am J Psychiatry*, vol. 163, no. 9, pp. 1549–1553, 2006.

[85] S. Pawlby, D. Hay, D. Sharp, C. S. Waters, and C. M. Pariante, "Antenatal depression and offspring psychopathology: the influence of childhood maltreatment.," *Br J Psychiatry*, vol. 199, no. 2, pp. 106–112, 2011.

[86] I. Jones, M. Hamshere, J.-M. Nangle, P. Bennett, E. Green, J. Heron, R. Segurado, D. Lambert, P. Holmans, A. Corvin, M. Owen, L. Jones, M. Gill, and N. Craddock, "Bipolar affective puerperal psychosis: genome-wide significant evidence for linkage to chromosome 16.," *Am J Psychiatry*, vol. 164, no. 7, pp. 1099–1104, 2007.

[87] I. Jones and N. Craddock, "Do puerperal psychotic episodes identify a more familial subtype of bipolar disorder? results of a family history study.," *Psychiatr Genet*, vol. 12, no. 3, pp. 177–180, 2002.

[88] N. Coyle, I. Jones, E. Robertson, C. Lendon, and N. Craddock, "Variation at the serotonin transporter gene influences susceptibility to bipolar affective puerperal psychosis.," *Lancet*, vol. 356, no. 9240, pp. 1490–1491, 2000.

[89] E. Robertson, I. Jones, F. Middle, J. Moray, and N. Craddock, "No association between two polymorphisms at the 5ht2a gene and bipolar affective puerperal psychosis.," *Acta Psychiatr Scand*, vol. 108, no. 5, pp. 387–391, 2003.

[90] I. Jones, F. Middle, F. McCandless, N. Coyle, E. Robertson, I. Brockington, C. Lendon, and N. Craddock, "Molecular genetic studies of bipolar disorder and puerperal psychosis at two polymorphisms in the estrogen receptor alpha gene (esr 1).," *Am J Med Genet*, vol. 96, no. 6, pp. 850–853, 2000.

[91] J. Feng, J. Yan, S. Michaud, N. Craddock, I. R. Jones, E. H. J. Cook, D. Goldman, L. L. Heston, L. Peltonen, L. E. Delisi, and S. S. Sommer, "Scanning of estrogen receptor alpha (eralpha) and thyroid hormone receptor alpha (tralpha) genes in patients with psychiatric diseases: four missense mutations identified in eralpha gene.," *Am J Med Genet*, vol. 105, no. 4, pp. 369–374, 2001.

[92] F. Middle, I. Jones, E. Robertson, C. Lendon, and N. Craddock, "Tumour necrosis factor alpha and bipolar affective puerperal psychosis.," *Psychiatr Genet*, vol. 10, no. 4, pp. 195–198, 2000.

[93] E. R. Blackmore, I. Jones, M. Doshi, S. Haque, R. Holder, I. Brockington, and N. Craddock, "Obstetric variables associated with bipolar affective puerperal psychosis.," *Br J Psychiatry*, vol. 188, pp. 32–36, 2006.

[94] V. Sharma, A. Smith, and M. Khan, "The relationship between duration of labour, time of delivery, and puerperal psychosis.," *J Affect Disord*, vol. 83, no. 2-3, pp. 215–220, 2004.

[95] I. Jones and N. Craddock, "Bipolar disorder and childbirth: the importance of recognising risk.," *Br J Psychiatry*, vol. 186, pp. 453–454, 2005.

[96] R. Cantwell, T. Clutton-Brock, G. Cooper, A. Dawson, J. Drife, D. Garrod, A. Harper, D. Hulbert, S. Lucas, J. McClure, H. Millward-Sadler, J. Neilson, C. Nelson-Piercy, J. Norman, C. O'Herlihy, M. Oates, J. Shakespeare, M. de Swiet, C. Williamson, V. Beale, M. Knight, C. Lennox, A. Miller, D. Parmar, J. Rogers, and A. Springett, "Saving mothers' lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. the eighth report of the confidential enquiries into maternal deaths in the united kingdom.," *BJOG*, vol. 118 Suppl 1, pp. 1–203, 2011.

[97] S. Jones, I ; Smith, "Puerperal psychosis: identifying and caring for women at risk," *Advances in Psychiatric Treatment*, vol. 15, pp. 411–418, 2009.

[98] J. Heron, M. McGuinness, E. R. Blackmore, N. Craddock, and I. Jones, "Early postpartum symptoms in puerperal psychosis.," *BJOG*, vol. 115, no. 3, pp. 348–353, 2008.

[99] National Institute for Health and Clinical Excellence, "Antenatal and postnatal mental health: clinical management and service guidance."

[100] E. Robertson, I. Jones, S. Haque, R. Holder, and N. Craddock, "Risk of puerperal and non-puerperal recurrence of illness following bipolar affective puerperal (post-partum) psychosis.," *Br J Psychiatry*, vol. 186, pp. 258–259, 2005.

[101] J. Evans, J. Heron, H. Francomb, S. Oke, and J. Golding, "Cohort study of depressed mood during pregnancy and after childbirth.," *BMJ*, vol. 323, no. 7307, pp. 257–260, 2001.

[102] V. Hendrick, L. L. Altshuler, and R. Suri, "Hormonal changes in the postpartum and implications for postpartum depression.," *Psychosomatics*, vol. 39, no. 2, pp. 93–101, 1998.

[103] M. Bloch, P. J. Schmidt, M. Danaceau, J. Murphy, L. Nieman, and D. R. Rubinow, "Effects of gonadal steroids in women with a history of postpartum depression.," *Am J Psychiatry*, vol. 157, no. 6, pp. 924–930, 2000.

[104] E. J. Corwin and K. Pajer, "The psychoneuroimmunology of postpartum depression.," *J Womens Health (Larchmt)*, vol. 17, no. 9, pp. 1529–1534, 2008.

[105] M. O'Hara and A. Swain, "Rates and risks of postpartum depression: a meta- analysis," *Int Rev Psychiatry*, vol. 8, pp. 37–54, 1996.

[106] S. A. Treloar, N. G. Martin, K. K. Bucholz, P. A. Madden, and A. C. Heath, "Genetic influences on post-natal depressive symptoms: findings from an australian twin sample.," *Psychol Med*, vol. 29, no. 3, pp. 645–654, 1999.

[107] P. B. Mahon, J. L. Payne, D. F. MacKinnon, F. M. Mondimore, F. S. Goes, B. Schweizer, D. Jancic, W. H. Coryell, P. A. Holmans, J. Shi, J. A. Knowles, W. A. Scheftner, M. M. Weissman, D. F. Levinson, J. R. J. DePaulo, P. P. Zandi, and J. B. Potash, "Genome-wide linkage and follow-

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up association study of postpartum mood symptoms.," *Am J Psychiatry*, vol. 166, no. 11, pp. 1229–1237, 2009.

[108] C.-L. Dennis and L. Ross, "Relationships among infant sleep patterns, maternal fatigue, and development of depressive symptomatology.," *Birth*, vol. 32, no. 3, pp. 187–193, 2005.

[109] C. T. Beck, "Predictors of postpartum depression: an update.," *Nurs Res*, vol. 50, no. 5, pp. 275–285, 2001.

[110] P. Boyce and A. Hickey, "Psychosocial risk factors to major depression after childbirth.," *Soc Psychiatry Psychiatr Epidemiol*, vol. 40, no. 8, pp. 605–612, 2005.

[111] J. Heron, T. G. O'Connor, J. Evans, J. Golding, and V. Glover, "The course of anxiety and depression through pregnancy and the postpartum in a community sample.," *J Affect Disord*, vol. 80, no. 1, pp. 65–73, 2004.

[112] E. Robertson, S. Grace, T. Wallington, and D. E. Stewart, "Antenatal risk factors for postpartum depression: a synthesis of recent literature.," *Gen Hosp Psychiatry*, vol. 26, no. 4, pp. 289–295, 2004.

[113] J. Milgrom, A. W. Gemmill, J. L. Bilszta, B. Hayes, B. Barnett, J. Brooks, J. Ericksen, D. Ellwood, and A. Buist, "Antenatal risk factors for postnatal depression: a large prospective study.," *J Affect Disord*, vol. 108, no. 1-2, pp. 147–157, 2008.

[114] A. Lane, R. Keville, M. Morris, A. Kinsella, M. Turner, and S. Barry, "Postnatal depression and elation among mothers and their partners: prevalence and predictors.," *Br J Psychiatry*, vol. 171, pp. 550–555, 1997.

[115] V. Glover, P. Liddle, A. Taylor, D. Adams, and M. Sandler, "Mild hypomania (the highs) can be a feature of the first postpartum week. association with later depression.," *Br J Psychiatry*, vol. 164, no. 4, pp. 517–521, 1994.

[116] C. Musters, E. McDonald, and I. Jones, "Management of postnatal depression.," *BMJ*, vol. 337, p. a736, 2008.

[117] P. J. Surkan, K. E. Peterson, M. D. Hughes, and B. R. Gottlieb, "The

role of social networks and support in postpartum women's depression: a multiethnic urban sample.," *Matern Child Health J*, vol. 10, no. 4, pp. 375–383, 2006.

[118] M. C. Logsdon, J. C. Birkimer, and W. M. Usui, "The link of social support and postpartum depressive symptoms in african-american women with low incomes.," *MCN Am J Matern Child Nurs*, vol. 25, no. 5, pp. 262–266, 2000.

[119] E. A. Howell, P. Mora, and H. Leventhal, "Correlates of early postpartum depressive symptoms.," *Matern Child Health J*, vol. 10, no. 2, pp. 149–157, 2006.

[120] A. C. of Obstetricians and G. C. on Obstetric Practice, "Committee opinion no. 453: screening for depression during and after pregnancy.," *Obstet Gynecol*, vol. 115, pp. 394–395, 2010.

[121] G. Stein and O. Van den Akker, "The retrospective diagnosis of postnatal depression by questionnaire.," *J Psychosom Res*, vol. 36, no. 1, pp. 67–75, 1992.

[122] J. L. Cox, J. M. Holden, and R. Sagovsky, "Detection of postnatal depression. development of the 10-item edinburgh postnatal depression scale.," *Br J Psychiatry*, vol. 150, pp. 782–786, 1987.

[123] C. T. Beck and R. K. Gable, "Postpartum depression screening scale: development and psychometric testing.," *Nurs Res*, vol. 49, no. 5, pp. 272–282, 2000.

[124] A. T. BECK, C. H. WARD, M. MENDELSON, J. MOCK, and J. ERBAUGH, "An inventory for measuring depression.," *Arch Gen Psychiatry*, vol. 4, pp. 561–571, 1961.

[125] R. C. Boyd, H. N. Le, and R. Somberg, "Review of screening instruments for postpartum depression.," *Arch Womens Ment Health*, vol. 8, no. 3, pp. 141–153, 2005.

[126] A. Gelenberg, M. Freeman, and J. Markowitz, "American psychiatric association. practice guideline for the treatment of patients with major depressive disorder, 3rd ed.."

[127] New Zealand Guidelines Group, "Identification of common mental disorders and management of depression in primary care. an evidence-based best practice guideline."

[128] H. N. Austin MP, *Guidelines Expert Advisory Committee. Clinical practice guidelines for depression and related disorders - anxiety, bipolar disorder and puerperal psychosis - in the perinatal period. A guideline for primary care health professionals.* Melbourne: beyondblue: the national depression initiative, 2011.

[129] C. Zubaran, M. Schumacher, M. R. Roxo, and K. Foresti, "Screening tools for postpartum depression: validity and cultural dimensions.," *Afr J Psychiatry (Johannesbg)*, vol. 13, no. 5, pp. 357–365, 2010.

[130] J. S. Abramowitz, S. A. Schwartz, K. M. Moore, and K. R. Luenzmann, "Obsessive-compulsive symptoms in pregnancy and the puerperium: a review of the literature.," *J Anxiety Disord*, vol. 17, no. 4, pp. 461–478, 2003.

[131] C.-L. Dennis, L. E. Ross, and A. Herxheimer, "Oestrogens and progestins for preventing and treating postpartum depression.," *Cochrane Database Syst Rev*, no. 4, p. CD001690, 2008.

[132] S. Conroy, C. M. Pariante, M. N. Marks, H. A. Davies, S. Farrelly, R. Schacht, and P. Moran, "Maternal psychopathology and infant development at 18 months: the impact of maternal personality disorder and depression.," *J Am Acad Child Adolesc Psychiatry*, vol. 51, no. 1, pp. 51–61, 2012.

[133] V. Sharma, M. Khan, C. Corpse, and P. Sharma, "Missed bipolarity and psychiatric comorbidity in women with postpartum depression.," *Bipolar Disord*, vol. 10, no. 6, pp. 742–747, 2008.

[134] K. L. Wisner, K. S. Peindl, T. Gigliotti, and B. H. Hanusa, "Obsessions and compulsions in women with postpartum depression.," *J Clin Psychiatry*, vol. 60, no. 3, pp. 176–180, 1999.

[135] E. G. Altman, D. Hedeker, J. L. Peterson, and J. M. Davis, "The altman self-rating mania scale.," *Biol Psychiatry*, vol. 42, no. 10, pp. 948–955, 1997.

[136] R. M. Hirschfeld, J. B. Williams, R. L. Spitzer, J. R. Calabrese, L. Flynn, P. E. J. Keck, L. Lewis, S. L. McElroy, R. M. Post, D. J. Rapport, J. M. Russell, G. S. Sachs, and J. Zajecka, "Development and validation of a screening instrument for bipolar spectrum disorder: the mood disorder questionnaire.," *Am J Psychiatry*, vol. 157, no. 11, pp. 1873–1875, 2000.

[137] D. A. Solomon, A. C. Leon, J. D. Maser, C. J. Truman, W. Coryell, J. Endicott, J. J. Teres, and M. B. Keller, "Distinguishing bipolar major depression from unipolar major depression with the screening assessment of depression-polarity (sad-p).," *J Clin Psychiatry*, vol. 67, no. 3, pp. 434–442, 2006.

[138] C. A. Chessick and S. Dimidjian, "Screening for bipolar disorder during pregnancy and the postpartum period.," *Arch Womens Ment Health*, vol. 13, no. 3, pp. 233–248, 2010.

[139] W. Heisenberg and F. Northrop, *Physics and philosophy: The revolution in modern science*, vol. 18. Prometheus Books New York, 1999.

[140] V. Sharma and V. K. Burt, "Dsm-v: modifying the postpartum-onset specifier to include hypomania.," *Arch Womens Ment Health*, vol. 14, no. 1, pp. 67–69, 2011.

[141] L. Dossus, N. Allen, R. Kaaks, K. Bakken, E. Lund, A. Tjonneland, A. Olsen, K. Overvad, F. Clavel-Chapelon, A. Fournier, N. Chabbert-Buffet, H. Boeing, M. Schütze, A. Trichopoulou, D. Trichopoulos, P. Lagiou, D. Palli, V. Krogh, R. Tumino, P. Vineis, A. Mattiello, H. B. Bueno-de Mesquita, N. C. Onland-Moret, P. H. M. Peeters, V. Dumeaux, M.-L. Redondo, E. Duell, E. Sanchez-Cantalejo, L. Arriola, M.-D. Chirlaque, E. Ardanaz, J. Manjer, S. Borgquist, A. Lukanova, E. Lundin, K.-T. Khaw, N. Wareham, T. Key, V. Chajes, S. Rinaldi, N. Slimani, T. Mouw, V. Gallo, and E. Riboli, "Reproductive risk factors and endometrial cancer: the european prospective investigation into cancer and nutrition," *Int J Cancer*, vol. 127, pp. 442–51, Jul 2010.

[142] J. K. Wing, T. Babor, T. Brugha, J. Burke, J. E. Cooper, R. Giel, A. Jablenski, D. Regier, and N. Sartorius, "Scan. schedules for clinical assessment in neuropsychiatry.," *Arch Gen Psychiatry*, vol. 47, no. 6, pp. 589–593, 1990.

[143] G. Leverich and R. Post, "Life charting the course of bipolar disorder," *Current review of mood and anxiety disorders*, vol. 1, no. 1, pp. 48–61, 1996.

[144] H. Wainer, *Picturing the Uncertain World.* Princeton University Press, 2009.

[145] S. Clopper, C. ; Pearson, "The use of confidence or fiducial limits illustrated in the case of the binomial," *Biometrika*, vol. 26, pp. 404–413, 1934.

[146] J. Neyman, "On the problem of confidence intervals," *The Annals of Mathematical Statistics*, vol. 6, p. 116, 1935.

[147] R. Scherer, "Propcis. r package version 0.1-7," 2010.

[148] T. A. Hochberg Y, *Multiple comparison procedures.* John Wiley and Sons, Ltd, 1987.

[149] L. Toothaker, *Multiple comparisons for researchers.* Sage Publications, 1991.

[150] J. Shaffer, "Multiple hypothesis testing," *Annual Review of Psychology*, vol. 46, no. 561–584, 1995.

[151] A. Agresti, *Categorical Data Analysis.* John Wiley and Sons, Ltd, 1990.

[152] S. J. Kuritz, J. R. Landis, and G. G. Koch, "A general overview of mantel-haenszel methods: applications and recent developments.," *Annu Rev Public Health*, vol. 9, pp. 123–160, 1988.

[153] D. Bates, "Linear mixed model implementation in lme4," *Ms., University of Wisconsin*, 2012.

[154] D. Bailey and F. Alimadhi, "logit. mixed: Mixed effects logistic model," *Zelig: Everyone's Statistical Software, edited by K. Imai, G. King, and O. Lau*, 2007.

[155] J. W. Graham and S. I. Donaldson, "Evaluating interventions with differential attrition: the importance of nonresponse mechanisms and use of follow-up data.," *J Appl Psychol*, vol. 78, no. 1, pp. 119–128, 1993.

[156] J. Honaker, G. King, and M. Blackwell, "Amelia ii: A program for missing data," *R package version*, pp. 1–2, 2012.

[157] R. Little and D. Rubin, *Statistical analysis with missing data.* John Wiley and Sons, Ltd, 2002.

[158] A. Dempster, N. Laird, and D. Rubin, "Maximum likelihood from incomplete data via the em algorithm," *Journal of the Royal Statistical Society. Series B (Methodological)*, pp. 1–38, 1977.

[159] J. Bilmes *et al.*, "A gentle tutorial of the em algorithm and its application to parameter estimation for gaussian mixture and hidden markov models," *International Computer Science Institute*, vol. 4, no. 510, p. 126, 1998.

[160] C. Wu, "On the convergence properties of the em algorithm," *The Annals of Statistics*, vol. 11, no. 1, pp. 95–103, 1983.

[161] K. Imai, G. King, and O. Lau, "Zelig: Everyone's statistical software," *R package version*, pp. 3–4, 2009.

[162] K. G. Imai K, Lau O, "Logit: Logistic regression for dichotomous dependent."

[163] T. Therneau, "coxme: Mixed effects cox models," *R package version*, vol. 2, 2009.

[164] J. Tenon, *Memoires sur les Hopitaux de Paris.* Ph.-D. Pierres, 1816.

[165] M. Hamshere, K. Gordon-Smith, L. Forty, L. Jones, S. Caesar, C. Fraser, S. Hyde, J. Tredget, G. Kirov, I. Jones, *et al.*, "Age-at-onset in bipolar-i disorder: mixture analysis of 1369 cases identifies three distinct clinical sub-groups," *Journal of affective disorders*, vol. 116, no. 1, pp. 23–29, 2009.

[166] J. C. Wayman, "Multiple imputation for missing data: What is it and how can i use it?," Paper presented at the 2003 Annual Meeting of the American Educational Research Association, Chicago, IL., 2003.

[167] S. Su, A. Gelman, J. Hill, and M. Yajima, "Multiple imputation with diagnostics (mi) in r: Opening windows into the black box," *Journal of*

Statistical Software, vol. 10, no. 2.

[168] G. King, M. Tomz, and J. Wittenberg, "Making the most of statistical analyses: Improving interpretation and presentation," *American Journal of Political Science*, vol. 44, pp. 341–355, 2000.

[169] R. E. Kendell, D. Rennie, J. A. Clarke, and C. Dean, "The social and obstetric correlates of psychiatric admission in the puerperium.," *Psychol Med*, vol. 11, no. 2, pp. 341–350, 1981.

[170] P. Videbech and G. Gouliaev, "First admission with puerperal psychosis: 7-14 years of follow-up.," *Acta Psychiatr Scand*, vol. 91, no. 3, pp. 167–173, 1995.

[171] I. Kirpinar, I. Coskun, A. Caykoylu, S. Anac, and H. Ozer, "First-case postpartum psychoses in eastern turkey: a clinical case and follow-up study.," *Acta Psychiatr Scand*, vol. 100, no. 3, pp. 199–204, 1999.

[172] G. J. Thomas CI, "Psychosis after childbirth: ecological aspects of a single impact stress.," *Am J Med Sci*, vol. 238, pp. 363–88, 1959.

[173] M. N. Marks, A. Wieck, S. A. Checkley, and R. Kumar, "Life stress and post-partum psychosis: a preliminary report.," *Br J Psychiatry Suppl*, no. 10, pp. 45–49, 1991.

[174] K. Glavin, L. Smith, and R. Sorum, "Prevalence of postpartum depression in two municipalities in norway.," *Scand J Caring Sci*, vol. 23, no. 4, pp. 705–710, 2009.

[175] H. Roman, B. Blondel, G. Breart, and F. Goffinet, "Do risk factors for elective cesarean section differ from those of cesarean section during labor in low risk pregnancies?," *J Perinat Med*, vol. 36, no. 4, pp. 297–305, 2008.

[176] S. Ji, Q. Long, D. J. Newport, H. Na, B. Knight, E. B. Zach, N. J. Morris, M. Kutner, and Z. N. Stowe, "Validity of depression rating scales during pregnancy and the postpartum period: impact of trimester and parity.," *J Psychiatr Res*, vol. 45, no. 2, pp. 213–219, 2011.

[177] K. S. Peindl and K. L. Wisner, "Successful recruitment strategies for women in postpartum mental health trials.," *J Psychiatr Res*, vol. 37,

no. 2, pp. 117–125, 2003.

[178] M.-P. Austin, D. Hadzi-Pavlovic, K. Saint, and G. Parker, "Antenatal screening for the prediction of postnatal depression: validation of a psychosocial pregnancy risk questionnaire," *Acta Psychiatr Scand*, vol. 112, pp. 310–7, Oct 2005.

[179] M. Steiner, M. Macdougall, and E. Brown, "The premenstrual symptoms screening tool (psst) for clinicians.," *Arch Womens Ment Health*, vol. 6, no. 3, pp. 203–209, 2003.

[180] C. W. Allwood, M. Berk, and W. Bodemer, "An investigation into puerperal psychoses in black women admitted to baragwanath hospital.," *S Afr Med J*, vol. 90, no. 5, pp. 518–520, 2000.

[181] H. Vislie, "Puerperal mental disorders," *Acta Psychiatr Scand*, vol. 111, 1956.

[182] T. F. McNeil, "A prospective study of postpartum psychoses in a high-risk group. 1. clinical characteristics of the current postpartum episodes.," *Acta Psychiatr Scand*, vol. 74, no. 2, pp. 205–216, 1986.

[183] T. F. McNeil and G. Blennow, "A prospective study of postpartum psychoses in a high-risk group. 6. relationship to birth complications and neonatal abnormality.," *Acta Psychiatr Scand*, vol. 78, no. 4, pp. 478–484, 1988.

[184] P. Agrawal, M. S. Bhatia, and S. C. Malik, "Postpartum psychosis: a study of indoor cases in a general hospital psychiatric clinic.," *Acta Psychiatr Scand*, vol. 81, no. 6, pp. 571–575, 1990.

[185] V. Sharma and D. Mazmanian, "Sleep loss and postpartum psychosis.," *Bipolar Disord*, vol. 5, no. 2, pp. 98–105, 2003.

[186] M. N. Marks, A. Wieck, S. A. Checkley, and R. Kumar, "Contribution of psychological and social factors to psychotic and non-psychotic relapse after childbirth in women with previous histories of affective disorder.," *J Affect Disord*, vol. 24, no. 4, pp. 253–263, 1992.

[187] T. F. McNeil, G. Blennow, and L. Lundberg, "A prospective study of psy-

chosocial background factors associated with congenital malformations.,” *Acta Psychiatr Scand*, vol. 78, no. 5, pp. 643–651, 1988.

[188] R. W. Cheetham, A. Rzadkowolski, and S. Rataemane, “Psychiatric disorders of the puerperium in south african women of nguni origin. a pilot study.,” *S Afr Med J*, vol. 60, no. 13, pp. 502–506, 1981.

[189] E. OSTERMAN, “Psychopathological states of the postpartum period. the incidence, development and prognosis of these states (apropos of 65 cases),” *Encephale*, vol. 52, pp. 385–420, 1963.

[190] D. Dowlatshahi and E. S. Paykel, “Life events and social stress in puerperal psychoses: absence of effect.,” *Psychol Med*, vol. 20, no. 3, pp. 655–662, 1990.

[191] I. F. Brockington, C. Martin, G. W. Brown, D. Goldberg, and F. Margison, “Stress and puerperal psychosis.,” *Br J Psychiatry*, vol. 157, pp. 331–334, 1990.

[192] G. W. Brown and T. O. Harris, *Life Events and Illness.* The Guilford Press, 1989.

[193] R. Kumar, K. M. Robson, and A. M. Smith, “Development of a self-administered questionnaire to measure maternal adjustment and maternal attitudes during pregnancy and after delivery.,” *J Psychosom Res*, vol. 28, no. 1, pp. 43–51, 1984.

[194] R. H. Corney and A. W. Clare, “The construction, development and testing of a self-report questionnaire to identify social problems.,” *Psychol Med*, vol. 15, no. 3, pp. 637–649, 1985.

[195] G. Koren, “Pharmacokinetics in pregnancy; clinical significance.,” *J Popul Ther Clin Pharmacol*, vol. 18, no. 3, pp. e523–7, 2011.

[196] M. Patel, V. Doku, and L. Tennakoon, “Challenges in recruitment of research participants,” *Advances in Psychiatric Treatment*, vol. 9, pp. 229–238, 2003.

[197] S. Champely and M. Champely, “The pwr package,” 2007.

[198] J. Cohen, *Statistical power analysis for the behavioural science*. L Erlbaum Associates, London, 1988.

[199] C. M. Pariante, G. Seneviratne, and L. Howard, "Should we stop using tricyclic antidepressants in pregnancy?," *Psychol Med*, vol. 41, no. 1, pp. 15–17, 2011.

[200] J. Cox, A. Rooney, P. Thomas, and R. Wrate, "How accurately do mothers recall postnatal depression? further data from a 3 year follow-up study," *Journal of Psychosomatic Obstetrics & Gynecology*, vol. 3, no. 3-4, pp. 185–189, 1984.

[201] D. J. Smith, E. Griffiths, M. Kelly, K. Hood, N. Craddock, and S. A. Simpson, "Unrecognised bipolar disorder in primary care patients with depression.," *Br J Psychiatry*, vol. 199, no. 1, pp. 49–56, 2011.

[202] D. Spence, "Bad medicine: bipolar ii disorder.," *BMJ*, vol. 342, p. d2767, 2011.

[203] C.-H. Hung, "The psychosocial consequences for primiparas and multiparas.," *Kaohsiung J Med Sci*, vol. 23, no. 7, pp. 352–360, 2007.

[204] P.-Y. Robillard, G. Dekker, G. Chaouat, T. C. Hulsey, and A. Saftlas, "Epidemiological studies on primipaternity and immunology in preeclampsia–a statement after twelve years of workshops.," *J Reprod Immunol*, vol. 89, no. 2, pp. 104–117, 2011.

[205] T. Cockrill, D. J. del Junco, F. C. Arnett, S. Assassi, F. K. Tan, T. McNearney, M. Fischbach, M. Perry, and M. D. Mayes, "Separate influences of birth order and gravidity/parity on the development of systemic sclerosis.," *Arthritis Care Res (Hoboken)*, vol. 62, no. 3, pp. 418–424, 2010.

[206] L. G. Greer, B. M. Casey, L. M. Halvorson, C. Y. Spong, D. D. McIntire, and F. G. Cunningham, "Antithyroid antibodies and parity: further evidence for microchimerism in autoimmune thyroid disease.," *Am J Obstet Gynecol*, vol. 205, no. 5, pp. 471.e1–4, 2011.

[207] I. Bulow Pedersen, P. Laurberg, N. Knudsen, T. Jorgensen, H. Perrild, L. Ovesen, and L. B. Rasmussen, "Lack of association between thyroid autoantibodies and parity in a population study argues against mi-

crochimerism as a trigger of thyroid autoimmunity.," *Eur J Endocrinol*, vol. 154, no. 1, pp. 39–45, 2006.

[208] M. A. S. d. O. Dode and I. S. dos Santos, "Non classical risk factors for gestational diabetes mellitus: a systematic review of the literature.," *Cad Saude Publica*, vol. 25 Suppl 3, pp. S341–59, 2009.

[209] J. Reid, "On the causes, symptoms and treatment of puerperal insanity," *Journal of Psychocological Medicine*, vol. 1, pp. 128–51, 1848.

[210] S. M. Cripe, I. O. Frederick, C. Qiu, and M. A. Williams, "Risk of preterm delivery and hypertensive disorders of pregnancy in relation to maternal co-morbid mood and migraine disorders during pregnancy.," *Paediatr Perinat Epidemiol*, vol. 25, no. 2, pp. 116–123, 2011.

[211] I. F. Brockington, *Eclamptic psychosis. Eileithyia's mischief: the organic psychoses of pregnancy, parturition and the puerperium.* Bredenbury: Eyry Press, 2006.

[212] M. C. Chames, J. C. Livingston, T. S. Ivester, J. R. Barton, and B. M. Sibai, "Late postpartum eclampsia: a preventable disease?," *Am J Obstet Gynecol*, vol. 186, pp. 1174–7, Jun 2002.

[213] R. Kurup and P. Kurup, "Hypothalamic digoxin and hypomagnesemia in human pre-eclampsic toxemia, cortical venous thrombosis, and postpartum psychosis," *The Journal of Trace Elements in Experimental Medicine*, vol. 15, no. 4, pp. 171–190, 2002.

[214] F. J. Barbosa, B. Hesse, R. B. de Almeida, I. P. Baretta, R. Boerngen-Lacerda, and R. Andreatini, "Magnesium sulfate and sodium valproate block methylphenidate-induced hyperlocomotion, an animal model of mania," *Pharmacol Rep*, vol. 63, no. 1, pp. 64–70, 2011.

[215] N. Gleicher *et al.*, "Postpartum depression, an autoimmune disease?," *Autoimmunity reviews*, vol. 6, no. 8, p. 572, 2007.

[216] V. Bergink, S. A. Kushner, V. Pop, H. Kuijpens, M. P. Lambregtse-van den Berg, R. C. Drexhage, W. Wiersinga, W. A. Nolen, and H. A. Drexhage, "Prevalence of autoimmune thyroid dysfunction in postpartum psychosis.," *Br J Psychiatry*, vol. 198, no. 4, pp. 264–268, 2011.

[217] C. Bufalino, N. Hepgul, E. Aguglia, and C. M. Pariante, "The role of immune genes in the association between depression and inflammation: A review of recent clinical studies.," *Brain Behav Immun*, 2012.

[218] M. Maes, W. Ombelet, R. Verkerk, E. Bosmans, and S. Scharpe, "Effects of pregnancy and delivery on the availability of plasma tryptophan to the brain: relationships to delivery-induced immune activation and early post-partum anxiety and depression.," *Psychol Med*, vol. 31, no. 5, pp. 847–858, 2001.

[219] M. Maes, W. Ombelet, R. De Jongh, G. Kenis, and E. Bosmans, "The inflammatory response following delivery is amplified in women who previously suffered from major depression, suggesting that major depression is accompanied by a sensitization of the inflammatory response system.," *J Affect Disord*, vol. 63, no. 1-3, pp. 85–92, 2001.