Perinatal Complications: Associations with Postpartum depressive symptoms and Neuroticism

PATRICIA ECKERDAL
Abstract


Even though most pregnancies and deliveries are uncomplicated, still fifteen percent of all women in developed countries suffer pregnancy-related complications. The aim of this thesis was to explore the associations between perinatal complications and perinatal maternal health, with emphasis on postpartum depressive symptoms (PPDS) and neuroticism taking into account potential confounding or mediating factors such as history of depression, antenatal depressive symptoms and delivery experience.

In the first study (n=446), the association between heavy postpartum haemorrhage and PPDS at six weeks postpartum was delineated by using path-analysis in order to provide insight into the complex mediating roles of several consequences of postpartum haemorrhage. There was no direct association between postpartum haemorrhage and PPDS, only an indirect one via anaemia at discharge and negative delivery experience.

The second study (n=3888) examined the association of mode of delivery with PPDS at 6 weeks postpartum. The results indicate that the association between elective caesarean section and PPDS is highly confounded by history of depression and fear of delivery, while emergency caesarean section and vacuum extraction increase odds for PPDS by leading to postpartum complications and negative delivery experience.

The third study (n=1503) investigated the association between the use of epidural analgesia during delivery and PPDS. A positive association in the crude analysis was no longer present after adjustment for sociodemographic, psychosocial and obstetrical variables, indicating that pain relief through epidural analgesia is not likely to affect risk for PPDS.

In the last study (n=1969), the association between neuroticism and perinatal complications was explored. Neuroticism was not associated with adverse perinatal outcomes, except for gestational diabetes mellitus. The association, however, became statistically non-significant after adjusting for psychiatric morbidity.

In summary, the current studies do no find evidence for a direct association between perinatal complications and postpartum depressive symptoms or neuroticism. However, several important mediators have been identified, among which postpartum anaemia and negative delivery experience deserve special attention. Also, earlier psychiatric history needs to be addressed as an important confounder.

Keywords: antenatal depression, cesarean section, delivery complications, Edinburgh postnatal depression scale, EPDS, epidural analgesia, gestational diabetes mellitus, instrumental delivery, neonatal complications, neuroticism, obstetric complications, personality, perinatal complications, postpartum depression, postpartum haemorrhage, pregnancy complications, vacuum extraction, vaginal delivery

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List of Papers

This dissertation is based on the following papers, which are referred to in the text by their Roman numerals.


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### Abbreviations

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<th>Full Form</th>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CS</td>
<td>Caesarean section</td>
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<td>EDA</td>
<td>Epidural analgesia</td>
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<td>EPDS</td>
<td>Edinburgh postnatal depression scale</td>
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<td>GDM</td>
<td>Gestational diabetes mellitus</td>
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<td>GSEM</td>
<td>Generalized structural equation modelling</td>
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<td>Hb</td>
<td>Haemoglobin concentration</td>
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<td>HPA-axis</td>
<td>Hypothalamic-pituitary-adrenal axis</td>
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<td>LGA</td>
<td>Large for gestational age</td>
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<td>MBR</td>
<td>Medical birth register</td>
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<td>NEO-PI</td>
<td>Neuroticism Extraversion Openness Personality Inventory</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PPD</td>
<td>Postpartum depression</td>
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<td>PPDS</td>
<td>Postpartum depressive symptoms</td>
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<td>PPH</td>
<td>Postpartum haemorrhage</td>
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<td>PTSD</td>
<td>Posttraumatic stress disorder</td>
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<tr>
<td>SEM</td>
<td>Structural equation modelling</td>
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<tr>
<td>SGA</td>
<td>Small for gestational age</td>
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<td>SSP</td>
<td>Swedish university Scales of Personality</td>
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<td>SSRIs</td>
<td>Selective serotonin reuptake inhibitor</td>
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<td>VE</td>
<td>Vacuum extraction</td>
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<td>W-DEQ</td>
<td>Wijma Delivery Expectancy/Experience Questionnaire</td>
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Preface

To become a parent is an overwhelming experience. The perinatal period is a time of intense change and transition, in both somatic and psychological modalities. The underlying hormonal and metabolic changes taking place in combination with psychosocial factors could increase the risk of depression after delivery. This may severely affect the mother, but also her partner and their child in both the short- and long-term perspective.

The multidisciplinary research field of perinatal depression has expanded during the last thirty years. Yet, there are still many unsolved questions on how to identify, treat, and even more desirably, prevent postpartum depression.

Mainly thanks to social media and user’s organizations, the last years have allowed for more open discussions about mental illness and depression in general. Yet, unfortunately, getting depressed while having a newborn is still associated with stigma.

As an obstetrician, I commonly encounter women who have just delivered a baby, sometimes under traumatic conditions. My clinical mission is to guide and help the individual woman who suffers from, or is at risk for, perinatal depression or other mental disorders. With my thesis, my intention has been to contribute to the collection of new knowledge about the association between perinatal complications and maternal mental health and move the field a step closer towards a more integrative approach considering both somatic and psychological aspects in perinatal health.
Introduction

Normal delivery

WHO defines normal delivery as follows: "spontaneous in onset, low-risk at the start of labor and remaining so throughout labor and delivery. The infant is born spontaneously in the vertex position between 37 and 42 completed weeks of pregnancy. After birth, mother and infant are in good condition" (1). The definition also stresses that “giving birth is not only safe but also a positive experience for women and their families” (2).

When the woman presents to the delivery ward and the first stage of delivery is affirmed, a risk assessment of the forthcoming delivery is performed. This assessment includes obstetric history, further medical history, blood pressure, and monitoring of the fetal heart rate by cardiotocography for at least 20 minutes (3).

There is no universal definition of the time point corresponding to the onset of delivery. The Swedish guidelines define the onset of the active first stage of delivery when two of the following three criteria are fulfilled: 1) cervix is dilated 4 cm or effaced and dilated >1 cm; 2) regular painful contractions with a frequency of 2-3/10 minutes; 3) rupture of membranes (4). Similarly to the definition of the onset of delivery, there is no well-established recommendation for the duration of the active first stage. WHO recommends the duration from the time of cervix dilation of 5 cm to delivery not to extend 12 hours in primiparas and 10 hours in multiparas (2). If augmentation is needed, the first intervention is amniotomy if the membranes are unruptured, otherwise oxytocin-infusion.

The second stage starts when the cervix is fully dilated and continues until the child is born. A duration up to three hours is considered normal for nulliparous women, as opposed to two hours for multiparous women (2).

The third stage of delivery starts after the child is born, and ends when the placenta is delivered, normally within 30 minutes (2).

Throughout the entire delivery process, foetal monitoring should regularly be performed by auscultation or cardiotocography (4). In almost all deliveries, the woman requires some form of pain-relief. As a first approach, non-pharmacological methods such as bath, massage acupuncture and transcutaneous nerve stimulation are preferred (5, 6). Later on, there is often a need for pharmacological interventions, like nitrous acid, paracervical blockade, local anaesthetic blockade or epidural analgesia (EDA) (2, 5).
Perinatal complications

In 2016, Lancet published a series of papers about maternal health, which affirm that improvement of global maternal health has a central role in achieving the United Nations Sustainable Development Goals (7, 8). The authors also stress the diversity and divergence of maternal health (9-14). Fortunately, the global maternal mortality has significantly decreased during the last two decades, but remains worryingly high in some low- and middle-income countries (7). Maternal morbidity is defined by WHO as “any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on the woman's wellbeing”. This definition implies that not only physical conditions but also conditions related to mental health and sense of wellbeing may be considered as maternal morbidity.

The causes of maternal mortality and morbidity are increasingly diverse, reflecting large-scale demographic, epidemiological, socioeconomic, and environmental transitions (10, 15). Poor maternal health often mirrors restrictions in human rights (10). The WHO recently initiated the Morbidity Working Group (MMWG) that identified 121 diagnostic categories of maternal morbidity (15, 16). According to their report, the five main direct obstetric causes of maternal morbidity include postpartum haemorrhage (PPH) (prevalence 6.2–10.8%), eclampsia (0.5%), pre-eclampsia (2.3%), severe abortion complications (0.6%), and puerperal sepsis (4.4%) (17). These prevalence rates are just rough estimations as the lack of common definitions and assessment methods may bias the estimates. For example, some studies included conditions existing before pregnancy in their definitions of maternal morbidity, whereas others excluded them (18, 19). Some studies even classified conditions like nausea, commonly experienced during pregnancy, as a type of morbidity, whereas others defined maternal morbidity strictly in terms of pregnancy-associated hospitalizations (18). There are also epidemiological limitations of studies on maternal morbidity. The most common limitation is facility-based instead of population-based studies, leading to selection bias (17). Hospital-based studies on maternal morbidity might only be representative of women who seek care (10). This is even more apparent in low- and middle-income countries, where organized registers for diagnosis are lacking (10) and the participation in perinatal care is lower, although fortunately increasing (20, 21). Commonly, studies rely on self-reported data, which might lead to an over-estimation of the complications, suggesting that self-perceived ill health is not only the result of biological changes but also depends on social support and social context (17). There is also a lack of globally representative systematic reviews on many conditions. Several of the published systematic reviews are based solely on studies from specific countries, which cast some doubt on the geographic representativeness of the findings (17). A further limitation for the comparability of the studies is the use of different methods for quantifying
morbidity rate. Overall prevalence is the most commonly used metric, but other studies may use point-prevalence or period-prevalence, and the assessment time-point may differ, thus leading to divergent results (17).

The forthcoming paragraphs present a brief summary of the perinatal complications examined in this thesis.

**Antenatal complications**

**Gestational Diabetes**

Gestational diabetes mellitus (GDM) is one of the most common antenatal complications with potential adverse effects for both the woman and the foetus/newborn if not optimally treated (22). The prevalence is increasing, in line with the worldwide epidemic of obesity, and is now estimated to 16.2% (23). However, the prevalence broadly varies worldwide depending on diagnostic criteria (24, 25) and ethnicity (26), ranging from 1.8% in Sweden (27) up to 74% in Barbados (28). Even in Sweden, the prevalence differs across regions according to screening procedures, ethnic group composition and changed diagnostic criteria during the last years (27, 29-31).

Numerous studies support an association between diabetes and depression in general (32), with a bidirectional causality (33-35). There is more scarce literature on associations between GDM and perinatal depression. Most studies report an association between GDM and antenatal depression (36) as well as PPD (36-40), but there are also studies reporting no association (41). Studies on the association between pre-existing diabetes and perinatal depression report contradicting results (39, 41).

There are several possible explanations for the reported associations of maternal mental health with GDM. These might include changes in the hypothalamic–pituitary–adrenal axis (HPA-axis), where heightened stress levels and chronic inflammation induce insulin resistance (42) via pregnancy-related intrinsic inflammatory mechanisms (43). Depression is further associated with lower physical activity and a change in dietary patterns, which both are risk factors for GDM (44, 45). The distress of getting the diagnosis of GDM may also lead to reactive depression, for example when more advanced treatment is needed or complications have occurred (46). Additionally, some studies report an overrepresentation of obesity and metabolic syndrome in individuals with high neuroticism (47, 48), which has been linked to perinatal depression. Some studies also report an association between obesity and PPD (49).
Fear of delivery

A woman’s expectations and experiences of pregnancy and delivery are often complex with both positive and negative thoughts, and most women experience some concerns about the forthcoming delivery. However, for many women the fear might affect the women’s quality of life and could also take phobic dimensions as to restrict their daily life and relationships (50, 51). The prevalence of fear of delivery varies between 4 and 40% depending on the definition of fear of delivery, study design, questionnaires and social context (52). A recent meta-analysis reports a prevalence of 14% for tokophobia, i.e. severe fear of delivery (51).

In Sweden, nearly all women participate in a system of regular visits at the maternal primary care unit (53). Except for health improvement and screening for pregnancy-related disorders, these visits include qualitative assignments like screening for fear of delivery, and parental education in order to improve strategies to deal with the forthcoming delivery and parenthood (53). In case of positive screening for fear of delivery, the woman is offered appointments to a midwife or consultant physician for helping strategies to handle the fear. However, there are no standardized guidelines for either definition, screening method or treatment of fear of delivery in Sweden (54). Eight percent of Swedish pregnant women obtain support and/or treatment for fear of delivery (27).

Fear of delivery is more common in nulliparous women, so called primary fear of delivery (51, 55). Secondary fear of delivery is associated with traumatic experiences from previous delivery, these could either be based on objective delivery complications or on psychological responses (50). Other factors associated with fear of delivery include sociodemographic factors, history of abuse, affective disorders, neuroticism, long period of infertility and exposure to negative stories about delivery (50). Thereby, even a medical uncomplicated vaginal delivery may be experienced as negative for the individual woman.

Women with fear of delivery have a higher risk of posttraumatic stress disorder (PTSD) after delivery (56) and may also, in the worst case, decide not to become pregnant again (57, 58). Some studies indicate that women with fear of delivery have a higher risk of prolonged delivery, instrumental delivery and caesarean section (CS) (59-62), although some other studies show contradicting results (63, 64). A woman with fear of delivery is also more prone to request induction of delivery (65) or CS (62, 66-69). This is probably in an attempt to deal with the expectant humiliation and loss of control, the fear of pain, and the fear of sequels for herself and the foetus (70). Apart from the psychological consequences, women with fear of delivery often require more perinatal healthcare from both midwives and physicians, which generates higher perinatal costs (69).

The Swedish national medical guidelines for CS on maternal request emphasize the importance of weighting risks between a non-medical intervention
versus the potential risks of not performing the intervention (71). In the case of CS on maternal request, a weighting of short and long-term consequences for the individual woman and the child is in focus, but also ethical considerations regarding the woman’s autonomy and the principle of justice should be taken into account (71).

The most widely used validated questionnaire, both in the clinic and the research setting, for assessing maternal expectations about and experience of delivery is The Wijma Delivery Expectancy/Experience Questionnaire (W-DEQ) (version A for expectancy, version B for experience) which consists of 33 items (72). However, some studies use just one or a few questions with three to five response options on a Likert-scale (73-76).

Delivery complications

Although diverse and divergent, the global maternal mortality and morbidity rates are fortunately decreasing (7). Nevertheless, the delivery process is inevitably associated with a number of maternal and infant complications. The most common maternal complications include PPH, severe vaginal lacerations, and infection (77). The delivery process itself can be prolonged and complicated, and unfortunately, become a negative experience that might even cause posttraumatic stress symptoms (78, 79). The strongest delivery-related risk factors associated with PTSD are operative delivery, pain, negative delivery experience, and infant-related complications (56, 79). There is also a strong co-morbidity between delivery-related PTSD and perinatal depression (56, 80, 81). Moreover, there are some studies reporting an association between pregnancy complications, negative delivery experience and PPD (38, 40, 82, 83). Summarized, this gives a hypothetical framework of a plausible association of delivery complications with PPD, which has been only partly studied (84, 85).

Postpartum Haemorrhage

PPH is a leading cause of global maternal mortality, accounting for 25% of all maternal deaths (86). The prevalence has a wide range, with estimations from 6 to 11% (87, 88). The last estimates from Sweden were 4.7% for vaginal delivery and 14% for CS (27).

There are several definitions of PPH. One of the most common ones, defines PPH as a blood loss of > 500 mL at vaginal delivery or > 1000 mL at CS (89). Another well-established definition, and the one used in Swedish clinical practice, defines PPH as a blood loss of > 1000 mL within 24 hours from delivery, regardless of mode of delivery (25). The reasoning for this cut-off is that bleeding below 1000 mL is likely to be well tolerated in women without chronic underlying medical disorders such as anaemia or cardiac disease (90).
Other definitions are based on the reduction in Haemoglobin concentration (Hb) (91) or the need for transfusion or uterotonics (92-95), hysterectomy (92), or embolization (96). It should be noted that the clinical estimation of the blood loss is usually underestimated in cases of bleeding > 500 mL (97-99).

The four most common causes of PPH are uterine atony, genital tract trauma, retained placenta, and coagulopathy (100) where atony is the most common cause. Multiparity, polyhydramnios, large foetus, chorioamnionitis obesity and induced or prolonged delivery predispose to uterine atony. (89) Other well-established risk factors for PPH are CS, especially emergency CS, instrumental delivery and retained placenta (100). Notably though, most women with PPH do not have any known risk factors (100).

During the last two decades, an increasing rate of PPH has been observed in high-income countries (97, 99, 101, 102). However, because of the heterogeneity in PPH classification, an accurate estimation of this overall increase is not possible. Nevertheless, Briley et al. reports a three times higher risk for PPH >1500 mL between 1997/98 and 2008/09 in Scotland (99). Interestingly, the increase in PPH incidence cannot be fully explained by the time trends in currently known risk factors such as higher maternal age, obesity, and CS (97, 101). Other proposed factors that might explain this increase include a more liberal approach for longer deliveries, changes in the management of the third stage of delivery, increasing rates of induction, and a complex interaction between several risk factors (97, 102, 103). Another hypothesis suggests the increasing use of antidepressants as an explanation for this increase (104-106). This hypothesis may not be the sole explanation, as only 2-3% of pregnant women in Europe and 10% of women in North America are treated with antidepressants (107), but in the context of perinatal complications and PPD, the hypothesis is worth taking into consideration. Selective serotonin-reuptake inhibitors (SSRIs) decrease thrombocyte aggregation and therefore contribute to an increased risk of bleeding (108), and thus PPH (106, 109). SSRIs may even have an atonic effect on the uterus (110, 111). Interestingly, however, even antidepressants other than SSRIs seem to have a positive association with PPH. Proposed explanations include an effect of these non-SSRIs drugs on coagulation by a shift in the neurotransmitter balance (105) or an effect of the underlying psychiatric disorder to prolonged delivery (105).

Consequences of PPH include anaemia and traumatic experience of delivery, which are both independently associated with increased risk for PPD (112-117). However, the literature on the association of PPH with PPD is sparse and the studies have diverging designs, definitions, and results (91, 96, 118). Importantly, the majority of the studies have not taken into account vulnerability in the form of earlier psychiatric morbidity or psychological or somatic consequences of PPH, for example the possible subjective experience of a threatening occurrence, or the following symptoms of anaemia.
Anaemia

The most common definition of anaemia during pregnancy is Hb < 110g/L (119, 120) which differs from the standard definition in the general population due to the haemodilution and hypervolemia present during pregnancy. The definition of postpartum anaemia is more heterogeneous, in both time and cut-off in Hb values, which might range from 100 g/L to 120 g/L (114, 121, 122). After delivery, Hb falls slightly during the first 24 hours because of blood loss, and then starts to increase again over the next 2 to 5 days due to haemoconcentration (119). Hb is expected to return to pre-pregnancy concentration, i.e. Hb ≥120 g/L, at 6-8 weeks postpartum. The Hb is followed up at 6-12 weeks postpartum at the maternal primary care unit where all women are offered an appointment. There is no consistent evidence on the association between anaemia and PPD, with some studies identifying anaemia as a risk factor (112-116), while others not (121).

Mode of delivery

Mode of delivery may be categorized in four groups: spontaneous vaginal delivery, instrumental vaginal delivery with vacuum extraction (VE) or forceps (the later uncommon in Swedish practice, according to the guidelines of the Swedish Society of Obstetrics and Gynaecology (123)), elective CS, and emergency CS. The distribution of the different modes of delivery is globally diverse, but there is a marked trend for increasing frequencies of CS worldwide with rates exceeding 40% in Latin America and 25% in Europe (124). There is also a substantial divergence within the countries, due to the population sample and the size of the study hospitals (27, 124). In Sweden, the respective figures in 2015 were 74 % for spontaneous vaginal delivery, 8% for VE, 8% for elective CS, and 10% for emergency CS (125).

The majority of studies examining the association between mode of delivery and PPD report no direct association (85, 126-130). However, there is recent evidence suggesting that specific factors might act as potential mediators or confounders of this association (85, 131, 132). For example, a Swedish register study reported an association of vaginal instrumental delivery or CS with severe PPD for women without history of depression but not for women with a history of depression (38). In the Netherlands, where a substantial but declining number of deliveries is performed at home, a study reported that emergency CS was associated with PPD (133). A Canadian study reported that CS was associated with increased risk of PPD only among native-born mothers, and with a lower risk in non-native women (85). These results indicate that sociocultural factors may influence the beliefs about CS and may thereby have a confounding role in the interplay between mode of delivery and PPD. Other studies report that antenatal depression (134, 135) as well as discrepancy between the women’s preference and actual mode of delivery might influence
the risk of PPD (134, 136). Finally, fear of delivery, which is associated with history of depression (137, 138) and might influence delivery experience (139) affects preferences for mode of delivery (66). Some studies indicate an association of fear of delivery with both elective and emergency CS (62, 75, 139-141).

Pain experience
One of the major components of delivery experience is pain (142). Pain during delivery is often more tolerantly accepted by the women, as compared to other forms of pain (143). Yet, pain may contribute to posttraumatic stress symptoms even though the overall delivery experience seems to be more important for the development of PTSD (144, 145). However, despite the central role of pain in delivery experience, there is no evidence that effective pain relief per se is associated with satisfaction with pain relief, sense of control, and general satisfaction with the delivery experience (6). This may seem a paradox, but the pain experience includes, apart from effective pharmacological analgesia, complex physiological, psychological, and cultural components (146-150). During the various stages of delivery, diverse physiological processes contribute. At the first stage of delivery, the pain originates from the dilation of cervix and uterine contractions, so a visceral component dominates. In the second stage, the visceral pain is combined with somatic pain caused by distention of the vagina and perineal structures (5). Psychological and cultural components might include fear of delivery (148), depression and anxiety (148, 151, 152), expectation of pain and actual intensity (146, 153, 154), sense of control (143, 146, 155-157), and support from partner and midwife (143). As Hall and her colleagues conclude:”… pain and comfort were not opposites, but rather part of the whole emotion-sensation-environment landscape of birth” (158).

Moreover, the experience and memory of pain during delivery might change over time. For most women, the pain experience, is less intense in retrospect (152, 153, 159), but this is not the case for women with an overall negative delivery experience (160, 161). A theoretical framework for pain experience is that sensory and emotional dimensions affect the momentary pain experience during delivery, whereas cognitive and evaluative dimensions influence the retrospective memory of pain, which thereby is a rather mental process (160, 162).

Epidural Analgesia
Most women require some sort of pain management during delivery. Non-pharmacological interventions aim to help women cope with pain, whereas the aim of the pharmacological interventions is to relieve pain (5). Among pharmacological interventions, EDA is the most effective method.
support and midwife-led care is associated with lower use of pharmacological pain relief (163, 164).

The frequency of EDA use during delivery varies across different settings, being as high as 90% in some hospitals for nulliparous women (165). The overall frequency of EDA use among nulliparous and multiparous women in Sweden is 53% and 21%, respectively (166), but with a high disparity between hospitals (27). Moreover, women receiving EDA more often report a history of depression and fear of delivery (167). EDA is associated with induction and high infant birth weight (167, 168). There seems to be an association between socioeconomic status and use of EDA, but whether low or high socioeconomic status is associated with a higher prevalence of EDA is not consistent across studies (167, 169, 170). A plausible explanation could include different health care systems (167, 169, 170).

Women with EDA report less pain in both the first and second stage of delivery, and are generally satisfied with pain relief (6). However, there are side effects associated with the use of EDA; hypotension (EDA may be used in the clinical practice if a women is hypertensive during delivery), motor blockade, maternal fever, longer second stage of delivery and thereby augmented need of oxytocin, higher risk of instrumental delivery, and CS (6).

As mentioned above, there is no evidence that women using EDA have a more positive delivery experience or that the sense of control is affected (6). Whether the intense pain during delivery is associated with PPD or other postpartum mental illnesses is still unclear (128, 171). Some studies have reported that effective pain relief leads to a reduction in the risk of PPD (172-174). Particularly, a Finnish study found that pain relief by EDA or paracervical blockade, but not by nitrous oxide, was associated with decreased odds of depressive symptoms directly after delivery (174). In the same context, a recent prospective study in China reported that use of EDA during delivery is associated with decreased rates of depressive symptoms 6 weeks postpartum (172). However, an English randomized trial and an Israeli cohort study did not find any association (175, 176), although the latter study reported a slightly increased risk of PPD when there was a mismatch between intended and actual use of EDA (175).

Delivery experience

The delivery experience is a complex, multidimensional, and subjective phenomenon (157, 177) that has been thoroughly studied during the last twenty years, especially in the Nordic countries. There is no consensus about the definition of delivery experience and different aspects of the phenomenon pinpointed in different contexts and studies. There are multiple instruments for scoring delivery experience with different psychometric values (178).
DEQ version B (72) is the most widely used one, which is an extensive questionnaire with cultural validation and translations (178).

Because of the multidimensionality, subjectivity and dynamical pattern, some researchers argue that it is not possible to quantify delivery experience. Thereby, they advocate for a qualitative approach (157, 179). However, despite the ongoing discussion on methodology, there are some factors associated with women’s overall experience of delivery that come up consistently; perceived control, social support and pain (157, 180). Women usually describe their delivery in a combination of negative and positive terms that may not be separated (158). But also, the delivery experience dynamically changes during delivery (158) as well as in the long-time course (181-183).

A negative delivery experience is a common reason for a request of elective CS in subsequent pregnancies (68, 184) whereas a positive delivery experience may result in feelings of empowerment and self-efficiency (149, 182) during the transition to motherhood (157, 185).

**Postpartum depression**

Like other psychiatric diseases, the diagnosis and treatment of PPD is ideally based on the LEAD (Longitudinal, Experts, All Data procedure) procedure (185). This implies that the diagnosis is based on anamnestic history of the patient, and sometimes even from relatives, in combination with physical examination and the use of questionnaires and diagnostic interviews. The results are compiled by a team of experts who discuss the diagnosis and the severity before taking a decision of treatment, which should always be discussed with the patient as well. Thereafter, the treatment is continuously evaluated, preferably with standardized questionnaires (186). However, this is a time-consuming process. Therefore, the Swedish recommendation is to base the diagnosis for affective disorders on structured or semi-structured interviews, such as MINI (Mini International Neuropsychiatric Interview), or SCID-I (Structured Clinical Interview for DSM-IV) which have both higher specificity and sensitivity compared with a solely clinically-based diagnosis (186).

**Definition**

There is no consensus about the diagnostic criteria for PPD between the two existing classification systems, ICD-10 (International statistical classification of diseases and related health problems, 10th revision), developed by the World Health Organization, and DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), developed by the American Psychiatric Association. In ICD-10, PPD is included in the diagnosis of “Mild mental and behavioural disorders associated with the puerperium” (F53.0) if onset within the first six weeks postpartum. In DSM-5, PPD is not categorized as a unique
diagnosis but as a major depressive episode with peripartum onset defined as onset of symptoms during pregnancy or within four weeks after delivery. However, in clinical praxis and for research purposes, this period is often prolonged up to a year postpartum (187-190). In Sweden, the DSM-5 is used for both psychiatric outpatient and inpatient care but the diagnostic codes are converted to ICD-10 for reporting to the National Patient Register.

Symptoms of PPD do not differ from those of depression in general. They include depressed mood, loss of interest or pleasure, change in weight or appetite, insomnia or hypersomnia, psychomotor retardation or agitation, loss of energy or fatigue, worthlessness or guilt, impaired concentration or indecisiveness, and recurrent thoughts of death or suicidal ideation or attempt. Nevertheless, obsessions and ruminations focusing on the newborn and suitability for mothering are more commonly present in PPD symptomatology (191, 192). Furthermore, changes in sleep and energy pattern are common postpartum and may thereby have a lower diagnostic reliability for diagnosing PPD than depression in general. Noteworthy, PPD should not be confused with the so called “baby blues“, which is a self-limiting feeling of low mood in the first weeks after delivery affecting up to half of all women (193).

The severity of PPD ranges from mild symptoms with natural recovery within some weeks to long-lasting episodes with psychotic symptoms that require in-hospital treatment (193).

Prevalence

PPD is one of the most common perinatal complications (188) and is often a continuation of an antenatal depression, especially if the latter has been sub-optimally treated (187, 194, 195). PPD is also more common among women with a history of depression even before pregnancy (187, 190, 193). In high-income countries, the point-prevalence of PPD at 3 months postpartum is estimated to 13%, (188), but up to 20% of the women experience some postpartum depressive symptoms (PPDS) (187). Some studies also indicate an increasing prevalence of PPD (112). However, the comparability of prevalence across different studies is difficult due to differences in definitions, study design, study population, and geographical setting (196-199). The majority of studies define PPD using symptom-based questionnaires instead of a structured clinical assessment. This approach may overestimate the prevalence because common maternal stressors, such as lack of sleep, may overlap with surveyed symptoms (200). On the other hand, the use of clinical diagnosis may lead to an underestimation of prevalence as women often suffer from depression in silence (196). In the literature, the most common study design is clinical follow-up studies based on care-based clinics or referral centres, which could negatively affect the representability (188). Although register-based studies also exist, they may underestimate prevalence estimates since many women do not seek medical care (201). According to a WHO report,
women from low and middle-income countries have a higher prevalence of PPD and other postnatal psychiatric morbidity (202).

Comorbidity
Postpartum as well as antenatal depression are often comorbid with anxiety and PTSD (203, 204). Experiencing the first-ever depressive episode during the first weeks postpartum is more often associated with a future diagnosis of bipolar disorder (205). Additionally, women with bipolar disorder have a very high risk for developing postpartum psychosis (190, 205).

Aetiology and risk factors
Stressful life events, lack of social support, domestic violence or history of abuse and a burdened psychiatric history are risk factors with strong associations with PPD (187, 190). Risk factors with moderate effect size are depression and anxiety during pregnancy, neuroticism, postpartum blues, and poor marital relationship (82, 187, 190). Other risk factors include low socioeconomic status, absence of partner, unwanted pregnancy, obstetrical stressors (38, 82, 131), lack of breastfeeding, and illness/problems with the infant (190, 193). From a pathophysiological perspective, there is also evidence that sleep disturbances, hormonal changes, and genetic variations associate with the risk of PPD (190, 196). Hormonal changes include gonadal steroid hormones which might modulate neurotransmission and neuroplasticity, oxytocin, thyroid hormones, changes in the HPA-axis, and neuroimmune pathways (190). Genetic factors might refer to either inherited variants that directly increase the risk of PPD or to epigenetic alterations that might influence expression of the genome and might be the consequence of environmental burden, such as psychological stressors (190). Also, some studies indicate differential gene expression in perinatal depression with an antenatal debut as compared to perinatal depression with postnatal debut (206, 207).

Screening
Although the diagnosis of PPD should be based on a clinical psychiatric interview evaluating the criteria for a major depressive episode (186), screening interviews, or even more common, self-reporting validated questionnaires are used in both research and in the clinical primary setting. A widely used questionnaire is Edinburgh Postnatal Depression Scale (EPDS) (208). The efficiency of EPDS for screening for PPD has been debated and ethical considerations have been raised (209). There is low to moderate strength of evidence for the efficacy of screening for reduction of depressive symptoms postpartum and improved mental health (186, 210) and EPDS is the only questionnaire with sufficient evidence (186, 211). The potential effectiveness of screening
for PPD appears to be dependent on the adequacy of follow-up for women with positive screening (186, 210). Also, as already mentioned, it is important to identify women with bipolar diagnosis with postpartum debut (190, 194).

The Swedish guidelines recommend screening for PPD by using the EPDS at 6-8 weeks postpartum at the child primary care unit or at the postpartum control at the maternal primary care unit (212, 213); the latter, however, is less common in practice.

The purpose of screening is to identify both women at high risk for PPD as well as to diagnose those who already have clinical depression. In case of scoring 12 or more points in EPDS, or if a need of psychological support becomes apparent during the consultation, the national guidelines recommend person-centred counselling at the paediatric nurse as a first step. The second line is referral to psychologist in the maternal or paediatric primary care, or physician in the primary care system (212, 213).

**Prevention**

There is evidence for the use of psychosocial or psychological interventions to decrease the risk for developing PPD (214-216). However, due to the limited number of high-quality studies, some uncertainty still remains (214, 215). Additionally, the notable diversity in study designs makes drawing firm conclusions difficult (214, 215). In 2016, the National Institute of Health Care in the United Kingdom performed a systematic review and meta-analysis of studies of antenatal and postnatal prevention of PPD. Based on the findings, they classified three levels of prevention: prevention for all pregnant women (universal), prevention for pregnant women with social problems (selective), and prevention for women with psychological risk factors (indicative). Result- and cost-effective methods include midwifery redesigned care (universal prevention), person-centred approach (universal), cognitive-behavioural therapy (universal), education on preparing for pregnancy (selective), and interpersonal therapy (universal and indicative). These interventions should be individually designed and could additionally include psychosocial interventions such as social support through group-based approaches (215), home visits by nursing staff close after the delivery, or lay-man based support by telephone (214). Overall, continuity of care is important for building a trustful relationship, which is an important determinant of the success of interventions (215).

A Cochrane systematic review in 2018 concluded that there is limited evidence about the efficacy of antidepressants for prevention of PPD in women at high risk for developing PPD (217).

**Treatment**

Women with PPD have described that the process of seeking professional help induced feelings of shame and reported different barriers for help-seeking.
Nevertheless, they express gratefulness after receiving help (200, 201, 218). The treatment of choice in mild to moderate depression is psychosocial (peer support guided self-help, person-centred approach) or psychological therapy (189, 219), preferentially interpersonal therapy (220, 221), or cognitive behavioural therapy (222). Other effective non-medical therapies as self-help interventions (223) and internet-based cognitive-behavioural therapy (224) may also be effective, but there is less evidence on these methods. Again, there is a lack of high-quality studies, which limits the extraction of meaningful conclusions (189, 191, 219). Also, most trials have compared non-medical treatment with standard care of PPD, which might also include antidepressants, thus making interpretations more difficult (189). Qualitative studies point out the importance of continuous and good relationship with the caregiver (201, 218).

Sometimes there is a need for pharmacological treatment, either alone or in combination with non-medical treatments (190). After ensuring that the woman does not suffer from bipolar depressive disorder, the first line medical treatment should be SSRIs, particularly sertraline that has only minimal passage to the breastmilk (190, 225, 226). However, for women with a history of depression and a former effective treatment, the same treatment approach should again be considered (190, 226). Since anxiety is commonly seen with PPD and metabolism may be slower in the first few weeks postpartum, starting the antidepressant at a low dose may be considered (198, 227). In case of treatment failure, the diagnosis should be re-evaluated. Differential diagnosis of PPD might also include underlying somatic disorders such as thyroid disease, bipolar disorder or an early presentation of a first episode of psychosis (190). After ensuring the diagnosis, an augmentation with benzodiazepines, antipsychotics and mood stabilizers may be necessary (225). For treatment-resistant severe depression, treatment with electroconvulsive therapy may be considered and is recommended by the Swedish Psychiatric Association (228-230).

Consequences
PPD is one of the most common contributors to maternal morbidity (231), even though the diagnosis is often ignored in studies focusing on maternal somatic morbidity (232). PPD might have major consequences for both the mother’s future affective status and the child’s development. In particular, PPD might impair the mother’s relationship with the partner and infant, impact on mother-infant bonding and negatively influence the child’s emotional and cognitive development (187, 190). Suicide in the prolonged puerperium is the most severe and feared consequence with a ratio of 3.7 per 100000 live births (233). However, it is also important to note that the rate of suicide in the first year postpartum is lower when compared to the respective rate for women who have not given birth (234-236).
Apart from all consequences for the individual woman, her child and her family (187, 190), there is also a need to address economic considerations from a public health perspective. In 2014, the London School of Economics reported that the aggregated cost for perinatal depression and anxiety was £6.6 billion in the United Kingdom and thereby concluded the need to allocate more resources to support women with perinatal mental illness (237, 238).

Personality

Personal characteristics may be described using concepts as temperament, character or personality. Temperament is closer to the ancient Greek “humoral theory” and represents the stable biological factors as genetics and inherent endowments that affect the individual’s activity level, mood, emotionality and sociability. Traditionally, temperament has been attributed to infant and children patterns (239). Character, on the other hand is more connected with nurture and refers to the competences acquired during development (46). Personality is a broader concept enclosing both constitutional and learned features associated with psychological and behavioural traits. Even if there is no universal definition, personality can be defined as the individual’s characteristic pattern of cognitions, emotions and behaviours (240). Traditionally, personality has been assumed to be relatively stable from adulthood and throughout life, but this assumption has been doubted during the last two decades (239, 241-244). The prevailing theory now is that personality starts to develop during childhood and although it becomes relatively stable over adulthood, it could still be influenced, for example, by current affective state (244). Later on, in the senescence, a normative change of the personality is common with higher emotional stability, sociability and conscientiousness (242, 245). Also, as the central nervous system ages and social circumstances change, the temperament may be enhanced (242).

There are several personality models and instruments that group personality into larger categories, or factors (246). The most widely used model is the Five-Factor Model (FFM), also called the Big Five, which includes the factors of Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness. NEO-PI (Neuroticism, Extraversion, Openness Personality Inventory) is the most well-known personality questionnaire consisting of 240 items (247).

Neuroticism

One of the most well-studied personality factors is neuroticism, which might also be termed as negative affectivity, low emotional stability or harm avoidance (239, 247, 248). Neuroticism is characterized by a tendency towards negative emotions, such as anxiety, fear, irritability, and anger (239). It is also
closely related to self-catastrophizing and with the belief of one’s inability to manage or cope with challenging events (239). Moreover, neuroticism is associated with problematic coping strategies, such as emotion-focused coping as opposed to problem-solving coping (249, 250), as well as withdrawal and wishful thinking (30). Individuals with high neuroticism have also been found to be more likely to have an apparent need for seeking health care (249).

It is well established that neuroticism is associated with anxiety and depressive disorders (239, 246) and has been suggested as a mediator between biological and psychological vulnerability leading to affective disorders (239, 242). Pregnant women with neuroticism report more concerns about their pregnancies and higher rates of fear of delivery (251-253). They are also at a higher risk for postpartum blues (254) and PPD (254-256). In terms of physical health, neuroticism is associated with smoking (255, 256), migraine (257), and cardiovascular disease (258, 259), whereas some studies point to a cluster of factors related to metabolic syndrome among individuals with high levels of neuroticism (260). Although neuroticism is one of the most extensively studies personality factors, studies exploring the role of neuroticism in perinatal outcomes remain scarce. A few studies have found significant associations between neuroticism and adverse perinatal outcomes including preterm contractions (261), failure to progress, assisted delivery, emergency CS, severe lacerations, foetal distress and foetal growth restriction (262-264). Studies on the association between neuroticism and preterm birth have reported diverging results (251-253).
Rationale for the Thesis

Pregnancy and delivery are complex physiological processes with potential complications. It is also a period of life full of emotions, and even existential thoughts. We know that complications can affect not only somatic health but also psychological health, for example through traumatic memories from delivery. However, it is still unclear if perinatal obstetric complications *per se* influence the development of PPD. The literature is contradictory, and some studies suggest that those diverging results could partly be explained by other factors, acting as confounders or mediators. The role of personality in this context, which is strongly associated with the risk for PPD, is sparsely studied. Therefore, the further exploration of the associations between perinatal complications, personality and perinatal depression is warranted.
Aims

General Aim
The general aim was to explore the associations between perinatal complications and perinatal mental health, with emphasis on postpartum depressive symptoms and neuroticism. Special focus has been put on major potential confounding or mediating factors such as history of depression, antenatal depressive symptoms and delivery experience.

Specific Aims
- to explore the association between postpartum haemorrhage and postpartum depressive symptoms taking into account possible confounders and mediators, such as anaemia and negative delivery experience. (Study I)

- to explore the association between mode of delivery and postpartum depressive symptoms and explore the role of sociodemographic covariates, history of depression, fear of delivery, obstetric complications, and delivery experience, as confounders and mediators. (Study II)

- to investigate the association between use of epidural analgesia and postpartum depressive symptom, considering several sociodemographic, psychosocial and obstetrical variables. (Study III)

- to assess if maternal neuroticism is associated with adverse perinatal complications. (Study IV)
### Table 1. Overview of included studies

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<td>Population based, nested case-control study</td>
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PPH: Postpartum haemorrhage  
PPDS: Postpartum depressive symptoms  
EDA: Epidural analgesia
Material and Methods

Study populations
All studies (studies I-IV) were based on the BASIC project, but the study populations in study I and study IV also included participants from other Uppsala-based studies.

The BASIC project (Studies I-IV)
The BASIC (Biology, Affect, Stress, Imaging and Cognition) project is a project with a special focus on perinatal maternal wellbeing. This longitudinal project started in September 2009 and is still ongoing with over 5200 individual women and 6100 pregnancies (March 2018). All pregnant women at 16th-18th gestational week attending the routine ultrasound examination in Uppsala University Hospital received written information about the study and were invited to participate. Exclusion criteria were inability to adequately communicate in Swedish, confidentially kept data, intrauterine demise, blood borne infectious disease, and age below 18 years. BASIC has a participation rate of 21%. Following informed consent, women were instructed to complete self-administered web-based questionnaires at recruitment (16th-18th gestational week), at the 32nd week of pregnancy and at 6 weeks, 6 months and 12 months postpartum. The response rate at 6 weeks postpartum was 81%.

Participating women differ from the background general pregnant women population as they report a higher educational level (61% with university education vs. 52% in the Swedish Birth Register) and are more likely to be primiparas (54% vs 44%).

The UPPSAT project (Study I)
The UPPSAT project (n=2318) is a population-based longitudinal study investigating maternal mental wellbeing after delivery in Uppsala County, Sweden. All women giving birth in Uppsala University Hospital between May 2006 and June 2007 were asked by their midwife at antenatal care to participate in the study. Exclusion criteria included inability to adequately communicate in Swedish, confidentially kept data, intrauterine demise or admission of the newborn to the neonatal intensive care unit. Informed consent was ob-
tained by 65% of the target population. The women were instructed to complete self-administered questionnaires at 5 days, 6 weeks, 6 months and 12 months postpartum. Besides the 5-day-questionnaire, which was distributed directly to the women by the midwife, all subsequent questionnaires were sent by postal mail. The response rate at 6 weeks postpartum was 73%.

We compared the women who participated in the study with aggregated data for all women delivering in Uppsala University Hospital during the study period. The only difference was that the UPPSAT cohort recruited more nulliparous women. No significant differences regarding maternal age, pregnancy complications, delivery outcome, weight of the baby, or area of residence were detected.

Studies including personality assessment (Study IV)

**Project of induced abortion**

A multi-center cohort study was conducted between September 2009 and June 2010 (n=1542). All women who requested an induced abortion before the end of gestational week 12 were approached for participation. Women were informed about the study during their registration for the first abortion visit. Those who agreed to participate received written information about the study and completed a questionnaire including Swedish universities Scales of Personality (SSP) during the first visit. Inability to read and understand Swedish was the only exclusion criteria. The participation rate in the project was 59%.

**Project on infertility**

This cohort study was conducted from August 2005 to April 2007 (n=323). All couples undergoing *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment at the Centre of Reproduction at Uppsala University Hospital, Sweden, were approached for participation in the project. Exclusion criteria included inability to read and understand written Swedish, couples undergoing cycles with gamete donation, and earlier IVF treatment during the study period. The SSP questionnaire was distributed and completed at the day of oocytes retrieval. The participation rate was 76%.

**Project on experience of combined oral contraceptive use**

For this case-control study women were recruited by announcement calls in newspapers and posters in health care centres between March and May 2006. In all, 285 women were screened by telephone interview. Exclusion criteria were ongoing pregnancy or breastfeeding, no presence of prior experience of combined oral contraceptives, treatment with hormonal contraceptives other than oral contraceptives, or current treatment with psychotropic drugs including SSRIs. After applying these exclusion criteria, 118 women participated in the project.
Project on Premenstrual Mood Disorder

Participants for this project were recruited between October 2005 and November 2006 among women seeking help for premenstrual symptoms in the outpatient ward of the Department of Obstetrics and Gynecology, Uppsala University Hospital, and from newspaper advertisements (n=85). Thirty women met the criteria for premenstrual mood disorder, defined according to DSM-IV and were included in the project. An additional 55 asymptomatic healthy women were included as controls. Exclusion criteria were ongoing treatment with any hormonal compound and treatment with benzodiazepines or other psychotropic drugs including SSRIs in the last three months. After written informed content, all women answered SSP during the follicular phase.

Study design

Study I

Study I is a nested cohort study (n=446) including 168 participants from the UPPSAT project and 278 participants from the BASIC project. Data for this study were collected from September 2009 to November 2012.

![Figure 1. Flowchart of included studies and participants in Study I](image)

Study II

Study II is a nested case-control using solely data from the BASIC project collected between September 2009 and December 2014. Exclusion criteria were duplex and women with missing data on mode of delivery, which resulted in a total of 3888 pregnancies. Some women participated more than once, resulting in 3508 unique individuals included in the analyses.
Study III

Study III is a nested case-control study based solely on data from the BASIC study that were collected from September 2009 to August 2017. Only nulliparous women were included. Exclusion criteria were duplex, prematurity (gestational length <37 weeks), breech position, induction of delivery, elective CS, preeclampsia, and hypertension, resulting in 1503 participating women.

Study IV

Study IV is a convenience cross-sectional study with participants from several projects based in Uppsala, Sweden (n=1969). Data for the study were collected during the period 2005-2011 and were linked to national health registers. Exclusion criteria were women who had not given birth or whose first delivery took place before 1984 or outside Sweden, and twin pregnancies.
Variables

The data were collected from self-administered questionnaires and medical journals (study I-III). For study IV, the data were also linked to several Swedish official health registers; the Medical Birth Register (MBR) (information about participants’ first delivery, somatic and psychiatric health, medication at first antenatal booking, pregnancy and delivery) (265), the Patient Register (diagnoses from hospital admissions and outpatient clinic visits from five years before delivery to one year after delivery) (266), the governmental agency Statistics Sweden (socioeconomic factors) and the Prescribed Drug Register (data for anxiolytic/sedative drugs and antidepressants) (267).

For the BASIC and UPPSAT projects, the first questionnaire (pregnancy week 17-19 and 5 days postpartum, respectively) contains socioeconomic background variables and information about earlier mental health. The majority of mental health variables were examined via validated questionnaires (see below). However, in order to achieve an acceptable questionnaire length (268), some factors were also examined by short questions specifically formulated for the current study.

Exposure

The main exposure variables for the four study were PPH (study I), mode of delivery (study II), use of EDA during delivery (study III) and Neuroticism (study IV).
PPH was defined as bleeding ≥1000 mL within 24 hours after delivery, in accordance with the clinical practice in Sweden. Non-exposed individuals were randomly selected by including one every 12th woman in the register of participants. To reduce misclassification, women with postpartum bleeding estimated between 650 and 999 mL were not considered, and the next available participant was instead included.

Mode of delivery was classified in four categories; vaginal delivery, VE, elective CS and emergency CS. Elective CS was defined as planned CS during day-time. The definition of emergency CS was an unplanned CS performed before or after onset of delivery due to foetal or maternal compromise. Mode of delivery status was retrieved from the medical records. Similarly, information on the use of EDA during delivery was obtained from the medical records.

Neuroticism was assessed using the validated SSP. In contrast to the other exposures which were categorical (study I-III), the neuroticism score was examined as a continuous variable.

Outcome
The outcome in study I-III was presence of PPDS, as a proxy for PPD. PPDS was defined by a score of ≥12 in EPDS at 6 weeks postpartum (186).

For study IV, the outcomes included perinatal complications based on register linked data: mode of delivery (vaginal delivery, VE, any CS, elective CS, emergency CS), GDM, gestational hypertension and preeclampsia (grouped together due to low frequency and common aetiology), induction of delivery, dystocia (prolonged first or second stage of delivery), severe lacerations (grade 3-4, cervix rupture, or complex vaginal lacerations), placental retention, and PPH. Neonatal outcomes included premature birth (before gestational week 37+0), small for gestational age (SGA) (below the 10th percentile, according to the Swedish sex-specific reference curves for gestational age) (269), large for gestational age (LGA) (above the 90th percentile) and Apgar score below seven at 5 minutes. A composite worst-case variable was created, including intrauterine demise, eclampsia, severe preeclampsia, premature birth before gestational week 32+0, SGA < -2.5 SD (lowest 0.6%), and placental abruption.

Covariates
For study I-III, the questionnaires collected information on a wide range of pregnancy- and postpartum-related covariates, including socioeconomic factors, history of depression, previous psychological contact (with psychologist or psychiatrist), mood during pregnancy, expectations of delivery, delivery experience, breastfeeding, sleeping habits in the postpartum period, and support by partner.
Anaemia postpartum is closely linked to PPH and is thereby an important variable for study I. The definition of postpartum anaemia used in this study was a Hb below 110 g/L at discharge. In Sweden, Hb directly after delivery or at discharge is routinely assessed only in cases of PPH; thus, there were high rates of missing data concerning anaemia status at discharge. Hemodynamic changes induce a rise in Hb during the first days postpartum (119). Thus, an algorithm was created in order to assign a value for subjects not having anaemia at discharge, even when not tested: the woman was classified as having no anaemia at discharge if the lowest antenatal Hb was 105 g/L and she had a postpartum bleeding less than 400 mL. Correspondingly, women with lowest antenatal Hb of >110 g/L and postpartum bleeding of <500mL and women with lowest antenatal Hb >125 g/L and postpartum bleeding of <650mL were considered as not suffering from anaemia at discharge. In all other cases, (i.e. in case of larger bleeding than the cut-off in the algorithm) women were classified as having anaemia at discharge.

History of depression was self-reported by the single question “Have you ever had a depression?” at gestational week 17.

Presence of antenatal depressive symptoms was defined as a score of ≥13 EPDS points at gestational week 32 (270).

Mood during pregnancy, i.e. a more general variable than antenatal depressive symptoms, was assessed at gestational week 32 (BASIC project) or retrospectively at 5 days postpartum (UPPSAT project) with the question “How have you been feeling during your pregnancy?”. The four alternative answers were “Better than usual”, “As usual”, “A little depressed” and “Depressed”. Based on these answers mood during pregnancy was dichotomized to “Good” (first two alternatives) vs “Depressed” (last two alternatives).

Expectations of delivery and fear of delivery were assessed by the question “How do you expect your forthcoming delivery?” with the possible answers: “okay”, “excited”, “good”, “longing for”, “worried”, “wish it was over”, “terrified”, “fear of vaginal delivery”, and “fear of caesarean section”. A dichotomized variable for expectations of delivery (positive: “okay”, “excited”, “good”, “longing for”; negative: “worried”, “wish it was over”, “terrified”) was created. Answers including both “positive” and “negative” choices, except for the answer “terrified” were classified as positive. If the woman answered that she was terrified, had fear of vaginal delivery or CS, or if she reported a visit to a consultant physician or midwife due to fear of delivery, she was classified as suffering from fear of delivery.

Delivery experience was assessed at 5 days postpartum in the UPPSAT study and at 6 weeks postpartum in the BASIC study with the question: “How would you describe your delivery experience?” with five alternative answers. The answers “Wonderful/Good/Ok” were grouped together, while the answers “Bad/Awful” were considered as suggestive of a negative self-reported delivery experience.
In study IV, covariates were extracted from the national registers, including year of delivery, maternal age at delivery, maternal height, body mass index (BMI) at first antenatal care visit, educational level, smoking during pregnancy, chronic somatic disease (pre-gestational hypertension, diabetes mellitus, or chronic kidney disease), involuntary childlessness (≥1 year or in vitro fertilization), and psychiatric morbidity (including ICD codes for ‘mental disorders due to psychoactive substance use’, ‘affective disorders’, ‘anxiety, stress-related and somatoform disorders’, ‘eating disorders’, ‘personality disorders’, ‘disturbances of activity and attention’, and the prescription of antidepressant or anxiolytic drugs during pregnancy).

Psychometric instruments

EPDS
EPDS is a self-administered instrument specifically developed for screening for postpartum depression. EPDS does not include any items concerning changes in appetite, sleeping disturbances, fatigue, and somatic symptoms that relate to depression in general but also normally occur in the puerperium. Specifi cally, it consists of 10 items and women are asked to answer questions on a fourth-grade Likert-scale based on their feelings in the last 7 days. The questionnaire is translated to numerous languages and is considered the only screening tool with sufficient evidence for clinical screening and for use in epidemiological studies focusing on depression in the postpartum setting. The optimal cut-offs for diagnosis of PPD differ across countries, but cut-offs of 9/10 in Asian countries and of 12/13 in most European countries seem to offer balanced rates of sensitivity and specificity. Particularly, a cut-off of 12/13, has a weighted sensitivity of 72% and specificity of 88% with SCID-I as the reference standard. The Swedish version of EPDS, compared to Montgomery-Asberg Depression Rating Scale (MADRS) as the reference standard, has a sensitivity of 96%, a specificity of 49% at a cut-off of 11/12.

The EPDS has also been validated as a screening tool for antepartum depression with a cut-off of 12/13 offering a sensitivity of 77% and specificity of 94% in the Swedish setting. In a review by the Swedish Council on Health Technology Assessment and Assessment of Social Services, the weighted specificity is 96%, but it was difficult to evaluate the sensitivity due to the heterogeneity of the included studies.

SSP
The Swedish universities Scales of Personality (SSP) is a self-reporting validated questionnaire assessing personality traits. SSP was further developed
from the Karolinska Scales of Personality (KSP) with the aim to have a high psychometric quality, to be suitable for both clinical work and research, and to be written in simple language for both psychiatric patients and healthy subjects. In contrast to many other personality inventories, SSP does not aim to cover the entire personality spectrum but to assess specific areas with research interest (273). The objective was to have a biological approach to personality traits (273). It consists of 91 items with the response format of a four-graded Likert-scale ranging from “does not apply at all” to “applies completely” (273). The answers are analysed into thirteen scales, all consisting of seven claims; Somatic trait anxiety, Psychic trait anxiety, Stress susceptibility, Lack of assertiveness, Impulsiveness, Adventure seeking, Detachment, Social desirability, Embitterment, Trait irritability, Mistrust, Verbal trait aggression, and Physical trait aggression. These scales could in turn be coalesced in three factors, including Neuroticism, Aggressiveness, and Extraversion. Because of mean gender differences in the trait anxiety, trait aggressiveness and detachment scales, the results on each scale have been gender-adjusted according to the Swedish reference population (273, 274), creating normative T-scores (mean =50, SD =10).

Neuroticism, the most well-studied factor, consists of 42 statements which format six traits; somatic trait anxiety, psychic trait anxiety, stress susceptibility, lack of assertiveness, embitterment, and mistrust.

Statistical analyses

Univariate analyses

In the first step of the statistical analysis for all studies, all covariates were cross-tabulated by the main exposure variable (study I-IV), and in Study I-III also by the main outcome, PPDS. Associations were statistically assessed with the Pearson chi-square test or Fisher’s exact test (in case of n ≤ 5) for categorical variables. For continuous and asymmetrically distributed variables the associations were assessed by Mann-Whitney for binary variables, and Kruskal-Wallis for three or more categories. P-values ≤0.05 were interpreted as statistically significant.

Logistic regression

Logistic regression models were designed with dichotomized EPDS score (≥12 vs. <12) at 6 weeks postpartum as the dependent variable in study I-III. The independent variable was the main exposure (PPH, Mode of delivery, and EDA, respectively). Furthermore, in Study I, logistic regression analysis was repeated with anaemia at discharge instead of PPH as the independent variable.
due to strong co-linearity with PPH. Adjusted models further included rele-
vant confounders.

In study IV, the logistic regression used neuroticism as the independent
variable, in its continuous form. Odds ratios (ORs) for the dependent variables
(perinatal complications), with 95% confidence intervals (CIs), were calcu-
lated for a 63-unit increase in neuroticism, which equals the interquartile range
(IQR). Since the model is linear, this may also be interpreted as the OR be-
tween women at the 75th and 25th percentiles of neuroticism.

Path Analysis

In order to explore an association characterized by a complex interplay be-
tween a number of potentially confounding or mediating variables, new sta-
tistical methods have been developed during the last decades. Path analysis is
such an example. Although it has been mainly used in behavioural sciences,
during the last decade an increasing number of studies in the fields of psychi-
atriy and even perinatal depression applies path analysis (275-280).

In the current thesis, path analysis was performed to delineate the associa-
tions of PPH and mode of delivery with PPDS at 6 weeks postpartum. We
applied Structural Equation Modelling (SEM) (study I) and Generalized
Structural Equation Modelling (GSEM) (study II), which is a further develop-
ment of SEM.

SEM is a multivariate statistical analysis for analysing structural associa-
tions between measured variables and latent constructs by using a combina-
tion of multiple regression analysis and factor analysis (281). Thereby, esti-
mates of multiple and interrelated dependence are obtained.

Based on relevant literature and results from the univariate analyses, we
designed conceptual models including associations between the main expo-
sure and outcome, as well as potential confounders and mediators (fig 5, fig
6).
Figure 5. Graphic display of the conceptual path analysis model reflecting the direct and indirect effects on postpartum depressive symptoms (PPDS) at 6 weeks postpartum with postpartum haemorrhage (PPH) as exposure.

Figure 6. Graphic display of the conceptual path analysis model reflecting the direct and indirect effects on postpartum depressive symptoms (PPDS) at 6 weeks postpartum with mode of delivery as exposure (VE: Vacuum extraction, CS: Caesarean section, VaD: Vaginal delivery)
Ethical considerations

All women were given oral and written information about the course and aim of the study and gave their written informed consent. Further, they received information on the voluntary nature of their contribution and that they had the freedom to withdraw from the study whenever they wished it, in accordance with the Declaration of Helsinki. The study protocols were approved by the Regional Research and Ethics Committee of Uppsala (UPPSAT: Dnr 2006/150, August 2006. BASIC: Dnr 2009/171, July 2009. Study IV: Dnr 2014/092, June 2014.)

Projects such as BASIC and UPPSAT have considerable ethical considerations relating to respect for both the woman and the child. Several questions and questionnaires evaluate very personal information and may thus evoke diverse feelings or even leave women in a more vulnerable status. Thereby, after every questionnaire all participating women are given explicit information on how to get professional psychological or psychiatric help if needed. The women are further provided with the contact details of the researchers responsible for the projects, in order to discuss and get support and further information. In some cases, women were offered a visit in the research laboratory for further evaluation and a referral for further care was sent, if needed. Because some of the questionnaires also include items about self-harm and suicidal attention, all women with affirmative answers in these questions were contacted for a clinical assessment and thereafter, if needed, referred to a therapist or physician. This procedure has in some cases allowed a rapid detection and treatment of PPD, which in other way may have been undiagnosed for a long time due to the shame and the experienced barriers for help-seeking. It is also possible that women, by completing the questionnaires, reflected on their psychological health and thereby sought help on their own.
Results

Study I

Totally, 466 women were included in the analysis of Study I. Among them 196 women experienced PPH, defined as bleeding of $\geq 1000$ mL. Fifty-three women had EPDS $\geq 12$ at 6 weeks postpartum, indicating presence of significant depressive symptomatology.

In the multivariate logistic regression analysis, there was no significant association between PPH and PPDS. However, there was a significant association between anaemia at discharge and PPDS (aOR 2.29, 95%CI 1.15-4.58), even after adjustment for confounders (table 2). Adjustments were made for previous psychological contact, mood during pregnancy and lack of exclusive breastfeeding 6 weeks postpartum.

Table 2. Multivariate logistic regression derived odds ratios (ORs) and 95% Confidence Intervals (95% CI) for postpartum depressive symptoms (PPDS) at 6 weeks postpartum

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95%)</th>
<th>Model 1* aOR (95% CI)</th>
<th>Model 2** aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postpartum haemorrhage ($\geq 1000$ mL vs $\leq 650$ mL)</td>
<td>1.38 (0.78-2.45)</td>
<td>1.81 (0.91-3.57)</td>
<td></td>
</tr>
<tr>
<td>Anaemia at discharge from hospital (Hb&lt;110g/L vs Hb$\geq 110$g/L)</td>
<td>2.10 (1.15-3.82)</td>
<td></td>
<td>2.29 (1.15-4.58)</td>
</tr>
<tr>
<td>Previous psychological contact</td>
<td>2.28 (1.22-4.25)</td>
<td>2.08 (1.05-4.10)</td>
<td>1.90 (0.95-3.80)</td>
</tr>
<tr>
<td>Mood during pregnancy (Depressed vs good/ok)</td>
<td>3.52 (1.18-8.83)</td>
<td>3.02 (1.51-6.06)</td>
<td>2.87 (1.40-5.87)</td>
</tr>
<tr>
<td>Lack of exclusive breastfeeding (6 weeks pp)</td>
<td>2.85 (1.58-5.15)</td>
<td>2.30 (1.16-4.56)</td>
<td>2.41 (1.20-4.85)</td>
</tr>
</tbody>
</table>

*Model 1 includes PPH and possible confounders (previous psychological contact, mood during delivery and lack of exclusive breastfeeding) as independent variables

**Model 2 includes anaemia and possible confounders (previous psychological contact, mood during delivery and lack of exclusive breastfeeding) as independent variables

Path analysis revealed direct and positive effects of previous psychological contact, depressed mood during pregnancy, anaemia at discharge, self-reported negative delivery experience, and postpartum stressors on odds for PPDS at six weeks postpartum (fig 7). PPH did not have a direct effect on PPDS but indirectly increased its odds through anaemia at discharge and negative delivery experience.
Figure 7. Graphic display of the estimated path analysis models through which post-partum haemorrhage (PPH), anaemia and other delivery related variables as well as earlier psychological contact, lack of exclusive breastfeeding and inadequate sleep at 6 weeks postpartum influence postpartum depression symptoms (PPDS) at 6 weeks postpartum.

The arrows represent regression equations used to assess mediation. The strength of the relationship between two variables was estimated as a standardised regression weight (i.e., path coefficient, a, corresponding to correlation coefficients). Pathways indicated with a continuous arrow were statistically significant (p<0.05). Dotted arrows represent pathways with a p=0.05-0.20.

**Study II**

A total of 3888 pregnancies were included in the study. Out of them, 363 (9%) referred to women who participated more than once. Seventy-four percent of women had spontaneous vaginal delivery, 8% VE, 9% Elective CS and 9% Emergency CS. Compared to vaginal delivery, women, who delivered by Emergency CS had higher odds for PPDS six weeks after delivery in the crude analysis (OR 1.45, 95%CI 1.04-2.01), but the association was completely attenuated in the multivariate model (table 3). Adjustments were made for parity, history of depression, fear of delivery, negative delivery experience, objective postpartum complications, and self-reported physical symptoms at 6 weeks postpartum.
Table 3. Multivariate logistic regression derived odds ratios (ORs) and 95% Confidence Interval (95% CI) for postpartum depressive symptoms (PPDS) at 6 weeks postpartum

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted Model aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>VE</td>
<td>1.36 (0.97-1.91)</td>
<td>1.10 (0.72-1.69)</td>
</tr>
<tr>
<td>Elective CS</td>
<td>1.34 (0.94-1.92)</td>
<td>1.19 (0.73-1.92)</td>
</tr>
<tr>
<td>Emergency CS</td>
<td><strong>1.45 (1.04-2.01)</strong></td>
<td>0.76 (0.48-1.21)</td>
</tr>
<tr>
<td>Parity</td>
<td>1.09 (0.84-1.42)</td>
<td></td>
</tr>
<tr>
<td>Self-reported history of depression</td>
<td><strong>2.68 (2.09-3.45)</strong></td>
<td></td>
</tr>
<tr>
<td>Fear of delivery</td>
<td>1.82 (1.39-2.38)</td>
<td></td>
</tr>
<tr>
<td>Negative delivery experience</td>
<td>2.46 (1.67-3.63)</td>
<td></td>
</tr>
<tr>
<td>Objective postpartum complications</td>
<td>1.08 (0.79-1.49)</td>
<td></td>
</tr>
<tr>
<td>Self-reported physical symptoms postpartum (6 w pp)</td>
<td><strong>1.49 (1.15-1.92)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted model includes possible confounders (parity, self-reported history of depression, fear of delivery) and mediators (negative delivery experience, objective postpartum complications, and self-reported physical symptoms postpartum) as independent variables.

In the path analysis, elective CS was not associated with PPDS, compared to vaginal delivery (fig 8). Delivery fear and history of depression were associated both with elective CS and the odds for PPDS at 6 weeks postpartum, thus acting as important confounders in the examined association. Elective CS was further associated with lower odds of negative delivery experience.
Figure 8. Graphic display of the estimated path analysis models of elective caesarean section (CS) vs vaginal delivery (VaD), reflecting the direct and indirect effects on postpartum depressive symptoms (PPDS) at 6 weeks postpartum.

The path coefficients represent the estimated odds ratios from the corresponding logistic regression models. Pathways indicated with a continuous arrow were statistically significant (p<0.05). Dotted arrows represent pathways with borderline significance (p 0.05-0.10). Red arrow represents a negative association.

When repeating the path analysis with emergency CS and VE as exposure, a strikingly different pattern appeared (fig 9). Both emergency CS and VE, as compared to vaginal delivery, increased 7-fold and 4-fold, respectively, the odds for negative delivery experience, which in turn increased the odds for PPDS. Other pathways through which emergency CS increased odds for PPDS included objective postpartum complications and self-reported postpartum physical symptoms, which also acted as mediators. Unlike elective CS, there was no association of VE and elective CS with fear of delivery or history of depression.
Study III

1503 nulliparas were included in study III, of whom 800 (53%) reported use of EDA during delivery.

In the crude analysis, use of EDA was associated with higher odds of PPDS at 6 weeks postpartum (OR 1.52, 95% CI 1.8-2.08). However, this association dissipated after adjusting for a set of a priori determined confounders including age, fear of delivery, and antenatal depressive symptoms, as well as when further adjusting for the mediators negative delivery experience and operative delivery (i.e. VE or emergency CS). In the fully adjusted model, significant associations with PPDS at 6 weeks postpartum were noted for fear of delivery (OR 2.29, 95% CI 1.57-3.32), antenatal depressive symptoms (OR 7.36, 95% CI 4.80-11.26) and negative delivery experience (OR 2.51, 95% CI 1.51-4.18) (table 4).
Table 4. Univariate and multivariate logistic regression derived Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for postpartum depressive symptoms (PPDS) at 6 weeks postpartum

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI)</th>
<th>Model 1* aOR (95% CI)</th>
<th>Model 2** aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural analgesia</td>
<td>1.52 (1.18-2.08)</td>
<td>1.22 (0.87-1.72)</td>
<td>1.11 (0.76-1.62)</td>
</tr>
<tr>
<td>Age ≥35 years</td>
<td>1.11 (0.75-1.74)</td>
<td>1.35 (0.82-2.20)</td>
<td>1.27 (0.75-2.15)</td>
</tr>
<tr>
<td>Fear of delivery</td>
<td>2.76 (1.99-3.81)</td>
<td>2.12 (1.49-3.01)</td>
<td>2.29 (1.57-3.32)</td>
</tr>
<tr>
<td>Antenatal depressive symptoms</td>
<td>8.81 (6.05-12.83)</td>
<td>7.36 (4.99-10.85)</td>
<td>7.36 (4.80-11.26)</td>
</tr>
<tr>
<td>Negative delivery experi-ence</td>
<td>3.02 (1.98-4.61)</td>
<td></td>
<td>2.51 (1.51-4.18)</td>
</tr>
<tr>
<td>Operative delivery</td>
<td>1.36 (0.98-1.91)</td>
<td></td>
<td>1.15 (0.73-1.70)</td>
</tr>
</tbody>
</table>

*Model 1: Includes EDA and possible confounders (age, fear of delivery, antenatal depressive symptoms defined as EPDS ≥13 pregnancy week 32) as independent variables

**Model 2: Adjusted for Model 1 + possible mediators (delivery experience, operative delivery, i.e. vacuum extraction or emergency cesarean section) as independent variables

Study IV

A total of 1969 woman were included in the study. Delivery started spontaneously for 78% and ended with non-instrumental vaginal delivery for 71% of the participants. Young age, lower educational level, underweight, overweight, smoking during pregnancy, and psychiatric morbidity were associated with neuroticism.

In this study, women with higher level of neuroticism (i.e. a 63-unit increase, corresponding to the IQR) did not have higher odds for adverse perinatal outcomes except for a significant crude association with GDM (OR 2.53, 95% CI 1.20-5.33) (table 5). This association was enhanced after adjustment for the sociodemographic factors maternal age, educational level, height, BMI, smoking and year of delivery (OR 3.57, 95% CI 1.32-9.65). The effect estimate was similar even after further adjustment for psychiatric morbidity but was no longer statistically significant.
Table 5. Logistic regression-derived odds ratios (ORs) with 95% confidence intervals (CIs) for perinatal outcomes, by an increase of 63 units in neuroticism score in SSP (equaling the interquartile range)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted OR(95% CI)</th>
<th>Model 1 aOR(95% CI)</th>
<th>Model 2 aOR(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery, non-instrumental</td>
<td>1.09 (0.95-1.26)</td>
<td>1.08 (0.92-1.28)</td>
<td>1.07 (0.91-1.26)</td>
</tr>
<tr>
<td>Vaginal delivery, vacuum extraction</td>
<td><strong>0.79 (0.65-0.95)</strong></td>
<td>0.82 (0.66-1.01)</td>
<td>0.85 (0.68-1.05)</td>
</tr>
<tr>
<td>Any caesarean section</td>
<td>1.06 (0.89-1.26)</td>
<td>1.06 (0.87-1.30)</td>
<td>1.05 (0.85-1.28)</td>
</tr>
<tr>
<td>Elective cesarean section</td>
<td>1.03 (0.76-1.41)</td>
<td>0.97 (0.68-1.39)</td>
<td>0.94 (0.65-1.34)</td>
</tr>
<tr>
<td>Emergency caesarean section</td>
<td>1.07 (0.88-1.29)</td>
<td>1.09 (0.87-1.38)</td>
<td>1.09 (0.87-1.38)</td>
</tr>
<tr>
<td>Gestational diabetes mellitus</td>
<td><strong>2.53 (1.20-5.33)</strong></td>
<td><strong>3.57 (1.32-9.65)</strong></td>
<td>2.70 (0.92-7.95)</td>
</tr>
<tr>
<td>Gestational hypertension or Preeclampsia</td>
<td>1.07 (0.82-1.39)</td>
<td>1.13 (0.85-1.50)</td>
<td>1.12 (0.84-1.50)</td>
</tr>
<tr>
<td>Induction of delivery</td>
<td>1.04 (0.88-1.23)</td>
<td>1.06 (0.88-1.28)</td>
<td>1.01 (0.84-1.22)</td>
</tr>
<tr>
<td>Dystocia</td>
<td>0.95 (0.82-1.11)</td>
<td>0.99 (0.84-1.17)</td>
<td>0.99 (0.83-1.17)</td>
</tr>
<tr>
<td>Severe lacerations</td>
<td>0.91 (0.71-1.17)</td>
<td>0.88 (0.67-1.17)</td>
<td>0.92 (0.70-1.22)</td>
</tr>
<tr>
<td>Placental retention</td>
<td><strong>0.66 (0.44-0.99)</strong></td>
<td>0.70 (0.45-1.09)</td>
<td>0.71 (0.46-1.11)</td>
</tr>
<tr>
<td>Postpartum haemorrhage</td>
<td>0.95 (0.74-1.23)</td>
<td>0.97 (0.73-1.29)</td>
<td>0.94 (0.70-1.26)</td>
</tr>
<tr>
<td>Premature birth &lt; 37 w a</td>
<td>0.87 (0.65-1.16)</td>
<td>0.95 (0.69-1.33)</td>
<td>0.96 (0.69-1.35)</td>
</tr>
<tr>
<td>SGA &lt;10th percentile a</td>
<td>1.12 (0.87-1.45)</td>
<td>1.15 (0.86-1.54)</td>
<td>1.11 (0.82-1.49)</td>
</tr>
<tr>
<td>LGA &gt;90th percentile a</td>
<td>1.14 (0.90-1.45)</td>
<td>1.07 (0.82-1.41)</td>
<td>1.06 (0.80-1.39)</td>
</tr>
<tr>
<td>Apgar 5 min &lt; 7</td>
<td>0.77 (0.42-1.41)</td>
<td>0.92 (0.48-1.77)</td>
<td>0.87 (0.45-1.70)</td>
</tr>
<tr>
<td>Composite worst-case variable b</td>
<td>0.86 (0.57-1.30)</td>
<td>0.86 (0.54-1.38)</td>
<td>0.83 (0.51-1.34)</td>
</tr>
</tbody>
</table>

SGA: Small for gestational age (according to Swedish sex-specific reference curves)
LGA: Large for gestational age (According to Swedish sex-specific reference curves)
*Model 1 adjusted for maternal age at delivery, educational level, height, body-mass index at first antenatal care visit, smoking at first antenatal care visit and/or at gestational week 32, year of delivery.
* Model 2 adjusted for Model 1 + psychiatric morbidity
a Excluding intrauterine demise (n=3). b intrauterine demise, eclampsia, severe PE, premature birth < 32 w, SGA below -2.5 SD (0.6%), placental abruption

Imputations for missing values for BMI, maternal height, and smoking during pregnancy, yielded similar results except that the association between neuroticism and GDM remained significant after adjustment for psychiatric morbidity.
Discussion

Main Findings

The current thesis elucidates the complex interplay between perinatal complications and perinatal mental health, with a special focus on PPDS at 6 weeks postpartum and neuroticism.

After adjustment for relevant confounders, no direct association was identified between the examined perinatal complications and PPDS at 6 weeks postpartum. However, this thesis identified a number of indirect effects through various mediators, thus allowing the delineation of the mechanisms connecting perinatal complications with PPD. In particular, the studies suggest that PPH increases the odds for PPDS via causing anaemia (study I), whereas an emergency setting delivery (VE or emergency CS) indirectly increases the risk of PPDS by leading to postpartum obstetrical complications, self-reported postpartum physical symptoms, and a negative delivery experience. On the other hand, history of depression or other psychiatric disease seem to act as confounders in the associations between elective CS and PPD, EDA and PPD, and even in the association between neuroticism and GDM. These findings can be explained by psychological (study I-IV) and pathophysiological (study I, IV) mechanisms.

Perinatal complications like PPH and operative delivery may cause psychological stress and even lead to psychological trauma, especially if women have been afraid for her own and/or the baby’s life (55, 79, 81). Additionally, during an acute event, when the staff at the delivery ward must act fast, communication gaps might emerge between the healthcare staff and the woman or her partner (282), which could further negatively influence the experience of delivery. Moreover, recent studies have shown that the mismatch between expectations or plans for the mode of delivery or pain relief method on the one side, and the actual delivery process on the other, might be an important contributor to delivery experience (175, 283). Thereby, negative delivery experience, a well-known risk factor for PPD may act as a key mediator of the effect of the perinatal stressors on PPD (83, 284).

Several biological mechanisms integrating stress regulation and pregnancy physiology have been suggested for explaining the association between perinatal complications and PPD. A recurring hypothesis includes the HPA-axis (190, 239), which may mediate the identified association of neuroticism with GDM (study IV). It may even be relevant in studies I-III, where a disruption
of the HPA-axis might occur as a result of the stress caused by complications coupled with negative delivery experience. Another pathophysiological mechanism highlighted in this thesis is anaemia, as an important mediator in the association between PPH and PPD.

Study I
We found that PPH increases risk of PPD by often leading to postpartum anaemia and to a negative delivery experience. Postpartum distress symptoms (285) and a negative experience of delivery (286) are known psychological consequences of PPH and have also been associated with PPD. A somatic consequence of severe bleeding is anaemia, which presents with a symptomatology including fatigue, reduced cognitive abilities, emotional instability, and subsequently depression (119, 287, 288). Both anaemia and traumatic experiences increase the risk for depression in general and should therefore be considered in studies assessing the association between PPH and PPD.

Study II
The path analysis verified no direct link between mode of delivery and PPDS at 6 weeks postpartum but indicated several indirect associations. Interestingly, two distinct patterns emerged for different modes of delivery. Women delivering by elective CS were not generally at increased risk of PPDS, if one considers that their burdened psychiatric history already predisposed them to depression. History of depression, an established strong predictor of PPD (289), has been associated with fear of delivery (290), which affects preference of mode of delivery mode and could lead to choice of elective CS (68), as verified in the path analysis.

The second pattern includes women who delivered by emergency CS or VE. These women neither had a psychosocial background predisposing to depression nor self-reported fear of delivery. However, the emergency setting of their delivery and the accompanying obstetric and neonatal complications increased the risk for PPDS (291, 292). Emergency CS is known to be associated with more complications and a more prolonged recovery time than vaginal delivery and elective CS (292-295). Women delivering by emergency CS may suffer both the physical fatigue of the delivery, as well as the psychological burden of the subjectively experienced inability to give birth vaginally (61, 282, 296, 297). Nevertheless, there are also qualitative studies where women also express gratefulness and relief (295, 298). Similarly to emergency CS, VE is also characterized by its emergency nature and similar consequences (299). All those parameters contribute to a negative delivery experience that could in itself trigger depressive symptomatology (83, 291).
Study III
There was no association between use of EDA during delivery and PPDS at 6 weeks postpartum after adjustments for antenatal depression and fear of delivery, both associated with low delivery self-efficacy, i.e. the woman’s own belief of act and master over the delivery process (300, 301). Women with low self-efficacy are more likely to choose EDA. Furthermore, antenatal depression is associated with low expectations and disappointment with delivery (300). Together, those factors could partially explain the interplay between antenatal depression, fear of delivery, EDA and PPDS.

Another contributing factor to the crude association between EDA and PPD could be the fact that the pain experience of delivery differs from other forms of extreme pain. Specifically, many women have a positive outlook on and a pragmatic acceptance of delivery pain (143), and might even express a wish to have a “natural delivery” without pharmacological analgesia (302). Nevertheless, there might be a mismatch between the woman’s expectation of pain and pain relief and the actual pain experience (154, 175) with the majority of nulliparas being administered EDA after all. This paradox and potential disappointment could partially explain the higher incidence of PPDS in women reporting use of EDA during delivery (175).

Study IV
No associations between high levels of neuroticism and a range of perinatal outcomes were found except for an association between high levels of neuroticism and GDM. However, this association became statistically non-significant after adjustment for psychiatric comorbidity. A possible explanation is that high stress levels cause an overactivation of the HPA-axis, which in turn induces insulin resistance and thus the development of GDM (42). Moreover, GDM has a strong association with obesity (31). In our cohort as well as in others (47, 48), there was a positive correlation between neuroticism and obesity. Therefore, large weight gain during pregnancy, which was not adjusted for in the analyses, could mediate the association of neuroticism with GDM.

Methodological considerations
Strengths
A principal strength of all included studies is the longitudinal prospective design and the relatively large sample sizes, which offer sufficient statistical power in order to extract robust conclusions. The prospective design reduces the risk of recall bias. The detailed questionnaires at multiple timepoints enabled us to obtain detailed information on many sociodemographic, psychiatric,
and obstetric variables at the individual level. This made it possible to exhaustively examine the effects of potential confounders and mediators.

The large sample sizes further enabled the use of more sophisticated statistical approaches, like path analysis, which are particularly designed to elucidate the complex interplays between several variables, as was the case in two of our research questions (study I-II). These studies are among the first to use such an approach to explore the complex association of delivery complications with PPDS.

Additionally, the detailed classification of mode of delivery (study II), which was not commonly applied in previous studies, enabled us to feature the differences between elective CS and emergency CS and also highlighted the similar psychological consequences of emergency CS and VE.

The study on use of EDA during delivery (study III) is one of the largest studies in the field and has also adjusted for a number of important covariates, something that had been explicitly indicated to be missing from the literature (303, 304). The covariates were selected by conceptualising an interaction framework and analysing it as a directed acyclic graph (see appendices 3 and 4), which reduces the risk of choosing non-appropriate covariates for adjustment (305).

Study IV is one of the few and largest studies on neuroticism and perinatal complications. By using a combination of self-report personality measures and by extracting data for perinatal complications from the national register, we reduced the risk of recall bias and secured high internal validity.

Limitations

General limitations

Both the BASIC and UPPSAT projects are population-based cohorts where nearly all pregnant women (BASIC) or new mothers (UPPSAT) in Uppsala County were invited to participate. However, the participation rate in BASIC was only 21%, possibly because of the comprehensive nature of the study, including multiple questionnaires and extended biological sampling. Thus, the question arises whether this sample is representative. Analyses have shown that there is an overrepresentation of first-time, highly educated mothers in the study. If the decision to participate was not clearly related to exposures and outcomes in this project, the lower participation rate is not expected to greatly influence associations reported in the current studies but may limit the generalizability of the findings. On the other hand, the two other dominant studies, the UPPSAT-project (study I) and the project on abortion (study IV), had relatively high participation rates, (56% and 58%, respectively), when compared to other cohort-studies (306).

In both the BASIC and the UPPSAT-projects, women were beforehand informed about the focus of the studies on perinatal mental health, which may
also have led to selection bias. For example, women with an own history of mental illness, might be more motivated to participate, thus introducing a form of self-selection bias (306). On the other side, depressive symptoms (307) and neuroticism (308) have been previously shown to be more common among non-participants in cohort studies. Also, women with a psychiatric history may decline participation because of their integrity and reluctance towards extensive biological sampling and questionnaires. Nevertheless, it is important to note that the prevalence of women reporting PPDS in these studies does not greatly differ from other Swedish studies (309, 310). No analyses on the prevalence of PPDS or neuroticism could be performed in any of the included studies, as we did not have data on either non-participants or non-responders.

The sociodemographic distribution of participants in all of the contributing studies was comparable to the general Swedish statistics of pregnant women (the Swedish Birth Register), except for a slightly higher age, and an overrepresentation of primiparas and women of higher educational level (306). Due to the exclusion of women unable to communicate in Swedish, there was also an underrepresentation of women not born in Sweden.

Furthermore, PPD was not diagnosed by a clinical interview, but by a screening questionnaire, EPDS, which may introduce information bias and a possible overestimation of the prevalence of PPD. However, EPDS has high sensitivity and specificity (186). It is also the most established instrument in clinical studies, thereby allowing for comparison between studies if using the recommended cut-offs, as was the case in the current studies (311).

Similarly, history of depression was assessed by self-report and despite the high reliability reported in previous studies (312, 313), recall bias cannot be ruled out. Also, in studies with focus on mental health, some degree of response bias can be anticipated.

Furthermore, in order to shorten the already extensive questionnaires, fear of delivery and delivery experience were assessed by single questions and not validated instruments, which could raise concerns about possible misclassification (74-76, 171). In the same context, the dichotomization of delivery experience assessed by a four-scale score might not be fully justifiable (314).

Despite the detailed questionnaires enabling adjusting for numerous covariates, residual confounding due to unknown factors cannot be ruled out. Finally, it is worth noting the substantial proportion of missing answers in some items. Some of these items may be perceived as sensitive information or as having moral connotations, for example smoking or experience of domestic violence, which might introduce response bias.

Specific limitations of individual studies
In study I, women were categorized in exposed and unexposed for PPH which might entail some risk for misclassification bias. To reduce that risk, all women with an estimated bleeding between 649 and 999 mL were excluded. The amount of bleeding was in most cases assessed by visual estimation,
which often leads to underestimation of blood loss (98, 99). From clinical experience, one may also presume that in situations where bleeding approaches 1000 mL, there is a tendency to report a bleeding below 1000 mL, in a, more or less, conscious attempt to normalize the delivery. Thereby, the potential association of exposure and outcome would be diluted. Another issue to be considered is the creation of an algorithm to reduce the proportion of missing data on anaemia at discharge. Nevertheless, the algorithm was strict and thus entailed low risk of misclassification.

The observational design in study III implicates that the use of EDA was subject to the preferences of women per se and may have thus been affected by personal characteristics as depression, fear of delivery (167), socioeconomic status (169, 170), and wish of a pain-free delivery (315). However, by designing a conceptual directed acyclic graph (305), we adjusted for all the necessary confounders, thus minimizing the risk of confounding by indication.

Even though study IV is the largest study in the field, the analyses for some outcomes like GDM, were still underpowered. Finally, the evaluation of outcomes through registry data and not through active assessment might introduce misclassification due to underreporting of some diagnoses in the registries.

Clinical implications of the results

The current studies indicate that perinatal complications are not directly associated with PPDS, but that history of depression in combination with negative delivery experience and somatic complications may confound or mediate an association, especially in the light of earlier psychiatric history, an important risk factor that should be assessed in the clinical setting.

The results from the first study indicate that postpartum anaemia and negative delivery experience increase the risk for PPDS. This in turn points to the importance for carefully monitoring and considering active treatment after heavy postpartum bleeding to prevent anaemia in the prolonged postpartum period. Timely interventions aiming at preventing an unresolved negative self-reported delivery experience should also be considered. These two measures are expected to decrease odds for PPD.

Women undergoing elective CS are, as a group, more vulnerable, with a burdened psychiatric history and more frequently reporting fear of delivery. By beforehand deciding to undergo a CS, these women have a positive delivery experience that possibly protects them against PPDS at 6 weeks postpartum. This implies that, in counselling women with fear of vaginal delivery, the clinician must carefully consider and weight the individual woman’s risk for psychological complications such as PPD in the case of vaginal delivery versus the risk of somatic complications in the case of elective CS. However,
it is also important to note that some women with fear of delivery may process their fear of delivery during counselling and may thereby be prepared for a vaginal delivery and be strengthened of that effort (50). Thereby, every consultation and decision based on an individual woman’s request for elective CS is an intricate task where the individual caregiver’s capability to tune into the woman’s balance of needs, fears and resilience level is of central importance (71).

On the contrary, emergency CS and VE more often lead to a negative delivery experience and postpartum physical complications that predispose to PPD. This pinpoints the need to focus on the prevention of unresolved negative delivery experience among women with an emergency setting delivery, as well as the importance of promptly attending to physical complications.

In contrast to our hypothesis, the use of EDA did not impact the risk for PPDS when adjusting for relevant sociodemographic, psychosocial, and obstetrical variables. This should be taken into account by midwives, obstetricians and the delivering couple, who are advising women on the use of epidural analgesia.

It is also important to note that no statistically significant associations were found between neuroticism and adverse perinatal outcomes among nulliparous women. This is valuable information to caregivers. The association between neuroticism and GDM was possibly compromised in the final adjusted model by power issues and thus no clinical implications can be drawn before new replication studies are conducted.
Summary

In the first study (n=446), we explored the association between PPH and PPDS at 6 weeks postpartum, addressing the role of postpartum anaemia, delivery experience, and psychiatric history. There was no direct and independent association between PPH and PPDS. However, anaemia at discharge from the maternity ward more than doubled the odds for PPD symptoms and mediated the association between PPH and PPD. Other principal factors in the association between delivery complications and PPDS were negative delivery experience and depressed mood during pregnancy.

The second study (n=3888) delineated the association of mode of delivery with PPDS at 6 weeks postpartum. The results indicate that there is no independent association between elective CS and risk of PPD, but the association is highly confounded by history of depression and fear of delivery. On the other hand, emergency CS and VE increase odds for PPD through the mediators postpartum complications and negative delivery experience.

The third study (n=1503) investigated the association between the use of EDA during delivery and PPDS. A positive association in the crude analysis was not apparent after adjustment for sociodemographic, psychosocial, and obstetrical variables, indicating that pain relief through epidural analgesia is not likely to affect the risk of PPDS.

In the last study (n=1969), the association of neuroticism and perinatal complications was explored. Neuroticism was not associated with adverse perinatal outcomes, except for an association with higher odds for GDM which, however, became statistically non-significant after adjusting for psychiatric morbidity.
Conclusion

The aim of the current thesis was to explore the complex association between perinatal complications and perinatal maternal health with focus on PPD and neuroticism. The debate on the potential association of perinatal complications and PPD has been on-going for a long time, but studies on personality traits and perinatal complications are sparse. These studies integrating somatic and psychological aspects, give us insight in possible mediating steps in these processes, which we can target by preventive efforts.

In the current studies, special emphasis has been given to delineate the examined associations by considering important covariates as history of depression, antenatal depression, and delivery experience. The results indicate no direct association of the delivery complications under investigation, and PPDS or neuroticism. However, there are indirect associations through modifiable and non-modifiable mediators. An important modifiable mediator seems to be anaemia postpartum. In today’s praxis, there is no clear guideline on which women to test for anaemia before discharge after delivery. The first and only follow up of Hb-levels postpartum takes place at the maternal primary care setting at 6-12 weeks postpartum. The results of the current thesis highlight that it is important to target postpartum anaemia before discharge from the maternity ward in order to prevent PPD. In parallel, women with psychological vulnerability or a negative delivery experience also need to be identified, as these variables were also identified as confounder and mediator, respectively, in the association between PPH and PPD. Those women are at higher risk to develop PPD and thereby need extra psychological care and support in the early postpartum period to prevent the development of PPD, especially after a complicated delivery. Collecting information on earlier history of depression or other psychiatric disorders as part of the obstetric care would guide the selection of women at high risk for PPD particularly in cases when perinatal complications occurred.
The first study that mentioned depression following delivery was published in 1968, but it was not before the 1980s that the research-field begun to flourish. The development of the EPDS questionnaire, focused on perinatal depression, was an important contribution towards this direction. Since then, the field has widely expanded in a broad spectrum of perspectives, including identification of sociological, psychological, and biological risk factors, qualitative and quantitative research approaches, and development of methods for screening and treatment in the clinics. But still, over 12,000 women and their families are affected by PPD in Sweden every year, with no decreasing trend. Many of these women suffer in silence due to the perceived stigma of getting depressed when having a newborn, whereas others misinterpret their symptoms as of somatic origin (201, 218).

Currently, there is good evidence for several major risk factors for PPD, but there are still numerous potential risk factors, for which the association with PPD remains ambiguous. More advanced methods including path analysis and multifactorial approaches are expected to elucidate these associations.

In this thesis I have tried to delineate the association of PPH, mode of delivery, and EDA with PPD, but there are still many other common perinatal factors and complications that might be interesting to investigate, for example severe lacerations and postpartum infection. During the last years, lacerations and their potential sequels have been spot-lighted as leading major concerns for pregnant women. This is something that midwives and doctors in the delivery ward and antenatal care face every day when they meet women with worries about the forthcoming delivery and possible laceration. Thereby, it would also be interesting to compare the rates of PPD in women with severe lacerations in two to three different time-periods, for example 2006-2007 (UPPSAT), 2009-2014 (BASIC) and 2015-2018 (BASIC).

Risk factors for PPD differ between different contexts, especially between low- and high-risk countries. Therefore, it would be interesting to examine in future studies whether the results presented in this thesis could be replicated in low-income countries.

Study I implies that treatment of postpartum anaemia may decrease the risk of PPD. The next step could thereby be a randomised controlled trial (RCT) on different treatment strategies for anaemia, comparing current practice with a more vigorous treatment of postpartum anaemia.
In contrast to the literature on PPD, studies on personality and pregnancy are scarce. The present study reports a crude association with GDM, which is however no longer statistically significant after adjusting for sociodemographic factors and psychiatric morbidity. This association has to be explored further due to the small number of diabetic cases in the current studies limiting the statistical power.

At the moment, the BASIC project includes more than 4000 women assessed with the psychometric instrument Vulnerable Personality Style Questionnaire (VPSQ) (316), which would allow for a replication study. Future studies should also investigate the association between perinatal outcomes and selected subscales of neuroticism, as different factors may mediate different outcomes (239).

Moreover, a subsequent study arising from the results of this thesis would be to incorporate perinatal complications in a path analysis on the association between neuroticism and PPD.


I den andra studien undersökte vi om det fanns något samband mellan förlossningssätt och förlossningsdepression. Även här använde vi oss av steg-analys. 3888 förlossningar följdes upp 6 veckor efter förlossningen. Vi kunde inte identifiera någon direkt association mellan förlossningssätt och förlossningsdepression. Däremot utkristallisade sig flera faktorer som bidrog till en indirekt association mellan förlossningssätt och förlossningsdepression. kvinnor vars förlossningar avslutats med ett akut kejsarsnitt eller med sugklocka hade, jämfört med kvinnor med spontan vaginal förlossning, en ökad risik att drabbas av förlossningsdepression ifall de även hade en negativ förlossningsupplevelse, drabbades av förlossningskomplikationer eller rapporterade att de hade fysiska besvär efter förlossningen. Även kvinnor med planerat kejsarsnitt
fick oftare förlossningsdepression, men detta kunde helt förklaras med att de oftare var förlossningsrädda och tidigare i livet haft en depression.

I den tredje studien undersökte vi om ryggbédovning under förlossningen minskade risken att drabbas av förlossningsdepression. 1503 förstföderskor deltog i studien. Vi fann inga belägg för att ryggbédovning i sig minskar risken för att drabbas av en förlossningsdepression.


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Appendix

Participants in BASIC

*Appendix 1. Flowchart of participants in BASIC September 2009 until March 2018*
Participants in UPPSAT

Appendix 2. Flowcharts of participants in UPPSAT June 2006 to May 2007
Conceptual Directed Acyclic Graph (Study III)

Appendix 3. Conceptual Directed Acyclic Graph of the association of epidural analgesia (EDA) during delivery and postpartum depression (PPD). Green arrows represent casual paths. Red arrows represent biasing paths.
Directed Acyclic Graph including available variables (Study III)

Appendix 4. Directed Acyclic Graph of the association of epidural analgesia (EDA) during delivery and postpartum depressive symptoms (PPDS) and variables included in the current study. Green arrows represent casual paths. Red arrows represent biasing paths.
A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)