

From Center for Family and Community Medicine, Department of  
Neurobiology, Care Sciences and Society  
Karolinska Institutet, Stockholm, Sweden

# **POSTPARTUM PSYCHOSIS AND THE ASSOCIATION WITH SOCIODEMOGRAPHIC AND OBSTETRIC FACTORS**

Anna Nager



**Karolinska  
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## ABSTRACT

*Objective* To examine the association between postpartum psychosis and the socio-demographic factors age, education, marital status and year of delivery (study 1). To examine the association between neighbourhood socioeconomic characteristics and postpartum psychosis (study 2). To examine the association between postpartum psychosis and obstetric factors (study 3). To examine the association between non-puerperal readmission and years of follow-up among women with postpartum psychosis and to examine the impact of age, type of psychosis, previous psychiatric hospitalisation and education on the risk of non-puerperal readmission (study 4) among these women.

*Methods* Data sources were the Swedish population registers and medical registers. Postpartum psychosis was defined as hospital admission due to psychotic disorder within three months after delivery, which was the outcome variable in studies 1–3. Study 1 followed 502,767 first-time mothers between Jan. 1, 1986, and Dec. 31, 1997, for postpartum psychosis. Study 2 followed 485,199 first-time mothers between Jan. 1, 1986, and Sept. 30, 1998, for postpartum psychosis. Study 3 followed 1,133,368 first-time mothers between Jan. 1, 1975, and Dec. 31, 2003, for postpartum psychosis. Study 4 followed 1,340 women with postpartum psychosis between Jan. 1, 1975, and Dec. 31, 2004, for non-puerperal readmission due to psychiatric disorder. The explanatory variables included age (studies 1–4), education (studies 1, 2, 4) marital status (studies 1, 2), year of delivery (studies 1–3), neighbourhood income (study 2), previous psychiatric hospitalisation (studies 3, 4), years of follow-up (study 4), type of psychosis (study 4), calendar year (study 4), and 19 different obstetric factors (study 3). Cox regression models (studies 1–3) and Cox frailty regression models (study 4) were used in the statistical analysis.

*Results* Old age in the mother, not living with the father of the child, living in a socio-economically deprived neighbourhood, preterm birth and acute caesarean section were associated with increased risk of postpartum psychosis among first-time mothers after adjustment for possible confounders. However, the HRs for these factors were only moderately increased, which implies that the absolute increase in risk is small. In contrast, previous hospitalisation for psychiatric disorders was associated with a more than 100-fold increased risk of postpartum psychosis. The risk of non-puerperal readmission due to a psychiatric disorder remained high for many years after the postpartum psychosis, for all women in the study group. In addition, the risk of non-puerperal readmission due to a psychiatric disorder was higher among women with low educational level, previous psychiatric hospitalisation and schizophrenia.

*Conclusion* Stress from adverse sociodemographic and obstetric conditions can possibly play a role in the development of postpartum psychosis, although these associations might be confounded by unknown previous psychiatric illness. Postpartum psychosis is often part of a severe and chronic psychiatric illness, with high non-puerperal readmission rates for many years after the postpartum psychosis. Finally, previous psychiatric disorder is a strong risk factor for postpartum psychosis. Therefore, it is very important to consider previous psychiatric disorder in antenatal and postnatal care.

*To Torbjörn,  
Johanna, Klara and Amanda*

## LIST OF PUBLICATIONS

- 1.** *Are sociodemographic factors and year of delivery associated with hospital admission for postpartum psychosis? A study of 500,000 first-time mothers:* Anna Nager, Leena Maria Johansson, Kristina Sundquist (Acta Psychiatr Scand. 2005 Jul;112(1):47–53). Reprinted with permission from Wiley-Blackwell.
- 2.** *Neighborhood socioeconomic environment and risk of postpartum psychosis:* Anna Nager, Leena Maria Johansson, Kristina Sundquist (Arch Womens Ment Health. 2006 Mar;9(2):81–6. Epub 2005 Sep 20). Reprinted with permission from SpringerLink.
- 3.** *Obstetric complications and postpartum psychosis: a follow-up study of 1.1 million first-time mothers between 1975 and 2003 in Sweden:* Anna Nager, Kristina Sundquist, Vania Ramírez-León, Leena Maria Johansson (Acta Psychiatr Scand. 2008 Jan;117(1):12–9. Epub 2007 Oct 12). Reprinted with permission from Wiley-Blackwell.
- 4.** *Years of follow-up and non-puerperal readmissions for psychiatric disorder among women with postpartum psychosis:* Anna Nager, Robert Szulkin, Sven-Erik Johansson, Leena Maria Johansson, Kristina Sundquist (Manuscript)

## LIST OF ABBREVIATIONS

CI	Confidence Interval
CRH	Corticotrophin-releasing hormone
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision
HPA	Hypothalamic-pituitary-adrenal axis
HR	Hazard Ratio
ICD	International Classification of Diseases
LGA	Large for Gestational Age
LOUISE	Longitudinal database of education, income and occupation (In Swedish: Longitudinell databas om utbildning, inkomster och sysselsättning).
SAMS	Small area market statistics
SCB	Statistiska Centralbyrån (In English: Statistics Sweden)
SD	Standard deviation
SES	Socioeconomic status
SGA	Small for Gestational Age

# CONTENTS

Introduction.....	9
Definition of postpartum psychosis .....	9
Definition of postpartum .....	9
Definition of psychosis.....	10
How to understand postpartum psychosis .....	10
Clinical presentation .....	10
Epidemiological presentation.....	10
Genetic factors .....	11
Hormonal factors .....	11
Life events, disruption of circadian rhythms and insomnia .....	12
Stress .....	12
Sociodemographic factors .....	13
Measurement of socioeconomic status (SES) .....	13
Socioeconomic status and psychotic disorders.....	13
Age of the mother.....	13
Neighbourhood .....	14
Compositional and contextual explanation.....	14
Obstetric factors .....	14
Consequences for the child.....	15
Consequences for the mother .....	16
Aims .....	17
General aim.....	17
Specific aims.....	17
Study 1 .....	17
Study 2 .....	17
Study 3 .....	17
Study 4 .....	17
Materials.....	18
WomMed .....	18
WomMed .....	18
The Swedish Hospital Discharge Register .....	18
The Medical Birth Register.....	18
LOUISE .....	19
Small area market statistics (SAMS) .....	19
Methods.....	20
Study 1 .....	20
Outcome variable.....	20
Explanatory variables .....	21
Statistical analysis.....	21
Study 2 .....	21
Outcome variable.....	22
Explanatory variables .....	22
Statistical analysis.....	22
Study 3 .....	22
Outcome variable.....	23

Exposure variables .....	23
Possible confounders adjusted for in the analysis .....	24
Statistical analysis .....	24
Study 4 .....	25
Outcome variable .....	25
Explanatory variables .....	25
Statistical analysis .....	26
Ethics .....	26
Main Results .....	27
Study 1 .....	27
Study 2 .....	29
Study 3 .....	30
Study 4 .....	32
Discussion .....	35
Main findings .....	35
Age of the mother .....	35
Marital status .....	36
Neighbourhood .....	36
Preterm birth .....	37
Caesarean section .....	37
Large-for-gestational-age (LGA) .....	37
Non-puerperal readmission due to psychiatric disorders .....	38
Years of follow-up .....	38
Type of postpartum psychosis .....	38
Educational level .....	39
Previous hospitalisation due to a psychiatric disorder .....	39
Decreased risk of postpartum psychosis during the 1990s .....	40
Strengths and limitations .....	40
Conclusions .....	41
Summary in Swedish / Sammanfattning på svenska .....	42
Acknowledgements .....	46
References .....	47
Study 1 .....	55
Study 2 .....	63
Study 3 .....	69
Study 4 .....	77



## INTRODUCTION

Becoming a mother involves adaptation to great changes physiologically, psychologically and socially. The normal postpartum period consists of physical exhaustion, sleep deprivation and dramatic changes in hormone and electrolyte balance. This challenge can provoke a wide variety of psychiatric disorders, of which postpartum psychosis is the most severe.

Postpartum psychosis is a relatively rare disease that leads to hospital admission in about one woman per 1,000 deliveries [1, 2]. It is often characterised by a rapid development of bizarre delusions, affective symptoms, sleeplessness and disorganised behaviour. The severe psychiatric symptoms jeopardise the safety of both the mother and the newborn child.

Some risk factors for postpartum psychosis have been identified, such as primiparity and previous psychiatric disorder [1, 3-8]. Women with bipolar disorder have a risk ranging between 20% and 50% of developing postpartum psychosis after delivery and are therefore recommended extra attention in postnatal care [5, 9-13].

However, our knowledge of the impact of sociodemographic and obstetric characteristics on the risk of postpartum psychosis is still scarce. Such knowledge might be helpful in the clinical risk assessment of postpartum psychosis and important in the understanding of the possible mechanisms leading to the disorder.

Most studies that have investigated postpartum psychoses and the association with sociodemographic and obstetric factors are relatively small, and the results of these studies are, to some extent, inconsistent [1, 5, 8, 14-18]. In large-scale epidemiological studies it is easier to detect possible associations between postpartum psychosis and sociodemographic and obstetric factors.

The aim of the present thesis was to perform a large-scale epidemiological study of the entire Swedish female population concerning postpartum psychosis and the association with sociodemographic and obstetric factors. Such an approach avoids several limitations of previous research.

## DEFINITION OF POSTPARTUM PSYCHOSIS

### Definition of postpartum

According to DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, published by the American Psychiatric Association) the term *postpartum onset* could be used if the symptoms start within 4 weeks after delivery [19]. ICD-10 (International Classification of Diseases, 10th revision, published by the World Health Organisation) has a broader definition in the code called “mental and behavioural disorders associated with the puerperium”, F53, with the qualifier: “commencing within six weeks of delivery”. However, many researchers have used the less restrictive limit of three months, because the risk of admission due to psychotic disorders has been shown to be increased within three months after delivery [5].

## Definition of psychosis

DSM-IV-TR also states that: “the narrowest definition of *psychotic* is restricted to delusions or prominent hallucinations, with the hallucinations occurring in the absence of insight into their pathological nature” [19]. According to ICD-10 the main psychotic disorders are schizophrenia, schizotypal disorder, schizoaffective disorder, persistent delusional disorders, acute and transient delusional disorders. In addition, affective disorders such as depression, mania and bipolar disorder can present with psychotic symptoms. Psychotic symptoms due to drugs, dementia and organic causes are usually not included in the term postpartum psychosis.

## How to understand postpartum psychosis

Researchers have discussed three main ways of understanding postpartum psychosis: (1) as a unique diagnostic entity, (2) as a variant of bipolar disorder and (3) as heterogeneous psychotic disorders triggered by delivery. The opinion that postpartum psychosis is a heterogeneous psychotic disorder (often bipolar disorder) triggered by delivery has been embraced by most researchers during the last decades [20].

## CLINICAL PRESENTATION

The clinical picture of postpartum psychosis is often a combination of clouding consciousness and affective symptoms. Hallucinations, confusion, perplexity and sleeplessness are common. Characteristic is the rapid change from normality to fully developed syndrome. Almost all psychotic symptoms have been described among women with postpartum psychoses in the literature: megalomania concerning the identity of the child, delusions about the child being a changeling, paranoia, verbal hallucinations, thought insertion, thought broadcasting, echo phenomena, mania and catatonia [21-25].

Brockington et al. performed a study in which psychotic symptoms in women with postpartum psychosis were compared with psychotic symptoms in a control group of fertile non-puerperal women with psychosis. The study concluded that women with postpartum psychosis had a higher degree of mania than the control group [26].

## EPIDEMIOLOGICAL PRESENTATION

According to a British study, the incidence of psychosis within three months after delivery has been shown to be 14 times higher than during the two years before pregnancy [5]. In addition, a large Danish study showed that the relative risk of first admission due to psychosis within three months after delivery was three times higher among puerperal women than among non-puerperal women in the general female population [27].

Although the incidence of psychosis is increased within three months after delivery, most psychotic symptoms start within the first two weeks. Especially manic symptoms present early after delivery [21], whereas schizophrenic symptoms present later [1, 28].

Epidemiological studies have shown that a history of mental illness is a risk factor for postpartum psychosis. In a Swedish register study, almost 10% of women hospitalised for psychiatric morbidity before delivery developed postpartum psychosis after

their first birth [7]. In addition, women with bipolar disorder have a highly increased risk of relapse in the postpartum period, suggesting that postpartum psychosis in many cases is a manifestation of bipolar disorder [5, 29]. In contrast, relatively few women with schizophrenia have been found to have arousal of symptoms in the postpartum period [26, 30].

## **GENETIC FACTORS**

Previous studies corroborate that genetic factors are important for the development of postpartum psychosis. In a British study the risks of psychosis in first-degree relatives of women with puerperal affective disorder and puerperal schizophrenia were found to be similar to the familial risks indicated in the literature for affective psychosis and schizophrenia in general [31]. This was also found by Whalley et al. in a group of women with puerperal affective psychosis [32]. In addition, research has demonstrated a higher incidence of psychiatric illness among first-degree relatives in women with both postpartum and non-postpartum psychosis compared to women with only postpartum psychosis [33].

Craddock et al. described a British family in which postpartum psychosis was found in three sisters. One brother had bipolar disorder. The pattern of illness in this family was consistent with autosomal recessive inheritance [34].

In recent years research in genes and psychiatric disorders has flourished. Thus, Coyle et al. have demonstrated that polymorphism in the serotonin transporter gene is associated with bipolar affective puerperal psychosis. The attributable fraction was as high as 69% [35]. However, it was also shown that approximately 75% of the white population in the UK has this variation. In addition, polymorphism in the serotonin transporter gene was also found to be associated with non-psychotic depression when considered together with life events [36].

## **HORMONAL FACTORS**

Many researchers have proposed that the sudden changes in hormone levels after childbirth trigger the onset of postpartum psychosis. After delivery a rapid change in serum levels of several hormones occurs. Oestrogen and progesterone reach normal serum levels immediately after delivery. The cortisol level normalises within two weeks [37]. Previous research has not found consistent differences in hormonal levels between women who develop postpartum psychosis and those who do not [38]. However, some women with postpartum psychosis in combination with low serum levels of oestrogen have been reported to recover during estradiol treatment [39], suggesting that oestrogen is important in the development of postpartum psychosis. Oestrogen binds to dopamine receptors [40, 41]. One hypothesis is that low oestrogen levels postpartum may precipitate psychosis through a supersensitisation of central dopamine receptors that has been induced during the high oestrogen levels in late pregnancy [42, 43].

Psychosis in association with oestrogen withdrawal has been found not only after delivery but also at menstruation, cessation of oral contraceptives, postabortion and

menopause [42-44]. The term EWAP (Estrogen Withdrawal Associated Psychosis) has been used by some researchers.

Since the start of corticosteroid treatment in 1950 there have been several reports on corticosteroid-induced psychosis [45], including corticosteroid-induced prepartum psychosis [46]. Interestingly, serum cortisol levels are very high in late pregnancy. Cortisol is a variant of corticosteroid, produced in the adrenal cortex. A normal pregnancy entails a large increase in plasma of corticotrophin-releasing hormone (CRH), released by the placenta. The high CRH levels increase the activity in the hypothalamic-pituitary-adrenal (HPA) axis, inducing high cortisol levels [47]. Cortisol levels in late pregnancy reach the same levels that are found in major melancholic depression. In addition, a small study of eight women with postpartum psychosis demonstrated that increased cortisol levels and hyperactivity in the HPA axis were more common among the patients than among controls [48]. It might be possible that cortisol levels and the HPA axis play a role in the development of postpartum psychosis.

Finally, thyroid hormone has been suggested to be involved in postpartum psychosis. The incidence of both hypothyroidism and hyperthyroidism is high in the postpartum period [49-51]. In addition, the literature reveals some case reports on thyroid disorders in temporal association with psychotic symptoms postpartum [21, 52].

## **LIFE EVENTS, DISRUPTION OF CIRCADIAN RHYTHMS AND INSOMNIA**

Major life events are associated with manic episodes among individuals with bipolar disorder [53, 54]. One of the greatest events in a woman's life is becoming a mother. After delivery the mother may alter her regular sleeping times, meal times, and times of activity and rest. Such disruptions in daily routines might disrupt circadian rhythms, which is implicated in the pathogenesis of both depression and mania [55-59]. Circadian rhythms are defined as "The regular recurrence, in cycles of about 24 hours, of biological processes or activities, such as sensitivity to drugs and stimuli, hormone secretion, sleeping, feeding, etc. This rhythm seems to be set by a 'biological clock' that seems to be set by recurring daylight and darkness" [60].

Insomnia is one of the most frequent symptoms in postpartum psychosis [61, 62]. Strouse et al. examined sleep deprivation and postpartum psychosis in three puerperal women with no prior history of psychotic disorder [63]. Two of the women became transiently manic and one of them became hypomanic after sleep deprivation, suggesting that sleep deprivation might play a role in the development of postpartum psychosis.

## **STRESS**

A couple of studies have demonstrated that life events during pregnancy and measures reflecting stress did not differ between mothers with and without postpartum psychosis [64, 65]. Some studies demonstrate higher risk of postpartum psychosis among primiparae [5]. This could be due to increased psychosocial stress among primiparae, but also to biological factors, such as long-lasting deliveries causing sleep deprivation.

## **SOCIODEMOGRAPHIC FACTORS**

### **Measurement of socioeconomic status (SES)**

Characterising SES is complex. It involves combinations of many factors, varies over time and may differ from society to society. The position that different groups occupy in the social structure can be based on income, education, occupation, sex, family relations, heredity, and political or religious affiliation. The different measures of SES are indicators of individual resources and “life chances”.

However, it is not possible to measure all potential variables predicting SES in epidemiological studies. Therefore, simple markers of SES – such as occupation, income or education – must be used.

Since the studies in this thesis examine women during a period in their lives when they became mothers, occupational status and income were not considered to be appropriate markers for SES. Therefore level of education is used as a marker of SES.

### **Socioeconomic status and psychotic disorders**

Previous studies in the general female population have examined the association between SES and psychotic disorders and demonstrated that psychotic disorders are associated with low SES and living alone [66]. However, SES has not been shown to influence the risk of postpartum psychosis in the few previous studies accomplished [1, 8, 67]. In an Indian study on 144 cases of psychosis within 3 months after delivery, SES was dichotomised into upper or lower class. That study did not reveal any association between SES and postpartum psychosis [8]. A Danish study on 50 cases of first-episode psychosis within one year after delivery confirmed this finding. There were no significant differences in SES among women with postpartum psychosis compared to non-psychotic women who had given birth at the same ward. However, the report on that study did not mention how SES was characterised [1]. Finally, a Swedish study on women with a history of psychosis compared sociodemographic characteristics between women with (n=25) and without psychosis within 6 months after delivery. Measurement of SES was based on the highest occupation in the family. There were no differences in SES among cases and controls [67].

Some studies have shown increased risk of postpartum psychosis in unmarried women [16, 68]. In contrast, Kendell et al. found no increased risk of postpartum psychosis among unmarried women in their relatively large British study [5].

### **Age of the mother**

The association between age and mood disorders postpartum has been examined in a few studies. A relatively small British study found that the presence of depression three months after delivery was associated with being a first-time mother aged 30 years or more [69]. According to some studies from the 1950s and 1960s including multiparas, old age in the mother was associated with an increased risk of hospital admission due to psychiatric disorder postpartum [15, 17, 70]. In contrast, a large British study did not find any significant association between age and psychiatric disorder postpartum [5].

None of these studies examined the association between age and postpartum psychosis separately from other psychiatric disorders postpartum.

## **Neighbourhood**

The social environment shared by individuals within a neighbourhood could influence mental health beyond individual characteristics. An association between the neighbourhood social environment and psychiatric hospital admission rates has been found in previous research [71-73].

No research on neighbourhood social environment and postpartum psychosis has previously been performed. After the birth of a child the mother spends a great amount of time in the immediate environment, i.e. the neighbourhood. In study 2 we hypothesised that the social environment in a neighbourhood could affect women's mental health during the vulnerable period postpartum.

Neighbourhood research is enabled by linking registers with incidences of diagnoses and information on socioeconomic characteristics in defined neighbourhood areas. Most neighbourhood studies are multilevel studies with at least two levels. The first level is characteristics of the individuals, such as smoking, age, income etc. The second level is characteristics of the neighbourhood, such as neighbourhood income, proportion of single parents, overcrowding etc. With this procedure it is possible to separate the neighbourhood effect from the individual effect on health. Previous research has demonstrated neighbourhood effects on mortality [74-76], poor self-rated health [77], infant mortality rates [78, 79], low birth weight [80], psychiatric disorders [81, 82] asthma [83, 84] and cardiovascular disorders [85, 86].

## **Compositional and contextual explanation**

There are two possible explanations for variations in health in different neighbourhoods: compositional or contextual. The compositional explanation suggests that variations in health in different places are due to the composition of people who live in the different places. For example, poor people have a higher incidence of morbidity than rich people and, consequently, areas with a high proportion of poor people will have a higher incidence of morbidity. The contextual explanation, on the other hand, suggests that the variations in health are due to differences between the places. This means that if individuals live in a neighbourhood that is likely to induce mental disorders, the incidence of mental disorders in the neighbourhood will rise, irrespective of each individual's characteristics. However, compositional and contextual effects should not be seen as distinct entities; they probably interact together, "People create places and places create people" [87].

## **OBSTETRIC FACTORS**

Few studies have investigated the association between obstetric factors and postpartum psychosis, and the results of these studies are inconclusive. Studies in this field require very large study populations since both postpartum psychosis and many of the obstetric complications are rare.

Kendell et al. performed a study of 51 women with postpartum psychosis in 1981 and found that caesarean section was associated with an increased risk of postpartum psychosis [6]. Six years later, Kendell et al. conducted a new study of 63 women with postpartum psychosis and found no association between caesarean section and postpartum psychosis [5]. A Swedish study from the late 1980s found non-significant trends towards increased rates of induction of labour, foetal distress, instrumental deliveries and offspring abnormality among 24 women with postpartum psychosis who were compared with 60 index cases without postpartum psychosis [88]. In a study performed in 1995, Videbech et al. found that women with postpartum psychosis had a higher risk of preterm delivery than controls, whereas birth complications did not occur more frequently than expected [1]. Finally, a study from 2006 of 129 women with postpartum psychosis found that the category “delivery complications” was associated with an increased risk of postpartum psychosis, whereas caesarean section was not [3].

## **CONSEQUENCES FOR THE CHILD**

Because of the severity and time of onset, postpartum psychosis carries important potential consequences for the child. Mothers with postpartum psychosis are at increased risk of injuring the infant either by practical incompetence or by misguiding delusions. Some research on consequences for children of mothers with puerperal psychiatric disorders has been done during recent decades. However, few of these studies describe the consequences for the children of mothers with postpartum psychosis, separated from other severe puerperal psychiatric disorders. For instance, it is still unclear whether postpartum psychosis is associated with an increased rate of infant death. A large register study of all Danish women admitted to a psychiatric hospital within one year postpartum during 1973–1993 showed that 3% of the admissions were associated with the death of the infant [89]. Bagedahl-Strindlund investigated 177 mothers in Stockholm County admitted to a psychiatric department during the second half of the pregnancy or within one year after delivery during the period 1976–1977. That study also showed increased mortality among children of mothers with severe parapartum mental illness. Seven index children and one control child died within the first year postpartum [90]. However, neither of these studies examined infant deaths for postpartum psychosis separately.

Bagedahl-Strindlund showed in her studies that children of mothers admitted due to parapartum psychiatric disorders had higher rates of behavioural and developmental disturbances than controls at the age of four. However, rates of behavioural and developmental disturbances were more frequent in children of mothers with addictive disorders, neuroses and temporary insufficiencies parapartum than in children of mothers with psychosis parapartum [91].

Long-term negative consequences for children of mothers with severe postpartum psychiatric disorder have also been suggested in previous research. A British study has shown high rates of adult psychiatric illness in young adult offspring of mothers with puerperal disorder requiring hospitalisation. The rate of psychiatric illness was lowest for offspring of mothers with psychotic disorders, i.e. 13% (bipolar disorder excluded). If the mother was diagnosed with bipolar disorder postpartum, the rate of psychiatric disorder in the offspring was 26%. Interestingly, that study also suggests that the early environment affects the risk of psychiatric illness later in life. The incidence was much

higher among offspring whose birth was associated with puerperal psychiatric disorder in the mother than among their matched controls. The controls comprised siblings whose births were not followed by puerperal psychiatric illness in the mother [92].

## **CONSEQUENCES FOR THE MOTHER**

In study 4 we examined the impact of year of follow-up and sociodemographic factors on the risk of non-puerperal readmission due to psychiatric disorders among women with postpartum psychosis. According to a previous study, postpartum psychosis often leads to the woman's first hospital admission due to psychiatric disorder [93], but in most cases not to the last. The relapse rate of psychiatric disorders after postpartum psychosis has been found to be 60%–69% for non-puerperal relapses [1, 94, 95] and 21%–34% for puerperal relapses [93-95].

Some studies have used working capacity and sick-leave days as indicators of the severity and long-term course of postpartum and parapatum psychiatric disorders [93, 96]. For example, a follow-up study of 50 cases of first-episode psychosis within one year after childbirth showed that 31% had no working capacity 7–14 years after the index episode, nearly all due to psychiatric disorders [93].

A Danish register study of women admitted to psychiatric hospital within the first year after childbirth during 1973–1993 showed high rates of deaths from natural and unnatural causes, particularly suicide. The suicide risk was increased 70-fold compared to age-specific mortality rates for the Danish female population over the study period. However, that study did not distinguish psychoses from other psychiatric disorders.

To the best of our knowledge, previous studies have not examined whether relapses in psychiatric disorders occur in an even pattern during the years after the postpartum psychosis or more frequently during the immediate years following the postpartum psychosis. In addition, the impact of sociodemographic factors on the risk of non-puerperal readmission later in life is largely unknown, and this will be addressed in study 4.



# **AIMS**

## **GENERAL AIM**

To examine postpartum psychosis and the association with sociodemographic and obstetric factors.

## **SPECIFIC AIMS**

### **Study 1**

The aim was to examine the association between first hospital admissions due to postpartum psychosis among first-time mothers and the explanatory variables age, educational level, marital status and year of delivery.

### **Study 2**

The first aim was to examine the association between neighbourhood socioeconomic characteristics, measured as proportions of people with low income, and risk of first hospital admissions due to postpartum psychosis. The second aim was to examine whether this hypothesised association remained after adjustment for individual socio-demographic characteristics.

### **Study 3**

The aim was to examine the association between postpartum psychosis and obstetric factors, after adjustment for age, year of delivery and previous hospitalisation for psychiatric disorder.

### **Study 4**

The first aim was to examine the association between non-puerperal readmission and years of follow-up among women with postpartum psychosis. The second aim was to examine the impact of age, type of psychosis, previous psychiatric hospitalisation and educational level on the risk of non-puerperal readmission due to psychiatric disorders among women with postpartum psychosis.

# MATERIALS

## WOMMED

### WomMed

The four studies in this thesis are based on data obtained from WomMed. WomMed is a national database at Karolinska Institute in Stockholm constituted by several national population registers, for instance the Medical Birth Register, the Swedish Hospital Discharge Register and Longitudinal Database of Education, Income and Occupation (LOUISE). A personal identification number, assigned to each individual in Sweden, enables linkage between the different registers. This personal identification number is replaced by an unidentified serial number in WomMed.

WomMed contains information on all women in Sweden and their children. In studies 1 and 2 we used a version of WomMed that included 2.2 million women, born during 1950–1984, and their 2.5 million children, born until 1999. In study 3 and 4 we used an upgraded version of WomMed that included 3.3 million women, born during 1932–1990, and their 5.1 million children, born until 2004.

### The Swedish Hospital Discharge Register

The Swedish Hospital Discharge Register contains data on hospital diagnoses in Sweden according to the International Classification of Diseases (ICD). The Swedish Hospital Discharge Register started in 1964. Since 1987 the register covers all public in-patient care in all Swedish counties. During the years 1973–1986 the register covers a majority of the psychiatric in-patient care. The Swedish Hospital Discharge Register is highly comprehensive by international standards. Only Denmark and Finland have similar registers. In the register ICD 8 was used between 1969 and 1986; ICD-9 was used between 1987 and 1996 and ICD-10 from 1997 onwards. The Swedish Hospital Discharge Register is tested regularly for misclassification. A main diagnosis was registered in 93%–99% of the psychiatric discharges during 1984–1998; of these 88% (1986) and 87% (1990) were registered with a correct main diagnosis [97].

### The Medical Birth Register

The Medical Birth Register contains information on e.g. pregnancies, manner of delivery, weight, height and health of the children at delivery, diagnosis in mothers and children at pregnancy and delivery. Information in The Medical Birth Register has been collected from medical files used in antenatal care, maternity care and postnatal care since 1973. In tests for misclassification during 1984–1998 data on marital status were correct in a range of 83%–96%, depending on the year that was tested. The age of the mother was correct in a range of 98%–100% [98].

## **LOUISE**

The demographic variables in WomMed, such as education, employment, and income, are obtained from LOUISE, a database distributed by SCB, Statistics Sweden, the Swedish government-owned statistical bureau.

## **Small area market statistics (SAMS)**

In Study 2 neighbourhoods were defined on the basis of SAMS. SAMS are small geographic areas covering the whole of Sweden. The boundaries are defined by similar type of buildings. The total number of SAMS in the whole of Sweden was 9,500 in 1995. The number of people in each SAMS was about 2,000 in Stockholm and 1,000 in the rest of Sweden.

## METHODS

The four studies constituting this thesis are summarised in Table 1.

**Table 1.** An overview of the four studies.

	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>	<b>Study 4</b>
Data source	WomMed	WomMed	WomMed	WomMed
Outcome	Postpartum psychosis	Postpartum psychosis	Postpartum psychosis	Non-puerperal readmission due to psychiatric disorder
Number of cases/readmissions	339	356	1,413	9,467
Study design	Follow-up	Follow-up	Follow-up	Follow-up
Measure of risk	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio
Statistical model	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard model	Cox frailty regression model
Follow-up	Jan. 1, 1986–Dec. 31, 1997	Jan. 1, 1986–Sept. 30, 1998	Jan. 1, 1975–Dec. 31, 2003	Jan. 1, 1975–Dec. 31, 2004
Population size	502,767 first-time mothers	485,199 first-time mothers	1,133,368 first-time mothers	1,340 women with postpartum psychosis

### STUDY 1

The study population consisted of all women in Sweden aged 20–44 years, who became first-time mothers during the 12-year period, from Jan. 1, 1986, to Dec. 31, 1997. Women in the general female population aged 20–44 years constituted the control group. Women hospitalised due to psychotic disorder two years preceding delivery or entries into the control group were excluded.

#### Outcome variable

The outcome variable was postpartum psychosis. Postpartum psychosis was defined as first hospital admission due to psychotic disorder within three months after delivery. The control group was followed for three months for first hospital admissions due to psychotic disorders. In order to avoid possible seasonal bias, the whole year of 1993 was used for the control group. The control group was divided into four three-month cohorts and an average for first hospital admissions was calculated for the whole year of 1993.

Diagnosis codes for psychotic disorders were obtained from the Swedish Hospital Discharge Register, based on ICD-9 and ICD-10. However, there is no official translation from ICD-9 to ICD-10. For this reason affective psychosis, code 296 in ICD-9,

was defined by a grouping of ICD-10 codes (F30, F31, F32.2, F32.3, F33.2 and F33.3), chosen to correspond as closely as possible to the previous 296 code in ICD-9, according to an approach used in a previous study [99].

At first, we intended to examine schizophrenic disorders in a separate group. However, the exclusion of women hospitalised due to psychotic disorder two years before delivery meant that very few cases of hospitalisation due to schizophrenic disorder postpartum remained and therefore this particular group was excluded.

The following ICD codes were included in the study: 296, 297 and 298 (ICD-9), and F22, F23, F24, F28, F29, F30, F31, F32.2, F32.3, F33.2, F33.3 and F53.1 (ICD-10).

## **Explanatory variables**

*Age* of the women was categorised into five groups: (1) 20–24, (2) 25–29, (3) 30–34, (4) 35–39 and (5) 40–44 years.

*Educational level* comprised three groups, based on years of education: (1)  $\leq 9$  years (some or completed compulsory school) (2) 10–12 years (some or completed high school) (3)  $> 12$  years (more than high school).

*Marital status* was divided into two groups: (1) living with the father of the child and (2) not living with the father of the child. Group 1 consisted of first-time mothers who were married or cohabiting with the father of the child. Group 2 consisted of first-time mothers that were living alone or living with someone else than the father of the child. Marital status was recorded by the midwives at the antenatal clinics and then linked to the Medical Birth Register.

*Year of delivery* was categorised into three groups: (1) 1986–1989, (2) 1990–1993 and (3) 1994–1997.

## **Statistical analysis**

The SAS software package, version 8, was used in the statistical analyses [100]. Age-standardised hospital admission rates (per 10,000 person years) were calculated by direct age standardisation with Sweden as standard population [101]. A Cox regression model was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for first hospital admission due to psychotic disorder in age-adjusted models for each of the explanatory variables and a full model including all explanatory variables [102]. Risk time was calculated from the delivery until the first admission to hospital due to psychotic disorder within three months after delivery, death from all causes, emigration from Sweden, or end of the follow-up three months after delivery.

## **STUDY 2**

The study population consisted of all women in Sweden aged 20–44 years who became first-time mothers from 1 January 1986 to 30 September 1998. Women hospitalised due to psychotic disorders two years preceding delivery were excluded. Women living in SAMS with fewer than 50 people (a total of 1,021 SAMS, 3,822 women) were excluded because of unstable statistical estimates. Women with missing home addresses (11%) were also excluded.

## Outcome variable

The outcome variable was postpartum psychosis, defined as in study 1. The same diagnosis codes that were used in study 1 for psychotic disorders were obtained from the Swedish Hospital Discharge Register. Schizophrenic disorders were excluded for the same reason as in study 1.

## Explanatory variables

*Age* of the women was grouped as in study 1.

*Educational level* was grouped as in study 1.

*Marital status* was grouped as in study 1.

*Year of delivery* was divided into three cohorts: (1) 1986–1989, (2) 1990–1993 and (3) 1994–1998.

*Neighbourhood income* was based on annual family income divided by the number of people in the family. Additionally, the family income measure considered the ages of people in the family and used a weighted system whereby small children were given lower weights than adolescents and adults. The proportion of people with incomes in the lowest national income quartile was calculated for each neighbourhood and divided into tertiles. Tertile 1 represented neighbourhoods with the lowest proportion of people with low incomes and tertile 3 represented neighbourhoods with the highest proportion of people with low incomes. Data used to calculate neighbourhood income were obtained from a national database for the entire Swedish adult population, containing annually collected data on income for each individual. Data for each year 1986–1998 was used to calculate neighbourhood income based on ages 20–64, i.e. the socio-economically active part of the population. These data were then linked to the SAMS neighbourhoods using geocodes. The home addresses of the women had previously been geocoded by the Swedish government-owned land-surveying bureau.

## Statistical analysis

Age-standardised incidence rates (per 10,000 person years) were calculated by direct age standardisation with Sweden as standard population [103]. A Cox regression model was used to calculate HRs with 95% CIs for first hospital admission due to postpartum psychosis by the explanatory variables [102]. Risk time was calculated from the delivery until the first admission to hospital due to psychotic disorder, death from all causes, emigration from Sweden, or end of the follow-up three months after delivery. Two different models were estimated; model 1 was adjusted for age and model 2 was adjusted for all the explanatory variables simultaneously. The SAS software package, version 8, was used [100].

## STUDY 3

The study population comprised all Swedish first-time mothers from 1 January 1975 to 31 December 2003. Women who had emigrated from Sweden within three months after giving their first live birth were excluded. Since the analysis was adjusted for hospitalisation for psychiatric disorder two years preceding delivery, the women who had im-

migrated to Sweden within two years before giving their first live birth were also excluded. In an additional analysis of acute and elective caesarean section first-time mothers with preterm birth infants were also excluded.

## Outcome variable

*Postpartum psychosis* was defined as first hospital admission due to psychotic disorder within three months after delivery according to diagnosis codes for psychotic disorders obtained from the Swedish Hospital Discharge Register. For postpartum psychosis the following ICD codes were included: ICD-8: 294.40, 295–299; ICD-9: 295–298; ICD-10: F20, F22–F25, F28–F31, F32.2, F32.3, F33.2, F33.3, F39, F53.1.

ICD-8 was replaced by ICD-9 in 1987 and ICD-9 was replaced by ICD-10 in 1997. Since there is no official translation between ICD-8, ICD-9 and ICD-10, we used an approach from a previous study [99], enabling the codes in ICD-8 and ICD-9 to correspond as closely as possible to those in ICD-10. Therefore, affective psychosis with code 296 in ICD-8 and ICD-9 was defined by a grouping of ICD-10 codes (F30, F31, F32.2, F32.3, F33.2 and F33.3).

## Exposure variables

*Anaemia*: ICD-8: 280–285, 653.2, 633, 676; ICD-9: 648.2, 280–285; ICD-10: D50–D59. In ICD-9 there is no distinction between anaemia during pregnancy and anaemia in the puerperium. Therefore, the exposure variable anaemia included anaemia both in pregnancy and in the puerperium.

*Pre-eclampsia*: ICD-8: 637.03, 637.04, 637.09; ICD-9: 642.4–5; ICD-10: O11, O14.

*Malposition and malpresentation of the foetus*: ICD-8: 650–662 (if the second decimal was 1, 2, 3, 4, 5 or 6); ICD-9: 652.0–5, 652.7–9; ICD-10: O64.

*Obstetric trauma of the mother*: ICD-8: 658.1, 658.2, 659.9, 660.0–660.4; ICD-9: 664.1–3, 665; ICD-10: O70.1–O70.3, O71.

*Postpartum haemorrhage*: ICD-8: 653.1, 653.2, 653.8, 677.91; ICD-9: 666; ICD-10: O72.

*Birth trauma in the neonate*: ICD-8: 772 (except 772.38–772.9), 764–768 (if any of the decimals .00, .10, .20, or .30 was present); ICD-9: 767; ICD-10: P10–P15.

*Respiratory disorder in the neonate*: ICD-8: 480–486, 764–768 (if any of the decimals .40 or .90 was present), 776; ICD-9: 768–770; ICD-10: P20–P28.

*Severe birth asphyxia* was defined as Apgar score 0–3 at 1 min after delivery [104].

*Mild/moderate birth asphyxia* was defined as Apgar score 4–7 at 1 min after delivery [104].

*Neonatal jaundice*: ICD-8: 774, 778.93, 774.94, 774.96; ICD-9: 773–774; ICD-10: P57–P59.

*Preterm birth* was defined as a gestation length <37 weeks, estimated from data on last menstruation period (1975–1982/83) or ultrasound of the foetus (1982/83 onwards) [105].

*Postterm birth* was defined as a gestation length >42 weeks, estimated from data on last menstruation period (1975–1982/83) or ultrasound of the foetus (1982/83 onwards) [105].

*Multiple births* were defined as two or more neonates.

*Caesarean section* was defined from 1982 as either elective or acute.

In general, elective caesarean section is defined as planned caesarean section that is executed before the natural onset of labour. Acute caesarean section is defined as start of section within hours after detection of an unexpected complication of pregnancy or delivery [105]. Information on acute and elective caesarean section as distinct entities was recorded in the Medical Birth Register from 1982. The additional analysis on acute and elective caesarean section was therefore performed for the time between 1982 and 2003. Data on elective or acute caesarean sections for mothers with preterm-birth infants had a relatively high rate of missing data in the Medical Birth Register [106]. Therefore women with preterm-birth infants were excluded from this additional study. In addition, this exclusion also diminished the possible confounding effect due to preterm birth in the analysis of the association between caesarean section and postpartum psychosis.

#### *Gender of the neonate*

*Perinatal death* was defined as death of the neonate within 27 days after delivery or as a stillborn child who had died before or during the delivery. According to the definition, a stillborn child should have a gestation length of >28 weeks, or, in case of uncertainty of gestation length, be  $\geq 35$  cm tall [107].

*Small-for-gestational-age (SGA)* infant was defined as a neonate with a birth weight of at least 2 standard deviations (SD) below the mean weight for the gestational length according to the Swedish standard [105].

*Large-for-gestational-age (LGA)* infant was defined as a neonate with a birth weight of at least 2 SD over the mean weight for the gestational length according to the Swedish standard [105].

### **Possible confounders adjusted for in the analysis**

*Age* was categorised into six groups: (1) < 20, (2) 20–24, (3) 25–29, (4) 30–34, (5) 35–39 and (6)  $\geq 40$  years. Age was included because a Swedish study has shown that the risk of postpartum psychosis among first-time mothers increases with age [108].

*Year of delivery* was categorised into four groups: (1) 1975–1981, (2) 1982–1988, (3) 1989–1995 and (4) 1996–2003. This variable was included because a Swedish study has shown that the risk of postpartum psychosis varied by the studied time period [108].

*Hospitalisation due to psychiatric disorder two years preceding delivery:* ICD-codes for psychiatric disorders were obtained from the Hospital Discharge Register. Adjustment for psychiatric disorder two years preceding delivery was based on the following ICD-codes: ICD-8: 295–302, 305–307; ICD-9: 295–298, 300–302, 306–309, 311–312; ICD-10: F20–F25, F28–F34, F38–F45, F48, F50–F54, F59–F69 and F99.

### **Statistical analysis**

The STATA software package version 9 was used in the statistical analyses [109]. A Cox regression model was used to estimate HRs with 95% CIs for first hospital admission due to psychotic disorder in one model adjusted for age and year of delivery and one model that also adjusted for hospitalisation due to psychiatric disorder two years preceding delivery. Each exposure variable was analysed separately. Risk time was calculated from the delivery until the first admission to hospital due to psychotic disorder within three months, death from all causes or end of the follow-up at three



months after delivery. The reference group consisted of first-time mothers without the exposure variable in question, i.e. unexposed mothers. Tests of proportional hazard assumptions were not performed because of the short follow-up of three months.

## STUDY 4

The study population in study 4 consisted of all women living in Sweden and hospitalised for the first time between 1 January 1975 and 31 December 2004 for postpartum psychosis within three months after delivery. Only women aged 20–44 at their first hospital admission for postpartum psychosis during the study period were included. The number of women in the study population was 1340 during the 30-year follow-up.

### Outcome variable

The women with a previous hospitalisation for postpartum psychosis were followed during the 30-year study period for non-puerperal readmissions due to a psychiatric disorder. Psychiatric disorders due to mental retardation, substance abuse and organic causes were excluded. The following codes (based on the 8th, 9th and 10th versions of the International Classification of Diseases, ICD) were included to define the outcome variable: ICD-8: 295–302, 305–307; ICD-9: 295–298, 300–302, 306–309, 311–312; ICD-10: F20–F25, F28–F34, F38–F45, F48, F50–F54, F59–F69 and F99.

In order to exclude subsequent postpartum psychoses, the period of three months following any subsequent delivery was left out of the analysis.

### Explanatory variables

*Years of follow-up* after the first hospitalisation for postpartum psychosis was categorised into nine groups: year 1, year 2, year 3, year 4, year 5, years 6–10, years 11–15, years 16–20 and >20 years.

*Age* at the first hospitalisation for postpartum psychosis was categorised into five groups: (1) 20–24, (2) 25–29, (3) 30–34, (4) 35–39 and (5) 40–44 years.

*Type of psychosis* at the first hospitalisation for postpartum psychosis was categorised into the following three groups: (1) Schizophrenia [ICD 8: 295.0–295.9 (except for 295.5 = latent schizophrenia); ICD 9: 295.0–295.9 (except for 295.5 = latent schizophrenia); ICD 10: F20, F23.2 and F25]. (2) Affective psychosis [ICD 8: 296.0–296.3, 296.9, 298.0 and 298.1; ICD 9: 296.0–296.4, 296.6, 296.9, 298.0 and 298.1; ICD 10: F30, F31, F32.3 and F33.3].

(3) Unspecified psychosis [ICD 8: 294.4, 297.9, 298.2, 298.3, 298.9 and 299; ICD 9: 297.9, 298.2–298.4, 298.8 and 298.9; ICD 10: F23 (except for F23.2 = acute schizophrenia-like psychotic disorder), F28, F29 and F53.1].

Hospital admission due to a psychiatric disorder within two years prior to the first hospitalisation for postpartum psychosis was defined as (1) no or (2) yes. The same ICD codes as for the outcome variable were used for this variable.

*Educational level* at the first hospitalisation for postpartum psychosis comprised three groups based on years of education: (1) >12 years (more than secondary school), (2) 10–12 years (some or completed secondary school), and (3) ≤9 years (some or

completed compulsory school). Educational level was included in an additional analysis of a subset of the study population (see below).

*Calendar year* at non-puerperal readmission was divided into six groups: (1) 1975–1979, (2) 1980–1984, (3) 1985–1989, (4) 1990–1994, (5) 1995–1999 and (6) 2000–2004. According to previous studies, psychiatric admission rates have varied over time in Sweden [108, 110]. Birth rates also vary over time [111]. In order to adjust for possible biases due to factors that vary over time, calendar year was included as a covariate in the analysis.

## **Statistical analysis**

The STATA software package version 10 was used in the statistical analyses [112]. Hospital admission rates (per person year) were calculated [113]. A Cox frailty regression model for repeated events was used to estimate HRs with 95% CI for non-puerperal readmission due to a psychiatric disorder because the risk of readmission for each woman was calculated for all nine time intervals (see the variable years of follow-up). This means that each woman could be counted more than once. The outcome was measured as gap time between events (readmissions). To account for within-subject correlation of event times, we fitted a shared frailty parameter for each woman [114]. A full model was estimated with an adjustment for all the included variables simultaneously.

## **ETHICS**

All four studies in this thesis were approved by the Ethics Committee at Karolinska Institute, Stockholm.

# MAIN RESULTS

## STUDY 1

During the study period there were 339 cases of first hospital admission due to postpartum psychosis among the first-time mothers after exclusion of women hospitalised for psychotic disorder two years preceding delivery.

Table 2 shows age-standardised rates (per 10,000 person years) for first hospital admissions for psychotic disorder among first-time mothers and the general female population, by the explanatory variables.

For both first-time mothers and the general female population there was an apparent gradient between age and rates of psychotic disorders: with increasing age, rates of psychotic disorders increased.

There were no differences in rates of postpartum psychosis by level of education among the first-time mothers. However, in the general female population rates of psychotic disorders were twice as high among women with the lowest educational level compared to women with the highest educational level. The rates of psychotic disorders were higher among first-time mothers who were not living with the father of the child. Test of difference in rates of psychotic disorders between the first-time mothers and the general female population is exhibited as p-values. The p-value was less than 0.01 in all the tests except among women with the lowest educational level. The highest ratio in rates of psychotic disorders between the first-time mothers and the general female population was found among women in the oldest age group: 5.35. However, there were only eight cases aged 40–44 years, which makes the results from the statistical analysis in this age group uncertain.

Table 3 shows HR with 95% CIs for first hospital admissions for postpartum psychoses among the first-time mothers in an age-adjusted model and a full model, adjusted for all the explanatory variables simultaneously.

In both models, the HRs for postpartum psychosis increased with increasing age. In the age group 40–44 years the HR was 6.56 (95% CI = 3.10–13.8) in the full model. No differences in HRs were found for education. Among first-time mothers who were not living with the father of the child the risk of postpartum psychosis was higher than among first-time mothers living with the father of the child (HR = 1.60; 95% CI = 1.09–2.34) in the full model. Year of delivery was significantly associated with postpartum psychosis. In years 1990–93 and 1994–97 the risk was significantly lower than during 1986–1989. HRs in the full model were 0.62 (95% CI=0.47–0.80) and 0.74 (95% CI=0.57–0.96), respectively.

**Table 2.** Age-standardised rates (per 10,000 person years) for first hospital admission due to psychotic disorder among first-time mothers and the general female population, by the explanatory variables.

Variable	Level	Admission rates		Test of difference <sup>1</sup>	Rate ratios first-time mothers/general female population
		First-time mothers	General female population	P-value	
Age	20–24	18.9	6.8	0.00001	2.78
	25–29	28.5	11.6	0.00001	2.46
	30–34	31.4	15.5	0.00001	2.03
	35–39	40.8	17.8	0.0002	2.29
	40–44	108.8	20.2	0.0002	5.35
Educational level	>12 years	27.4	10.3	0.00001	2.66
	10–12 years	28.0	14.0	0.00001	2.00
	≤9 years	25.8	20.4	0.60	1.26
Marital status	Living with the father of the child	26.1	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>
	Not living with the father of the child	42.9	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>
Year of delivery	1986–1989	34.1	–	–	–
	1990–1993	21.6	–	–	–
	1994–1997	25.2	–	–	–

<sup>1</sup>Test of difference is performed on the crude admission rate

<sup>2</sup>Data on marital status were not included for the general female population.

**Table 3.** Hazard Ratios with 95% confidence intervals for first hospital admission due to psychotic disorder among first-time mothers by the explanatory variables.

Variable	Level	Psychotic disorder	
		Age-adjusted model	Full model <sup>1</sup>
		HR (95% CI)	HR (95% CI)
Age <sup>2</sup>	20–24	1 (Reference)	1 (Reference)
	25–29	1.51 (1.15–1.99)	1.58 (1.19–2.10)
	30–34	1.66 (1.21–2.27)	1.75 (1.26–2.44)
	35–39	2.16 (1.39–3.35)	2.30 (1.46–3.62)
	40–44	5.75 (2.78–11.9)	6.56 (3.10–13.8)
Educational level	>12 years	1 (Reference)	1 (Reference)
	10–12 years	1.07 (0.83–1.38)	1.05 (0.82–1.36)
	≤9 years	1.06 (0.73–1.56)	0.97 (0.66–1.43)
Marital status	Living with the father of the child	1 (Reference)	1 (Reference)
	Not living with the father of the child	1.60 (1.10–2.34)	1.60 (1.09–2.34)
Year of delivery	1986–1989	1 (Reference)	1 (Reference)
	1990–1993	0.62 (0.48–0.80)	0.62 (0.47–0.80)
	1994–1997	0.73 (0.57–0.95)	0.74 (0.57–0.96)

<sup>1</sup>Adjusted for all the explanatory variables simultaneously.

<sup>2</sup>Stratified by age

## STUDY 2

During the study period there were 356 cases of first hospital admissions due to postpartum psychosis among first-time mothers after exclusion of women hospitalised for psychotic disorder two years preceding delivery. For the neighbourhood variable, the highest incidence rates of first hospital admissions due to postpartum psychosis were found in tertile 3, which represented neighbourhoods with the highest proportion of people with low income.

Table 4 shows the age-adjusted and the full model. In tertile 3, the age-adjusted HR was 43% higher than in tertile 1, which represented neighbourhoods with the lowest proportion of people with low income. In the full model, after adjustment for the individual variables, the increased risk in tertile 3 remained, i.e. HR = 1.49 (95% CI = 1.15–2.91). In addition, the full model showed higher risks of first hospital admissions for psychotic disorder with higher age. During the periods 1990–1993 and 1994–1998 the risk of first hospital admissions for psychotic disorder was lower than during 1986–1989. No significant differences in risk were found for the individual variables educational level and marital status in the full model.

**Table 4.** Hazard Ratios with 95% confidence intervals for first hospital admission due to postpartum psychosis among first-time mothers by the neighbourhood and individual variables.

Variable	Level	Postpartum psychosis	
		Age-adjusted model	Full model <sup>1</sup>
		HR (95% CI)	HR (95% CI)
<i>Neighbourhood variable</i>			
Neighbourhood income	Tertile 1 (richest)	1.00	1.00
	Tertile 2	1.00 (0.76–1.31)	1.02 (0.78–1.34)
	Tertile 3 (poorest)	1.43 (1.12–1.84)	1.49 (1.15–1.91)
<i>Individual variables</i>			
Age <sup>2</sup>	20–24	1.00	1.00
	25–29	1.68 (1.27–2.22)	1.78 (1.34–2.37)
	30–34	1.82 (1.33–2.48)	1.97 (1.41–2.73)
	35–39	2.18 (1.41–3.38)	2.38 (1.52–3.74)
	40–44	6.54 (3.37–12.67)	7.36 (3.73–14.53)
Educational level	>12 years	1.00	1.00
	10–12 years	1.09 (0.85–1.39)	1.05 (0.82–1.34)
	≤9 years	1.02 (0.70–1.48)	0.90 (0.61–1.32)
Marital status	Living with the father of the child	1.00	1.00
	Not living with the father of the child	1.50 (1.02–2.20)	1.46 (0.99–2.15)
Year of delivery	1986–1989	1.00	1.00
	1990–1993	0.64 (0.49–0.83)	0.61 (0.47–0.80)
	1994–1998	0.78 (0.61–1.00)	0.74 (0.58–0.95)

<sup>1</sup>Adjusted for all the explanatory variables simultaneously.

<sup>2</sup>Stratified by age

### STUDY 3

There were 1,413 cases of first hospitalisation due to postpartum psychosis among the first-time mothers between Jan. 1, 1975, and Dec, 31, 2003. Among these cases 493 women, i.e. 35%, were hospitalised for psychiatric disorder two years preceding delivery (data not shown).

Table 5 shows the HRs for postpartum psychosis among first-time mothers exposed to each of the obstetric variables. Unexposed first-time mothers represented the

**Table 5.** Hazard Ratios with 95% confidence intervals for postpartum psychosis among first-time mothers exposed to each obstetric variable. Sweden, 1975–2003. N = 1,133,368.

<b>Obstetric variable</b>	<b>Model 1<sup>1)</sup></b> <b>HR (CI)</b>	<b>Model 2<sup>2)</sup></b> <b>HR (CI)</b>
Anaemia	0.87 (0.60–1.25)	0.84 (0.58–1.22)
Pre-eclampsia	1.19 (0.88–1.60)	1.13 (0.84–1.53)
Malposition and malpresentation of foetus	0.78 (0.61–1.00)	0.82 (0.65–1.05)
Obstetric trauma of the mother	0.95 (0.76–1.18)	1.04 (0.83–1.30)
Postpartum haemorrhage	0.83 (0.64–1.07)	0.87 (0.67–1.13)
Birth trauma in the neonate	0.89 (0.67–1.17)	0.97 (0.73–1.29)
Respiratory disorder in the neonate	<b>1.27 (1.07–1.51)</b>	1.18 (0.99–1.40)
Severe birth asphyxia	<b>1.39 (1.00–1.95)</b>	1.26 (0.90–1.77)
Mild/moderate birth asphyxia	1.16 (0.97–1.39)	1.11 (0.93–1.32)
Neonatal jaundice	0.94 (0.75–1.19)	0.94 (0.75–1.19)
Preterm birth	<b>1.46 (1.22–1.74)</b>	<b>1.20 (1.01–1.44)</b>
Postterm birth	0.82 (0.51–1.32)	0.80 (0.49–1.29)
Multiple birth	0.81 (0.45–1.47)	0.84 (0.47–1.52)
Caesarean section	1.32 (1.15–1.51)	1.13 (0.99–1.30)
Male gender of the neonate	1.02 (0.92–1.13)	1.02 (0.91–1.13)
Perinatal death	<b>1.59 (1.01–2.50)</b>	1.18 (0.75–1.86)
Small-for-gestational-age (SGA) infant	<b>1.42 (1.17–1.77)</b>	1.15 (0.92–1.43)
Large-for-gestational-age (LGA) infant	0.62(0.38–1.02)	<b>0.60 (0.37–0.99)</b>

<sup>1)</sup> adjusted for age and year of delivery

<sup>2)</sup> adjusted for age, year of delivery and previous hospitalisation for psychiatric disorder

The reference group for each variable (row) consisted of first-time mothers unexposed to each obstetric variable. Significant results are in bold.

reference group for each obstetric variable (i.e. in each row). Model 1 is adjusted for age and year of delivery and Model 2 is also adjusted for hospitalisation for psychiatric disorder two years preceding delivery. There was a significantly increased risk of postpartum psychosis if any of the following obstetric variables were present: respiratory disorder in the neonate (HR = 1.27; CI = 1.07–1.51), severe birth asphyxia (HR = 1.39;

CI = 1.00–1.95), preterm birth (HR = 1.46; CI = 1.22–1.74), caesarean section (HR = 1.32; CI = 1.15–1.51), perinatal death (HR = 1.59; CI = 1.01–2.50) and SGA infant (HR = 1.42; CI = 1.17–1.77). However, after adjustment for hospitalisation for psychiatric disorder two years preceding delivery, only preterm birth remained a significant risk factor for postpartum psychosis although the HR decreased markedly (HR = 1.20; CI = 1.01–1.44). In addition, mothers having an LGA infant had a *lower* risk of postpartum psychosis (HR=0.60; CI = 0.37–0.99) after adjustment for hospitalisation for psychiatric disorder two years preceding delivery.

The strongest risk factor was previous hospitalisation for psychiatric disorder, which meant a more than 100-fold increased risk of postpartum psychosis (HR = 109.4; 95% CI = 97.9–122.1) (data not shown). Table 6 shows the additional analysis on acute and elective caesarean section. In Model 1, all types of caesarean section were associated with an increased risk of postpartum psychosis. However, after adjustment for hospitalisation for psychiatric disorder only acute caesarean section remained a significant risk factor for postpartum psychosis (HR = 1.31; CI=1.01–1.68).

Table 6 shows the additional analysis on acute and elective caesarean section. In Model 1, all types of caesarean section were associated with an increased risk of postpartum psychosis. However, after adjustment for hospitalisation for psychiatric disorder only acute caesarean section remained a significant risk factor for postpartum psychosis (HR = 1.31; CI=1.01–1.68).

**Table 6.** Hazard Ratios with 95% confidence intervals for postpartum psychosis among first-time mothers by type of caesarean section. Sweden, 1982–2003.

Type of caesarean section	Model 1 <sup>1)</sup> HR (CI)	Model 2 <sup>2)</sup> HR(CI)
Acute	<b>1.49 (1.15–1.92)</b>	1.31 (1.01–1.68)
Elective	<b>1.38 (1.07–1.79)</b>	1.21 (0.94–1.56)
No information on acute or elective	<b>1.54 (1.09–2.18)</b>	1.33 (0.94–1.88)

<sup>1)</sup> adjusted for age and year of delivery

<sup>2)</sup> adjusted for age, year of delivery and previous hospitalisation for psychiatric disorder

The reference group for each variable (row) consisted of first-time mothers unexposed to caesarean section.

Significant results are in bold.

## STUDY 4

During the study period from Jan. 1, 1975, to Dec. 31, 2004, 1340 women were hospitalised for postpartum psychosis within three months after delivery. The most common psychosis was unspecified psychosis, which comprised about 70% of the women. Nearly 10% were classified as schizophrenic. Thirty per cent of the women



had been hospitalised for a psychiatric disorder within two years preceding postpartum psychosis.

The incidence rate of non-puerperal readmission due to psychiatric disorder was about 0.50 per person year during the first five years after the postpartum psychosis and gradually decreased to 0.20 after more than 20 years of follow-up. A diagnosis of schizophrenia at the time of the episode of postpartum psychosis was associated with a higher readmission rate (0.64) than affective psychosis (0.42) and unspecified psychosis (0.30). The incidence rate of non-puerperal readmission due to a psychiatric disorder was higher among women with a lower level of education (data not shown).

Table 7 shows HRs with 95% CIs for non-puerperal readmissions due to a psychiatric disorder in the study population. The full model is adjusted for all the explanatory variables simultaneously. There was an apparent gradient in years of follow-up and the risk of readmission: when the years of follow-up increased, the HRs decreased. Six to ten years after the diagnosis of postpartum psychosis, the risk of readmission was about 50%, compared to the risk during the first year after postpartum psychosis. After 20 years, the risk was less than one third compared to the risk during the first year (HR= 0.29; CI= 0.24–0.33). The type of postpartum psychosis was also associated with the risk of readmission. The HRs were significantly lower among women with affective psychosis (HR=0.82; CI=0.71–0.96) and unspecified psychosis (HR=0.73; CI=0.64–0.84) than among those with schizophrenia (HR = 1, reference). Women hospitalised due to a psychiatric disorder within two years prior to the hospitalisation for postpartum psychosis had a significantly higher risk of readmission (HR=1.56; CI=1.42–1.72) than women not hospitalised due to a psychiatric disorder within two years prior to the postpartum psychosis. The level of education was also significantly associated with the risk of non-puerperal readmission due to a psychiatric disorder. The significant HRs were 1.37 (1.20–1.58) and 1.19 (1.05–1.36) for women with  $\leq 9$  years and 10–12 years of education, respectively, when women with the highest educational attainment were used as reference (data not shown). Education was not included in the full model due to a high proportion of missing values. However, educational level was included in an additional analysis of a subset of the study population (those without missing values for education) and the results were almost identical (data not shown). The age at postpartum psychosis was not associated with the risk of readmission later in life, whereas the calendar year was.

**Table 7.** Hazard ratios with 95% confidence intervals of non-puerperal readmission due to any psychiatric disorder, adjusted for all the explanatory variables simultaneously. Sweden, 1975–2004.

<b>Variable</b>	<b>Level</b>	<b>Full model</b>
		HR (95% CI)
Years of follow-up	Year 1	1 (ref)
	Year 2	0.76 (0.67–0.85)
	Year 3	0.64 (0.57–0.72)
	Year 4	0.61 (0.54–0.69)
	Year 5	0.58 (0.51–0.65)
	Years 6–10	0.50 (0.45–0.56)
	Years 11–15	0.48 (0.43–0.55)
	Years 16–20	0.48 (0.42–0.55)
	>20 years	0.29 (0.24–0.33)
Age	20–24	1
	25–29	0.96 (0.85–1.08)
	30–34	0.93 (0.82–1.05)
	35–39	0.96 (0.83–1.11)
	40–44	0.85 (0.67–1.08)
Type of psychosis	Schizophrenia	1
	Affective psychosis	0.82 (0.71–0.96)
	Unspecified psychosis	0.73 (0.64–0.84)
Hospital admission due to psychiatric disorder within two years prior to postpartum psychosis	No	1
	Yes	1.56 (1.42–1.72)
Calendar year	1975–1979	1
	1980–1984	0.95 (0.85–1.06)
	1985–1989	1.08 (0.96–1.21)
	1990–1994	1.15 (1.00–1.32)
	1995–1999	1.19 (1.03–1.39)
	2000–2004	0.41 (0.35–0.48)

# DISCUSSION

## MAIN FINDINGS

Our results show that some sociodemographic and obstetric factors were associated with increased risk of hospitalisation due to postpartum psychosis among first-time mothers. These factors were old age in the mother, not living with the father of the child, living in a socioeconomically deprived neighbourhood, preterm birth and acute caesarean section. However, HRs for these factors were only moderately increased, which implies that the absolute increase in risk is small. In contrast, previous hospitalisation for psychiatric disorders was associated with a more than 100-fold increased risk of postpartum psychosis. According to studies 3 and 4, 30–35% of the women with postpartum psychosis were hospitalised due to a psychiatric disorder within two years preceding delivery.

Our results also show that the risk of non-puerperal readmission due to a psychiatric disorder, although gradually decreasing with time, remained high for many years after the postpartum psychosis. In addition, the risk of non-puerperal readmission due to a psychiatric disorder was associated with educational level, previous psychiatric hospitalisation and type of psychosis. The high readmission risk also applied for women that were not hospitalised due to psychiatric disorder within two years prior to postpartum psychosis.

## AGE OF THE MOTHER

The increased risk of hospitalisation due to postpartum psychosis among older mothers is important since the average age of first-time mothers is increasing in Sweden and in other western countries [115-118]. The increased risk among older mothers could partly be explained by normal age variations in hospital admissions for psychotic disorders in the general female population [119]. However, it is possible that old age per se is a risk factor for postpartum psychosis, beyond normal age variations in hospital admissions due to psychotic disorders, mediated by some biological or psychological factors.

Some medical complications in pregnancy and delivery are more common among older mothers, for example, caesarean section and preterm birth [120, 121]. In study 3 we showed that acute Caesarean section and preterm birth were associated with a slightly increased risk of postpartum psychosis [108].

Several studies have examined psychosocial aspects of first-time mothering comparing younger and older mothers. According to these studies, older mothers are more tired and have a longer recovery after delivery, have less positive marital relationships, and less overall gratification in the maternal role [122-126].

It is possible that the association between older age in the mother and postpartum psychosis is due to residual confounding of previous psychiatric disorder that we were not able to adjust for, i.e. outpatients and psychiatric admission more than two years before delivery. Women with psychiatric illnesses might become first-time mothers at older ages than mentally healthy women.

## MARITAL STATUS

The association between marital status and postpartum psychosis was examined in study 1 and 2. In study 1, not living with the father of the child was associated with an increased risk of postpartum psychosis. In study 2, this association was not significant in the full model. Previous studies on this association have also been inconsistent. One study from the 50s found that unmarried women exhibited an increased risk of postpartum psychosis [16]. Another study from the early 90s reported that marital difficulties, including not having a partner, were a predictor of postpartum psychosis [127]. However, Kendell et al. found no increased risk of postpartum psychosis among unmarried women in their large Scottish study [5]. A study from India was in agreement with Kendell's study, finding no association between postpartum psychosis and marital status [8].

One possible pathway between not living with the father of the child and increased risk of postpartum psychosis is sleep deprivation after delivery, which is surely worse among mothers not living with the father of the child.

However, the increased risk of hospitalisation due to postpartum psychosis among mothers not living with the father of the child might also be a nosocomial effect. There might be a higher tendency of admitting mentally ill mothers if there is no one at home taking care of the mother and the child. If this is the case, it is not an increased risk of postpartum psychosis, but an increased risk of *hospitalisation* for postpartum psychosis among mothers not living with the father of the child. Unfortunately, this could not be tested for in our register-based studies.

In conclusion, there are possible biases that make interpretation of the association between marital status and postpartum psychosis difficult.

## NEIGHBOURHOOD

Study 2 shows that low neighbourhood socioeconomic status, measured as proportions of people with low income, was associated with an increased risk of first hospital admissions due to postpartum psychosis after adjustment for the individual socio-demographic characteristics age, education, marital status and year of delivery.

There are two possible explanations for our finding. First, physical environment in neighbourhoods with low socioeconomic characteristics might negatively influence mental health among first-time mothers (contextual explanation). Second, the finding of an increased risk of postpartum psychosis for women living in socioeconomically deprived neighbourhoods could be due to a higher rate of women with psychiatric disorders living in these neighbourhoods before delivery (compositional explanation). We had no data on outpatients and hospitalisations due to psychiatric disorder that occurred more than two years prior to the postpartum psychosis. This implies that the number of women with a psychiatric disorder before the postpartum psychosis is probably underestimated, which is important to take into account in the interpretation of the results. However, even though our study does not reveal the casual pathway for the association between low neighbourhood income and postpartum psychoses, it shows that women living in a socioeconomically deprived neighbourhood have higher rates of postpartum psychosis.

## **PRETERM BIRTH**

Study 3 shows that preterm birth is associated with a slightly increased risk of postpartum psychosis. In most cases of preterm birth the labour starts spontaneously. However, preterm birth is sometimes a consequence of caesarean section related to pregnancy complications, for instance hypertension, pre-eclampsia, placenta praevia, ablatio placentae, intrauterine growth retardation, diabetes mellitus and Rh immunisation [105]. Risk factors associated with preterm birth are young or old age of the mother, primiparity, smoking, genetic factors, stress, and social deprivation [105, 128-133]. Moreover, living in a deprived neighbourhood or being a single mother are risk factors for both preterm birth and postpartum psychosis [108, 110, 131, 133].

Prior studies have indicated that depression and anxiety during pregnancy increase the risk of spontaneous preterm delivery [134, 135]. It is possible that residual confounding of previous psychiatric illness can explain the association between preterm delivery and postpartum psychosis.

However, biological factors might also increase the risk of both preterm birth and postpartum psychosis. Cortisol is one such risk factor. High maternal plasma cortisol levels early in pregnancy could increase the risk of preterm birth by stimulating release of corticotrophic-releasing hormone (CRH) from the placenta [132]. In addition, a small study of eight women with postpartum psychosis demonstrated that increased cortisol levels were more common among cases than controls [48].

Another factor in the possible causal pathway between preterm birth and postpartum psychosis is the fact that preterm born infants often need extra medical care and a longer stay in hospital. The resulting stress and worry for the preterm born infant might predispose for postpartum psychosis in certain vulnerable mothers.

## **CAESAREAN SECTION**

Unlike other studies, study 3 distinguished between elective and acute caesarean section. It is interesting that acute caesarean section, but not elective caesarean section, was associated with an increased risk of postpartum psychosis after adjustment for previous hospitalisation for psychiatric disorder. It supports the theory that difficult labour and delivery during the night might precipitate for postpartum psychosis, with sleep loss as a possible causal pathway [3, 136].

## **LARGE-FOR-GESTATIONAL-AGE (LGA)**

Our finding indicates that having an LGA infant protects from postpartum psychosis. Major risk factors for having an LGA infant are gestational diabetes and obesity in the mother [137, 138]. There is a possibility that the association between having an LGA infant and the decreased risk of postpartum psychosis is due to hormonal causes. Excess visceral fat is of endocrine importance, affecting sex hormones, cortisol and the HPA axis [139]. However, the confidence interval was broad and therefore it is possible that this is a chance finding.

## **NON-PUERPERAL READMISSION DUE TO PSYCHIATRIC DISORDERS**

In study 4 we examined non-puerperal readmission and years of follow-up among women with postpartum psychosis. We also investigated the impact of age, type of psychosis, previous psychiatric and educational level on the risk of non-puerperal readmission due to psychiatric disorders.

### **Years of follow-up**

To the best of our knowledge, study 4 is the first on the association between non-puerperal readmission due to a psychiatric disorder and years of follow-up after postpartum psychosis. Surprisingly, the incidence rate of non-puerperal readmission due to a psychiatric disorder, although gradually decreasing with time, was still as high as 0.20 per person year after more than 20 years of follow-up. This implies that postpartum psychosis in many cases is part of a severe and chronic psychiatric disorder.

The high readmission rate among women without psychiatric hospitalisation within two years prior to postpartum psychosis suggests that delivery often is the start of a severe chronic psychiatric disorder. One explanation for this might be that delivery triggers a severe chronic psychiatric disorder that would have developed sooner or later in life, regardless of delivery, in certain vulnerable women. Another possible mechanism for severe chronic psychiatric disorder triggered by delivery is autoimmunity. Delivery is associated with activation of autoimmune disorders, such as thyroiditis and rheumatoid arthritis [140, 141] In addition, recent studies have revealed a relationship between schizophrenia and autoimmune disorders. It might be possible that some cases of postpartum psychoses are due to autoimmune activity that is triggered by delivery [142, 143].

However, the high readmission rate among women without psychiatric hospitalisation within two years prior to postpartum psychosis could also be due to residual confounding of previous psychiatric illness that we could not adjust for (i.e. outpatients and psychiatric hospitalisation more than two years before postpartum psychosis).

Although the design of the study did not allow any inferences about causal relationships, some possible mechanisms might be considered as explanations of the decreased risk of non-puerperal readmission with increasing years of follow-up. Firstly, previous studies have suggested that oestrogen withdrawal at, for instance, delivery, menstruation and menopause is associated with psychoses [42-44]. After the menopause the large fluctuations of oestrogen levels disappears and it is likely that many of the women in the present study had reached the menopause 20 years after the start of the follow-up. In addition, some psychiatric disorders, such as depression, are more common among women of fertile age [119]. Secondly, it is possible that effective pharmacological and/or non-pharmacological treatments lower the risk of hospitalisation for psychiatric disorders. Some women might also have developed other coping factors that protect them from exacerbations after several years of living with a chronic psychiatric disease.

### **Type of postpartum psychosis**

Study 4 shows, in conformity with previous studies, that the type of psychosis is associated with the risk of non-puerperal readmission due to a psychiatric disorder. For example, a Danish study of 1041 women with postpartum psychosis showed that those

with schizophrenia had a higher relative risk (RR = 2.4) of readmission than women with non-schizophrenic psychoses [93]. A Scottish study demonstrated that subsequent non-puerperal psychoses occurred in 85% (11/13) of the women with a schizophrenic disorder post partum. In addition, a Swedish long-term follow-up study of 79 women with a parapartum psychiatric disorder showed a relapse rate of 100% for the 5 women diagnosed with schizophrenic disorders at delivery. The Swedish study also demonstrated considerably more sick-leave days per year for women diagnosed with schizophrenic disorder at delivery compared to women diagnosed with affective psychosis or unspecified psychosis at delivery [96].

## **Educational level**

Previous research has shown that low educational level is associated with an increased risk of psychotic and depressive disorders [66]. In contrast, educational level did not seem to be associated with postpartum psychosis, in the present study [108]. This suggests that delivery itself is such a strong risk factor for psychosis that it rules out the effect of low educational level. However, when it comes to non-puerperal readmission due to a psychiatric disorder among women with postpartum psychosis, study 4 shows that lower educational level is a risk factor.

Educational level could be regarded as a proxy for socioeconomic status (SES). To the best of our knowledge, neither educational level nor SES (measured in other ways) has been examined previously as a potential risk factor for readmission due to a psychiatric disorder after postpartum psychosis. It is possible that higher education might protect from psychiatric relapses because a higher educational level implies a higher socioeconomic position in society with less stress, better social networks and perhaps more effective pharmacological and non-pharmacological treatment of the psychiatric disorder. However, a psychiatric disorder might also lead to lower educational achievement if the woman cannot pursue higher education owing to her illness.

## **Previous hospitalisation due to a psychiatric disorder**

In the study population of study 4, 30% had been hospitalised for a psychiatric disorder within two years prior to the postpartum psychosis. These women had a roughly 50% higher risk of non-puerperal readmission than the women not hospitalised for a psychiatric disorder within two years prior to the postpartum psychosis (HR=1.56; CI=1.42–1.72). These findings agree with those of a Danish study including 1041 women with postpartum psychosis, demonstrating an increased readmission risk (RR=1.8) for women with previous psychiatric admission compared to women without previous psychiatric admissions [93].

In order to test the validity of our data, we checked the percentage of women readmitted for a non-puerperal psychiatric disorder and found that 65% (n = 867) had been readmitted during the 30-year study period (data not shown). Previous studies have shown almost identical relapse rates of about 65% up to 35 years after the postpartum psychosis [1, 10, 94, 95]. Our data therefore confirm that postpartum psychosis is often part of a recurrent psychiatric disorder [1, 93-95, 144]

## DECREASED RISK OF POSTPARTUM PSYCHOSIS DURING THE 1990S

Study 1 and 2 shows a decreased risk of postpartum psychosis during the 1990s, when a reduction in psychiatric beds occurred. This suggests that the decision on whether to admit mentally ill mothers or not is probably influenced not only by the severity of the disease, but also by surrounding factors. Indeed, many psychiatric disorders are suitable for open care. However, our studies are based on severe psychiatric disorders such as psychosis, manic-depressive disorder and major depression in women that have to take care of a newborn baby. It is not recommended that women with severe psychiatric disorders postpartum should be treated in open care. The risk of suicide and infant mortality among women with postpartum psychosis is largely unknown since previous studies did not separate psychosis from other severe psychiatric disorders postpartum. However, mothers with postpartum psychosis ought to be at increased risk of injuring themselves or her infant. Therefore the finding of decreased risk of postpartum psychosis during the 1990s is remarkable.

## STRENGTHS AND LIMITATIONS

There are several strengths in our studies. First, the registers allowed us to include all women aged 20–44 years in Sweden during long periods, i.e. 12–30 years. This gave us the opportunity to examine the associations between several sociodemographic and obstetric variables and the rare but severe disorder postpartum psychosis. Second, the registers allowed us to adjust for previous psychiatric admission two years preceding delivery. Third, data from the registers are highly complete and the quality of the registers is tested regularly and proved to be high.

There are also some limitations. First, our data did not allow us to examine the causal pathways between the explanatory variables and the outcomes in the studies. Second, the registers included only hospital admissions for psychiatric disorders, i.e. outpatients were not included in the study. In addition, the design of the study did not allow us to include data on hospitalisations due to psychiatric disorder that occurred more than two years prior to the postpartum psychosis. This means that the number of women with a psychiatric disorder before and/or after the postpartum psychosis is probably underestimated, which is important to take into account in the interpretation of the results. Third, in study 3 there might have been some missing data for the obstetric variables that were based on ICD codes of the mothers' diagnoses (anaemia, pre-eclampsia and malposition or malpresentation of foetus) because only four diagnoses per delivery were registered in the Medical Birth Register until 1998. Fourth, even though we have adjusted for several possible confounders in the studies, residual confounding might exist. This means that there might remain confounders that would have affected the results if we had been able to adjust for them. For instance, in study 3 we could not adjust for smoking. Research has shown that smoking is associated with an increased risk of preterm birth [145]. If smoking is more common among women with postpartum psychosis it could explain why preterm birth was associated with a higher risk of postpartum psychosis. Fifth, due to multiple statistical tests, some significant results might have occurred by chance (study 3).

Finally, the validity of administrative registers for research purposes has been insufficiently investigated in previous validity studies [146, 147].



## CONCLUSIONS

In conclusion, this thesis shows that some sociodemographic and obstetric factors, such as age of the mother, not living with the father of the child, living in a socioeconomically deprived neighbourhood, preterm birth and acute caesarean section, are associated with increased risk of postpartum psychosis, but only to a moderate degree. Therefore stress from adverse sociodemographic and obstetric conditions possibly plays a role in the development of postpartum psychosis. However, the associations above might also be due to confounding of e.g. previous psychiatric illness.

Postpartum psychosis is often part of a severe and chronic psychiatric illness with high non-puerperal readmission rates during at least 20 years. Non-puerperal readmissions are associated with educational level, previous psychiatric hospitalisation and type of psychosis.

Finally, and most important, previous psychiatric disorder is a very strong risk factor for postpartum psychosis. Therefore, it is important to consider previous psychiatric disorder in the antenatal and postnatal care.

## SUMMARY IN SWEDISH / SAMMANFATTNING PÅ SVENSKA

Psykos efter förlossning, så kallad postpartum psykos, drabbar ca 1–2 kvinnor per 1000 förlossningar [1, 2]. Incidensen (antal insjuknanden/tidsenhet) av förstagångspsykos är förhöjd de tre första månaderna efter förlossning [5]. Sjukdomen innefattar psykotiska och ofta samtidigt affektiva symtom som vanligen debuterar inom två veckor efter förlossningen [21]. Tidigare studier har visat att svår psykisk sjukdom efter förlossning hos modern är förknippad med självmord, ökad barnadödlighet, utvecklings- och beteenderubbningar hos barnet vid fyra års ålder samt ökad psykisk sjuklighet hos barnet i vuxen ålder [89-92]. I dessa studier har man inte separerat psykos från andra svåra psykiska sjukdomar efter förlossning. Om enbart psykos leder till ovanstående konsekvenser är således inte klargjort.

Flera tidigare studier har visat att förstagångsfödelse och tidigare psykisk sjukdom [1, 3-7], framförallt bipolär sjukdom (manodepressivitet) är associerat med postpartum psykos [5, 9-13]. Sociodemografiska och obstetriska faktorer för postpartum psykos har studerats i relativt små studier och gett motstridiga resultat [1, 5, 8, 14-18]. Det kan bero på att postpartum psykos är relativt ovanligt. I storskaliga, epidemiologiska studier är det lättare att finna eventuella samband mellan postpartum psykos och sociodemografiska och obstetriska faktorer.

Syftet med denna avhandling är att klargöra eventuella samband mellan postpartum psykos och vissa sociodemografiska och obstetriska faktorer i registerstudier som innefattar alla svenska kvinnor under en period av flera år. Förhoppningsvis kan detta leda till ökad förståelse av postpartum psykos och öka medvetenheten om riskfaktorer.

### SYFTEN

Att undersöka om det finns något samband mellan postpartum psykos och vissa sociodemografiska och obstetriska faktorer.

*Studie 1:* Att analysera om det finns något samband mellan inläggning på grund av postpartum psykos och moderns ålder, civilstånd, utbildningsgrad och förlossningsår.

*Studie 2:* (a) Att analysera om det finns något samband mellan den socioekonomiska miljön i moderns bostadsområde, beräknad utifrån andel invånare i bostadsområdet med låg inkomst, och risk för inläggning på grund av postpartum psykos, samt (b) att undersöka om ett eventuellt sådant samband kvarstår efter justering för individuella sociodemografiska faktorer.

*Studie 3:* Att analysera om det finns något samband mellan vissa variabler vid graviditet och förlossning och postpartum psykos.

*Studie 4:* Att analysera risken för sjukhusinläggning pga. psykisk sjukdom, ej sammanhängande med barnsängstiden, bland kvinnor med tidigare postpartum psykos. Risken beräknas beroende på antal år av uppföljning, utbildningsnivå, typ av psykos, ålder och tidigare inläggning pga. psykisk sjukdom.

## MATERIAL

Materialet till studierna togs från databasen WomMed som innehåller information om alla kvinnor i Sverige och deras barn. I WomMed är flera register sammanlänkade, bl.a. medicinska födelseregistret, patientregistret, dödsorsaksregistret och LOUISE (register från SCB med uppgifter om inkomst, utbildning och sysselsättningsgrad). Även uppgifter om kvinnornas bostadsområden ingår.

I studie 1 och 2 användes en version av WomMed som innehöll de 2.2 miljoner kvinnor som föddes åren 1950–1984 och deras 2.5 miljoner barn födda fram till 1999. I studie 3 och 4 användes en uppgraderad version som innehöll de 3.3 miljoner kvinnor som föddes åren 1932–1990 och deras 5.5 miljoner barn som föddes fram till 2004.

### Studie 1

Studiebas: 502 767 förstföderskor, ej inlagda på sjukhus pga. psykisk sjukdom inom två år före förlossningen och i åldrarna 20–44 år, under den studerade tiden från den 1 januari 1986 till den 31 december 1997.

Utfallsvariabel: Första inläggningen på sjukhus pga. psykos inom tre månader efter förlossning.

Förklarande variabler: Ålder, utbildningsnivå, civilstånd och förlossningsår.

Statistisk analys: HR räknades ut med Cox proportional hazard model, i den fulla modellen med justering för alla förklarande variabler samtidigt.

### Studie 2

Studiebas: 485 199 förstföderskor, ej inlagda på sjukhus pga. psykisk sjukdom inom två år före förlossningen och i åldrarna 20–44 år, under den studerade tiden från den 1 januari 1986 till den 30 september 1998. Individerna länkades till sitt bostadsområde (SAMS).

Utfallsvariabel: Första inläggningen på sjukhus pga. psykos inom tre månader efter förlossning.

Förklarande variabel: Andelen låginkomsttagare i kvinnans bostadsområde (SAMS).

Statistisk analys: HR räknades ut med Cox proportional hazard model, i den fulla modellen med justering för de individuella variablerna ålder, utbildningsnivå, civilstånd och förlossningsår.

### Studie 3

Studiebas: 1 133 368 förstföderskor under den studerade tiden från den 1 januari 1975 till 31 december 2003.

Utfallsvariabel: Första inläggningen på sjukhus pga. psykos inom tre månader efter förlossning.

Förklarande variabler: Anemi, preeklampsi, förlossningshinder orsakat av onormalt fosterläge och felaktig fosterbjudning, förlossningsskador på modern, blödning i efterbördsskedet, förlossningsskador på barnet, perinatale sjukdomar i barnets andningsorgan, allvarlig syrebrist hos barnet i samband med förlossningen, mild/måttlig syrebrist hos barnet i samband med förlossningen, gulsot hos barnet, underburenhet, överburenhet,

flerbörd, akut och planerat kejsarsnitt, barnets kön, perinatal död, underviktighet och överviktighet hos barnet.

Statistisk analys: HR räknades ut med Cox proportional hazard model för varje förklarande variabel separat, i den fulla modellen med justering för ålder, inläggning pga. psykisk sjukdom inom två år före förlossning och förlossningsår.

## Studie 4

Studiebas: 1 340 kvinnor med första inläggningen pga. postpartum psykos inom 3 månader efter förlossningen i åldrarna 20–44 år mellan 1 januari 1975 och 31 december 2004.

Utfallsvariabel: Inläggning på sjukhus pga. psykisk sjukdom, ej sammanhängande med barnsängstiden.

Förklarande variabler: Antal år efter postpartum psykos, ålder, typ av psykos, inläggning pga. psykisk sjukdom inom två år före postpartum psykos, utbildningsnivå och kalenderår.

Statistisk analys: HR beräknades med Cox frailty regression model efter justering för alla förklarande variabler samtidigt.

## RESULTAT

*Studie 1:* Sammanlagt 339 förstfödorskor lades in på sjukhus pga. postpartum psykos inom tre månader efter förlossningen. Risken för postpartum psykos ökade med åldern hos modern. Risken för postpartum psykos var 60 % högre bland de som inte bodde med barnets far jämfört med de som bodde med barnets far (HR = 1,60 (95 % konfidensintervall = 1,09–2,34)). Utbildningsgrad påverkade inte risken för postpartum psykos. Förlossningsår påverkade signifikant risken för inläggning pga. postpartum psykos. Under perioderna 1990–1993 och 1994–1997 var risken betydligt lägre än under perioden 1986–1989 (Hazard Ratio=0,62 (95 % konfidensintervall=0,47–0,80) respektive Hazard Ratio=0,74 (95 % konfidensintervall=0,57–0,96)).

*Studie 2 :* Sammanlagt 356 förstfödorskor lades in på sjukhus pga. postpartum psykos inom tre månader efter förlossningen. Det var signifikant högre risk för postpartum psykos bland kvinnor som bodde i den tertil av bostadsområden (SAMS) med högst andel låginkomsttagare jämfört med kvinnor som bodde i den tertil av bostadsområden (SAMS) med lägst andel låginkomsttagare. Denna skillnad kvarstod efter justering med de individuella variablerna ålder, utbildningsnivå, civilstånd och förlossningsår (Hazard Ratio=1,49 (95 % konfidensintervall=1,15–2,91)).

*Studie 3:* Sammanlagt 1 413 förstfödorskor lades in på sjukhus pga. postpartum psykos inom tre månader efter förlossningen. Bland dessa hade 35 % varit inlagda på sjukhus för psykisk sjukdom inom två år före förlossningen. Följande variabler markerade ökad risk för postpartum psykos: perinatale sjukdomar i barnets andningsorgan, allvarlig syrebrist hos barnet i samband med förlossningen, underburenhet, kejsarsnitt, perinatal död och underviktighet hos barnet. Efter justering för tidigare psykisk sjukdom kvarstod endast underburenhet (HR = 1.20; CI = 1.01–1.44) och akut kejsarsnitt (HR = 1.31; CI=1.01–1.68) som riskfaktorer för postpartum psykos. Överviktighet hos barnet

*minskade* signifikant risken för postpartum psykos efter justering för tidigare psykisk sjukdom (HR=0.60; CI = 0.37–0.99). Den absoluta riskökningen var dock liten jämfört med riskökningen som tidigare psykisk sjukdom medförde (HR = 109.4; 95 % CI = 97.9–122.1).

*Studie 4:* Incidensen av sjukhusinläggning pga. psykisk sjukdom var synnerligen förhöjd under de första fem åren efter förlossning. Därefter minskade incidensen successivt, men var dock fortfarande hög under ca 20 år efter postpartum psykos. Schizofreni medförde fler inläggningar än affektiv psykos och ospecificerad psykos. Risken för inläggning pga. psykisk sjukdom ökade med lägre utbildningsgrad och om kvinnan hade varit inlagd för psykisk sjukdom inom två år före postpartum psykos.

## SLUTSATSER

Efter justering för sjukhusinläggning för psykisk sjukdom inom två år före förlossning visar denna studie att följande variabler är associerade med något ökad risk för postpartum psykos: hög ålder hos modern, att ej vara sammanboende med barnets far, att bo i ett bostadsområde med låg socioekonomisk status, förtidsbörd och akut kejsarsnitt. En del av dessa samband kan sannolikt förklaras av psykisk sjukdom som vi ej kunde ta hänsyn till i analysen (t.ex. öppenvårdspatienter och kvinnor med psykisk sjukdom mer än två år före förlossning). Överviktighet hos barnet *minskade* signifikant risken för postpartum psykos.

Hög incidens av sjukhusinläggningar, pga. psykisk sjukdom, under många år efter postpartum psykos talar för att postpartum psykos i många fall är en del av en allvarlig och kronisk psykisk sjukdom.

Så många som 30–35 % av kvinnorna med postpartum psykos var inlagda pga. psykisk sjukdom inom två år före förlossningen. Tidigare psykisk sjukdom är således den mest betydelsefulla riskfaktorn för postpartum psykos. Därför är anamnes av tidigare psykiska sjukdomar mycket viktig inom mödravården.

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