Personality and the HPA-axis in Association with Postpartum Depression

STAVROS I ILIADIS
Postpartum depression is a psychiatric disorder affecting a substantial proportion of newly delivered women, and remains a significant cause of childbirth-related morbidity. The aim of the present thesis was to examine psychological, endocrine and genetic aspects of postpartum depression in a large, population-based sample of women in Uppsala, Sweden. All included studies were undertaken as parts of the BASIC-project, a longitudinal study on psychological wellbeing during pregnancy and the postpartum period. Study participants were screened for depressive symptoms in pregnancy week 17 and 32 as well as at six weeks and six months postpartum, mainly by use of the Swedish version of the Edinburgh Postnatal Depression Scale (EPDS). Furthermore, personality was assessed with the Swedish universities Scale of Personality (SSP) in pregnancy week 32. Evening cortisol levels in saliva were measured in pregnancy week 36 and at six weeks postpartum. Blood samples were obtained to measure corticotropin-releasing hormone levels (CRH) and to perform genetic analyses. The results of this thesis demonstrate that neuroticism is a strong and independent predictive factor of depressive symptoms at six weeks and six months postpartum, and has a significant mediatory role in the association between a single nucleotide polymorphism in the hydroxysteroid (11-beta) dehydrogenase 1 gene (HSD11B1) and postpartum depression. Furthermore, women with postpartum depressive symptoms present with a dysregulated hypothalamic-pituitary-adrenal axis activity in terms of elevated cortisol levels postpartum, as well as elevated CRH levels in mid-gestation. In conclusion, this thesis develops current knowledge on several attributes of postpartum depression. Further studies are required to replicate and expand on these results, which would further contribute to early identification of women at risk of postpartum depression and adoption of proper interventions that may moderate the short- and long-term consequences of the disorder.

Keywords: Corticotropin-releasing hormone, cortisol, HPA-axis, HSD11B1, hydroxysteroid (11-beta) dehydrogenase 1, neuroticism, peripartum depression, personality, postpartum depression, rs12565406, stress

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To those that gave me life
and those that keep giving it a meaning
This thesis is based on the following papers, which are referred to in text by their Roman numerals.


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<tbody>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic Hormone</td>
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<td>CBG</td>
<td>Corticosteroid-Binding Globulin</td>
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<tr>
<td>CRH</td>
<td>Corticotropin-Releasing Hormone</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th edition</td>
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<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision</td>
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<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th edition</td>
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<tr>
<td>DSRS</td>
<td>Depression Self-Rating Scale</td>
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<td>EPDS</td>
<td>Edinburgh Postnatal Depression Scale</td>
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<tr>
<td>HPA-axis</td>
<td>Hypothalamus-Pituitary-Adrenal axis</td>
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<tr>
<td>pCRH</td>
<td>placental Corticotropin-Releasing Hormone</td>
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<td>PPB</td>
<td>Postpartum Blues</td>
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<td>PPD</td>
<td>Postpartum Depression</td>
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<td>SLE</td>
<td>Stressful Life Events</td>
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<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
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<td>SSP</td>
<td>Swedish universities Scale of Personality</td>
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<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
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Introduction

Postpartum and Peripartum Depression

Definition

Peripartum depression is the most recent term introduced by the Diagnostic and Statistical Manual of Mental Disorders to describe depressive episodes in concomitance with pregnancy and childbirth. According to the fifth and latest version (DSM-5), peripartum depression comprises major depressive episodes occurring during pregnancy or in the first four weeks following delivery [1]. In contrast, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR) made use of the term postpartum depression (PPD) as a depressive episode with onset exclusively in the postpartum period [2], without referring to depressive episodes arising during pregnancy. In fact, up to 50% of major depressive episodes identified after delivery have their onset during pregnancy [1]. On the other hand, in clinical and research settings, the term postpartum depression often comprises the first 12 months after delivery [3].

Postpartum depression should be distinguished from postpartum blues (PPB), a mild and transient mood disturbance emerging the first few days after delivery in a large proportion (30% - 80%) of newly-delivered women [3, 4], possibly due to drastic changes in hormonal levels occurring within the first postpartum days [5]. This condition is characterized by emotional lability, irritability and sleep as well as appetite disturbances and does not require treatment [4], as the symptoms usually decline within ten days postpartum. However, no established diagnostic criteria exist [6]. Moreover, the condition has been suggested as a risk factor for PPD [6].

Epidemiology

Prevalence rates of depression in the peripartum period vary widely between studies, and this can be partly attributed to the different criteria used to define depression during pregnancy and the postpartum period as well as different population samples and time frames considered for prevalence estimates. A systematic review of peripartum depression prevalence has estimated the period prevalence (percentage of population with depression over a period of time) for major or minor depression to be 18.4% during pregnancy and 19.2% during the first three months postpartum. The corresponding
estimates for major depression alone are 12.7% and 7.1%, for pregnancy and postpartum, respectively [7]. A later study estimated the one-year postpartum prevalence for major and minor depression to be 9.6% [8]. Regarding point prevalence (percentage of population with depression at a given time point), estimates vary between 8.5 - 11% during pregnancy and 6.5 - 13% during the first year postpartum (major and minor depression) [9].

Interestingly, despite the fact that in some studies most of the depressive episodes accounting for the estimated postpartum period prevalence have a postpartum onset, it remains unclear whether depression during postpartum is more common than other periods in a woman’s life [3, 7, 10].

Symptoms, Clinical manifestations and Diagnosis

According to the DSM-5, the clinical manifestations of a major depressive episode occurring in the peripartum period are not different from those in non-pregnant and non-newly delivered individuals. To fulfill the criteria for a major depressive episode, one has to have been experiencing, over a two-week period, depressed mood most of the day, diminished interest or pleasure, weight loss/gain or appetite disturbance, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to think or concentrate and recurrent thoughts of death or suicidal ideation, suicide attempt or plan to attempt suicide. In total, at least five symptoms are required to set the diagnosis, provided that the first and/or the second symptoms are present. The symptoms should impair everyday functioning and should not be a result of a medical condition or medication. Furthermore, in the case of peripartum onset, women may, more often, experience anxiety or panic attacks, disinterest in the infant, and subsequently feelings of guilt [1].

Consequences

Peripartum depression is a common cause of pregnancy and postpartum related morbidity and may have severe consequences for women, their offsprings and their partners. Regarding maternal health, peripartum depression may diminish the woman’s ability to function in every-day life, as is the case in depressive disorders in general. A series of studies has demonstrated the increased risk of harmful substance misuse such as alcohol, tobacco and drugs, and risk of self-harming and suicide, among women experiencing peripartum depressive symptoms [11, 12]. In fact, maternal suicide is now known to be more common than previously thought, and is one of the leading causes of maternal death in developed countries [13, 14]. A recent study has reported that although overall suicide incidence has decreased over the past 20 years in Sweden, maternal suicide incidence remains unaltered [15]. In addition, the well-known risk of subsequent depressive episodes [3, 16] may negatively affect maternal wellbeing and complicate future pregnancies.
A meta-analysis has found that prenatal depression may be associated with adverse obstetric outcomes, i.e. preterm birth and low birth weight [17].

An important aspect of peripartum depression, that distinguishes it from non-perinatal depressive disorders, is the short-term and long-term consequences on the offspring. In fact, peripartum depression has been associated with negative infant-feeding outcomes [18]. Specifically, depressed mothers are at greater risk of experiencing breastfeeding problems and have reduced odds for continuing breastfeeding [19]. Additionally, abusive behavior or rejection of the infant may occur more frequently among depressed mothers [20, 21] and their descendants have lower rates of preventive healthcare utilization and vaccination [22, 23]. Child mental health can also be affected since behavior problems [24], developmental delay [25] and internalizing, externalizing as well as general psychopathology problems [26] may occur through childhood and into adolescence, as a consequence of maternal depressive symptomatology [27]. Finally, peripartum depression may also have an impact on the partner’s mental health, since studies report an association between maternal and paternal depression [28].

Screening and Prevention

The variety and severity of the adverse effects of peripartum depression call for effective methods, which should have the ability to identify, at an early stage, the occurrence of peripartum depression, allowing the application of proper interventions to alter disease outcomes. Since pregnancy is a period characterized by frequent healthcare contacts of otherwise healthy individuals, opportunities for screening and prevention arise [3, 4]. Being an under diagnosed and under treated health condition with high prevalence, peripartum depression seems a suitable target for screening efforts [29, 30].

In Sweden, the National Board of Health and Welfare (Socialstyrelsen) recommends screening of all newly delivered mothers, six to eight weeks postpartum, since screening with valid instruments can, with acceptable certainty, assess the risk and detect women with PPD [29, 31, 32]. Screening is often performed by midwives or nurses in the antenatal care or pediatric outpatient clinic [33]. However, even though screening is rather extensive in certain regions, many women, especially those of foreign background, are missed [33, 34].

In a recent report, the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) comments that certain psychosocial and psychological interventions in late pregnancy or postpartum can reduce the risk of PPD, based on a recently published Cochrane review [35]. Specifically, individualized professional-based postpartum home visits may reduce the risk of PPD by 40%. Among psychological interventions, interpersonal psychotherapy was the only method with effect on reducing the occurrence of PPD. Moreover, telephone-based peer support also reduced the number of women who develop PPD. These interventions are more ef-
fective if applied to women with high risk for PPD, compared to the general population, and should be introduced shortly after delivery [33, 35]. Additionally, national guidelines in several developed countries generally recommend screening for depression in pregnancy and postpartum [36, 37] pointing out, however, that definitive evidence of benefit is still limited. Indeed, it should be noted that, according to some authors, it remains controversial whether health care professionals should screen for depression during pregnancy or postpartum, since it is unclear if screening definitely improves depression outcomes, also considering that existing screening tools, especially in the prenatal period, have not been proven successful in predicting women who will develop PPD [38-40]. Thus, further research focusing on the development of ways facilitating the identification of women at risk of developing PPD is required.

Risk factors – Etiology

Several risk factors associated with PPD have been described in the literature. Meta-analytic and large-scale studies have summarized the moderate to strong predictors of postpartum depression into: depression and anxiety during pregnancy, previous history of depression, neuroticism, life stress (i.e. stressful life events (SLE) during pregnancy or the early puerperium and childcare stress), low levels of social support, low self-esteem, marital relationship problems, and postpartum blues [16]. Factors with smaller effect on the occurrence of PPD include unplanned or unwanted pregnancies, socioeconomic status and difficult infant temperament [16, 41, 42]. Additionally, some studies support the contribution of certain obstetric stressors (i.e. emergency cesarean section and preeclampsia) in PPD, even after adjusting for confounding factors [16, 43]. However, it is still unclear whether other factors leading to emergency interventions may account for the observed association. As suggested in another study, PPD risk factors can be alternatively categorized into three main risk factor patterns, namely history of psychiatric illness, life stress and poor social relationships [6]. Regarding breastfeeding, recent reviews suggest almost unequivocally that depressed mothers breastfeed less. The exact direction of the association between PPD and lactation however remains unclear. Moreover, depression during pregnancy appears to be associated with failure of breastfeeding while establishing successful breastfeeding might be a protective factor for PPD [44].

Furthermore, a number of biological factors have been implicated in the pathophysiology of PPD including dysregulated reproductive, stress and thyroid hormones as well as immunological and inflammatory factors [45, 46]. The literature on the biological background of PPD is relatively extensive and several markers have been proposed [46]. However, results are often contradictory and cannot fully explain the mechanisms leading to depressive symptoms through a simple endocrine model. The genetic component of PPD has
also been studied through twin, family and genetic association studies. Specific hormonal and genetic aspects are separately addressed in this thesis.

The Hypothalamic-Pituitary-Adrenal axis

One of the principal systems mediating the stress response in humans is the hypothalamic-pituitary-adrenal axis (HPA-axis) [47].

Corticotropin-releasing hormone (CRH) is a 41-amino acid peptide hormone and neurotransmitter that sets into motion the HPA-axis by regulating the synthesis of adrenocorticotropic hormone (ACTH) through stimulation of proopiomelanocortin gene expression in the anterior pituitary gland [48-50]. The human CRH gene has been mapped to chromosome 8 (8q13) and it is expressed widely in several tissues, including the hypothalamus, brain and peripheral nervous system, lung, liver, gastrointestinal tract, immune cells and organs, gonads, and placenta [51].

ACTH is a 39-amino acid polypeptide tropic hormone produced by the anterior pituitary corticotroph cells. It is the key effector of CRH action, acting as a regulator of glucocorticoid secretion by the adrenal cortex. The regulatory influence of CRH on pituitary ACTH secretion changes in stress conditions [52]. Subsequently, ACTH action on the adrenal gland, through binding to membrane receptors of the adrenal cells, increases cholesterol transport into cells, promoting cortisol synthesis [51, 53].

Glucocorticoids, including cortisol, are the final effectors of the HPA-axis and participate in the control of whole-body homeostasis and the organism’s response to stress. Most tissues of the body are affected by an excess or deficiency of glucocorticoids [51, 54]. Cortisol exerts negative feedback on its own secretion, through inhibition of ACTH secretion and suppression of ACTH and CRH production in non-stress conditions [52, 53].

Physiological HPA-axis changes during pregnancy and postpartum

Physiological endocrine changes occurring during the course of pregnancy alter the profile of several hormones including those related to the HPA-axis. Subsequently, a transient, yet physiologic, state of hypercortisolism is noted [55]. Urine free cortisol, total and free plasma cortisol as well as corticosteroid-binding globulin (CBG) levels increase during pregnancy [56]. Placental estrogen production stimulates hepatic production of CBG [57], which initially may cause a transient drop in free cortisol levels [56]. As a result of that, ACTH stimulates further cortisol production to maintain normal levels of free cortisol. Across pregnancy, total and free plasma cortisol levels progressively rise two to four-fold, compared to non-pregnant subjects [56, 58]. Baseline salivary cortisol is another measure of free cortisol that maintains
diurnal variation throughout pregnancy. Salivary cortisol follows a pattern similar to plasma cortisol, starting to rise gradually soon after conception, to reach, during late pregnancy, levels that surpass those in non-pregnant women by more than two times. Thereafter, salivary cortisol levels peak shortly before partus and decline through the postpartum period [55, 57, 59].

During the course of pregnancy, the increase in free cortisol concentrations has been mainly attributed to alterations of the maternal HPA-axis [56, 58, 60, 61]. A main component in these alterations is the production of CRH from the placenta (pCRH) [62, 63], decidua and amniotic membranes [64-66]. Although glucocorticoids normally exert an inhibitory effect on hypothalamic CRH synthesis through negative feedback mechanisms in non-pregnant individuals, maternal cortisol acts reversely by enhancing a positive feed-forward loop including glucocorticoids, ACTH and CRH. This promotes CRH synthesis by syncytiotrophoblast and intermediate trophoblast cells as early as in gestational week 8, making pCRH detectable in maternal blood at around 16-20 gestational weeks [67, 68]. Circulating pCRH increases exponentially in maternal blood up to 1000-fold [56], reaches levels similar to those in the pituitary portal system by 30 weeks’ gestation [69] and continues to rise during the third trimester [52]. Thereafter, pCRH peaks during labor and finally becomes undetectable rapidly after parturition [53, 68, 69].

It should be mentioned that the detectable CRH in maternal blood is mainly attributed to the placenta [56], as hypothalamic CRH, even in stress conditions, is difficult to detect since it is enzymatically degraded at the pituitary level [52] and rapidly diluted after leaving the hypothalamic-pituitary portal system [70]. On the other hand, pCRH is constantly and in large amounts produced by placenta throughout pregnancy and although pCRH secretion is pulsatile, it does not follow a circadian rhythm [65]. Hypothalamic and pCRH are identical in structure [65] and genetic origin [71], however CRH gene expression is regulated differently in placenta in comparison to hypothalamus, a phenomenon attributed to the expression of different transcription factors, co-activators and co-repressors in these tissues [53, 70].

The HPA-axis in depression during pregnancy and postpartum

The physiological changes described above contribute to elevated levels of bioactive free CRH and subsequent secretion of ACTH and cortisol during pregnancy [69]. Meanwhile, hypothalamic CRH is down regulated, leading to low cortisol levels after partus and placental expulsion [65, 69, 72]. While, in most cases, the HPA-axis is normalized within a few weeks after delivery, an abnormal adjustment to this state may result in a persistent HPA-axis dysregulation, which has been suggested to be a vulnerability factor contributing to the occurrence of postpartum depressive symptoms [65, 69, 73].
Several studies have investigated the associations between cortisol levels and peripartum mood disturbances (Study II, Table 1). However, sample size and time-point of cortisol assessment during the course of pregnancy as well as during the day vary between studies. Some authors focused on salivary cortisol while other studies measured blood or urinary cortisol. The time range of cortisol assessment is broad, covering a period from the third pregnancy trimester to 12 weeks postpartum. The majority of studies evaluated morning samples or cortisol awakening response (CAR), while fewer measured afternoon and evening cortisol. In these studies, a variety of screening tools were used for detection of depressive symptoms. Not surprisingly, findings are contradictory. While many studies show an increase in cortisol levels during pregnancy in the presence of antenatal depressive symptoms [74-83], others have not been able to confirm such an association [59, 84-89]. Likewise, a number of studies support the hypothesis of elevated peripartum cortisol levels in individuals with postpartum depression [77, 90-92] or postpartum blues [93-95], while other studies point to either lower postpartum cortisol levels [96-99] or no association at all [59, 65, 88, 89, 100-104]. Thus, these results are inconclusive, necessitating further studies in different settings as well as in different subgroups of PPD patients. Moreover, the literature on evening cortisol, in particular, is sparse. A dysregulated HPA-axis might be reflected in an alteration of measured evening cortisol levels [105]. Following a diurnal secretion pattern, cortisol levels are higher in the morning and decrease during the day, becoming lowest in the evening [84]. Thus, evening salivary cortisol levels might be less variable between individuals, and more suitable for the identification of smaller differences in cortisol concentration, as described in other research fields [106].

Regarding CRH, a few studies have examined possible associations between CRH and the presence of depressive symptoms during pregnancy and postpartum (Table 6, Appendix). Some authors report a positive association between CRH levels and/or a greater increase in CRH at various time points after pregnancy week 25 and depressive symptoms (assessed with various depression screening tools and cut-offs) 8-12 weeks postpartum [102, 103, 107]. On the contrary, two other studies report a lack of association between CRH and postpartum depression [108, 109]. In a recent study from our group, focusing on prenatal depressive symptoms and CRH levels, it was shown that women on selective serotonin reuptake inhibitor (SSRI) treatment had higher second trimester CRH levels than controls or untreated depressed women [110].

Two subtypes of major depression have been described, namely melancholic and atypical depression. Melancholic depression is a state of pathological hyper arousal where patients experience intense anxiety, insomnia and loss of appetite. On the other hand, atypical depression can be described as nearly the opposite of melancholia. Indeed, these individuals exhibit a reverse symptomatology where feelings of emptiness, fatigue, sleepiness and increase in food intake dominate the clinical manifestations of the condition.
The same pattern has been demonstrated at the hormonal level, where melancholic depression has been associated with elevated CRH while atypical depression is characterized by decreased CRH production [47, 69]. It has also been suggested that peripartum depression is a heterogeneous disorder with substantial differences in the pathophysiology and clinical expression of depressive symptoms occurring before and after delivery. The idea that depression with antenatal onset may resemble melancholic while depression with postpartum onset is more like atypical depression has been introduced by previous studies [73].

**Personality traits and factors**

Personality can be defined as the characteristic patterns of thoughts, feelings and behaviors that make a person unique. It arises from within the individual and remains fairly consistent throughout life. Personality is often described in the literature in terms of personality traits. A personality trait attempts to quantify the marked variations in typical responses to the environment that distinguish one person from another [112]. Through time, studies have grouped these traits into larger categories, or factors. Consensus on personality taxonomy began to emerge in the 1980s, when classification models such as the five-factor model (“Big-Five”) and the three-factor model (“Big-Three”) were proposed in order to categorize personality traits [113]. The five-factor model grouped personality traits into neuroticism, extraversion, conscientiousness, agreeableness, and openness to experience. On the other hand, the three-factor model included negative emotionality, positive emotionality and disinhibition, where a certain overlap exists between these models [113, 114]. These models recognized that personality is ordered hierarchically from a large number of traits into fewer more general factors [114, 115]. Several other scales have been developed in later years. Many of the existing models overlap and specific factors from one model correspond to equivalent factors in other models [113]. A more recently introduced diagnostic inventory, the Swedish universities Scale of personality (SSP) identifies three different personality factors, namely neuroticism, aggressiveness and extraversion [116].

The term neuroticism originates from the Freudian theory. However, the modern use of the term is entirely based on descriptive psychometric terms [117]. According to Eysenck, neuroticism can be described as almost the opposite of stability [118]. According to other authors, neuroticism is essentially identical to negative emotionality [115] and has been traditionally a central part of personality theories with a substantial role in nearly all major models of personality [117]. Neuroticism often refers to the experience of negative affect upon frustration, threat or loss, and relates to measures of reactivity, vulnerability, hostility, irritability, sensitivity to criticism, and
anger as well as feelings of tension, emotional lability and insecurity [119, 120].

Personality, Neuroticism and Depression

A possible link between personality and mental disorders has been hypothesized since the time of the ancient Greeks [121]. In modern times, studies have attempted to establish an association between various personality factors and risk of depression in non-pregnant individuals [122-126] as well as in women in the peripartum period [127-131], in order to identify those at risk of developing depressive symptoms at a later stage. Early identification of specific personality factors is important from a public health perspective, since neuroticism, for instance, has been associated with greater health-care use, medical comorbidities and economic costs [132-134].

Neuroticism has been linked to most aspects of psychopathology [113, 117, 120]. Depressive disorders, in particular, are characterized by negative affect and several studies have established a link between personality factors and risk of depression in non-pregnant individuals [122-126, 135, 136]. Moreover, some studies have focused on the association between neuroticism and depression among women in the postpartum period. However, a substantial variation among studies exists, in terms of study design, personality scales and diagnostic tools used to assess depressive symptoms during the perinatal period. Personality assessments of study subjects are often performed during the postpartum period when the personality evaluation can be distorted due to depressive symptoms depending on either PPD or depression with onset prior to childbirth. As a result, many authors fail to take into consideration that personality features can be state-dependent, possibly leading to biased conclusions [137, 138]. In general, findings of previous studies point to an association between neuroticism and risk for PPD [127-131, 139-142].

To address questions about the etiology of diseases with complex phenotypes, such as depression, the concept of intermediate phenotypes has been introduced in this field of research. An intermediate phenotype is defined as an “internal” phenotype, between genotype and clinical phenotype, which cannot be identified unless a biochemical test or another type of examination is carried out [143]. In general, endocrinological, cognitive or neuropsychological factors may be considered as intermediate phenotypes in psychiatric disorders [143]. Neuroticism has been proposed as having the most comprehensive support in the literature to be considered as a candidate intermediate phenotype of depression [144]. This role of neuroticism is, to a significant extent, supported by the common genetic basis of personality and depression. This issue is further addressed in the “Genetic Background of Neuroticism and Depression” section of this thesis.
Personality and the stress system

In an attempt to understand the biological basis of neuroticism, it has been suggested that it is associated with lower activation threshold and higher activity in the limbic system, which would make persons with high neuroticism levels to react to a greater extent to stressors [118, 119]. The limbic system comprises the hypothalamus, amygdala, hippocampus and septum and regulates fear, aggression and anxiety [119]. The underlying mechanisms mediating this response are quite complex. Briefly, the amygdala initially responds to negative information, which may consist of discrete stimuli that generate fear and non-explicit stimuli that generate uncertainty and anxiety. The amygdala is further connected to specific areas in the hypothalamus and brain stem that are involved in emotion expression [119, 145]. Activation of this system coordinates the initial response to external stressful stimuli, intending to inform and prepare the individual for potential action and suitable response strategy [119, 145]. Specifically, the central CRH system mediates prolonged anxiogenic effects and central nervous system arousal as long as an environmental stimulus is interpreted as uncertain and potentially dangerous [145]. CRH efferents from the bed nucleus of the stria terminalis activate thereafter the peripheral CRH system in the paraventricular nucleus. This mechanism initiates activation of the HPA-axis that leads to cortisol secretion from the adrenal cortex [119, 145].

The association between personality and dysregulated HPA-axis has been investigated, and studies report a positive [146-150] or negative association [151-154] between neuroticism and cortisol levels, CAR, stress-induced cortisol response or cortisol secretion following the dexamethasone suppression test. These facts may suggest the involvement of the HPA-axis in the pathophysiology of neuroticism. However, study results regarding the exact underlying mechanisms are equivocal, calling for further research in the field.

Genetic background of Neuroticism and Depression

Single-nucleotide polymorphisms (SNPs) are a common type of genetic variations among individuals. SNPs may help predict an individual’s response to certain drugs, susceptibility to environmental factors and risk of disease development. To date, more than 10 million genetic variants, mostly common (minor allele frequency, MAF ≥ 5%), have been identified and genotyped by international projects, such as the HapMap project [155-157]. The majority of SNPs are strongly correlated to proxies (marker alleles) at nearby loci, a phenomenon called haplotype and this association remains stable for many generations, a phenomenon termed linkage disequilibrium [158]. Lately, genome-wide association studies (GWAS) have successfully identified hundreds of genomic loci that may influence human disease [159].
Genetics factors have been implicated in the etiology of peripartum depression, along with the fact that psychosocial factors have not been able to completely explain the occurrence of depressive symptoms in relation to childbirth. Despite the fact that hormonal fluctuations occur in all women in the postpartum period, only some individuals appear to be sensitive to these changes, suggesting that other underlying factors may contribute to the individual susceptibility to mood disturbances postnatally [160, 161]. A familial component in postpartum depressive symptoms has previously been reported in twin and family studies [162-164]. In a study of 838 twin pairs, genetics factors accounted for 38% of variance in postnatal depressive symptoms, indicative of a modest genetic influence on depression [163], while in a more recent larger study the heritability of perinatal depression was estimated at 44 - 54% [165]. Moreover, the genetic component in PPD is believed to be larger than that in major depression [165].

Over the past years, studies have examined possible associations between common genetic variants and postpartum depression. SNPs in candidate genes, including the serotonin transporter (5HTT), catechol-O-methyltransferase (COMT), monoamine oxidase A (MAOA), and tryptophan hydroxylase 1 and 2 (TPH1 and TPH2), have been associated with PPD [166-168]. Concerning the HPA-axis, the glucocorticoid receptor, nuclear receptor subfamily 3, group C, member 1 (NR3C1), corticotropin-releasing hormone receptor 1 (CRHR1), corticotropin-releasing hormone receptor 2 (CRHR2), corticotropin-releasing hormone binding protein (CRHBP), and FK506 binding protein 5 (FKBP5) are the most commonly studied genes in relation to PPD. However, the literature concerning many other HPA-axis related genes and their influence on postpartum depression is still scarce.

In a recent study of haplotype-tag SNPs in several stress-regulatory genes and their association to postpartum depression, the SNP rs12565406 in the hydroxysteroid (11-beta) dehydrogenase 1 (HSD11B1) gene was found to be associated with the occurrence of depressive symptoms in the postpartum period (Comasco et al., manuscript). This SNP is an intronic variant of the HSD11B1, which is located on chromosome 1. The gene product, 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), catalyzes the conversion of inactive cortisone to active cortisol and its isoenzyme 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) catalyzes the inverse reaction [169]. The 11β-HSD1 protein is expressed in many tissues, including hypothalamus and the pituitary [169] and regulates central HPA-axis activity. In a study of non-pregnant subjects, 11β-HSD1 activity was increased in depressed women, suggesting that this enzyme influences important stress responses in major depression [170].

Studies have investigated the genetic basis of neuroticism and have reported that a substantial proportion of the genetic vulnerability for depression is reflected in neuroticism [144, 171, 172]. Specifically, twin studies have reported that around half of the genetic variance in depression is shared with neuroticism [173, 174]. On the genetic variant level, a significant pro-
portion of the variance of neuroticism is explained by single nucleotide polymorphisms and the same polymorphisms may influence both neuroticism and depression [172]. However, this field is largely under-researched.
Aim

The overall aim of this thesis was to examine psychological, biological and genetic aspects of postpartum depression in a large, population-based sample of women in Uppsala, Sweden.

The specific aims of the studies were:

I To test the hypothesis that certain personality factors and traits, assessed in non-depressed women in late pregnancy, influence the risk of developing postpartum depressive symptoms and postpartum depression.

II To assess the possible association between evening salivary cortisol levels and depressive symptoms during the peripartum period.

III To assess, in non-depressed pregnant women, the possible association between pCRH in mid-gestation and the development of depressive symptoms in the postpartum period.

IV To examine the possible mediatory role of neuroticism in the association between a single nucleotide polymorphism in the hydroxysteroid (11-beta) dehydrogenase 1 gene and postpartum depression.
Materials and Methods

An overview of the studies’ designs is provided in Figure 4 (Appendix).

The BASIC-project

All included studies were undertaken as parts of the BASIC-project (Biology, Affect, Stress, Imaging, Cognition), a population-based, longitudinal study on psychological wellbeing during pregnancy and the postpartum period in Uppsala County, Sweden. The study is conducted at the Department of Obstetrics and Gynecology at Uppsala University Hospital. All women attending the routine ultrasound examination are invited to participate. Upon invitation, information is given and a written consent is obtained from women who choose to participate. In Uppsala, all routine ultrasound examinations are performed at Uppsala University Hospital and 97% of pregnant women participate. Moreover, the delivery ward of the Hospital is the only available within the county.

The BASIC-project was initiated in 2009, after an initial one-week pilot period. As of January 2016, more than 4700 pregnancies have been included in the project, with a participation rate of 22%. Women contribute to the study at: pregnancy week 17 (blood samples and a web-based questionnaire including psychometric measures and demographic data), pregnancy week 32 (psychometric measures and demographic data), pregnancy week 36 - 38 (sub-group invitation to clinic visit for psychiatric interview, biological, cognitive and emotional tests, blood and saliva sampling), delivery (maternal and umbilical cord blood samples, sub-group cerebrospinal fluid, amniotic fluid, uterus and placenta samples) and at 6 weeks (psychometric measures and demographic data as well as sub-group invitation to clinic visit for biological, cognitive and emotional testing, blood and saliva sampling), 6 months (psychometric measures, demographic data and mother-infant bonding questionnaire), and 1 year postpartum (psychometric measures and infant temperament assessment). Exclusion criteria are (1) inability to adequately communicate in Swedish, (2) protected identity, (3) pathologic pregnancies as diagnosed by routine ultrasound, and (4) age less than 18 years. Women with high scores on the Edinburgh Postnatal Depression Scale (EPDS) or with answers indicating suicidal ideation are being contacted by a study doctor, assessed and referred when appropriate.
Study population

Study I

Women participating in this study were recruited through the BASIC-project between September 2009 and September 2010. They were instructed to complete a web-based self-administrated structured questionnaire containing questions on personal history, sociodemographic and pregnancy related data and the Swedish validated version of the EPDS [175] at pregnancy week 17 and 32, as well as at six weeks and six months after delivery. Participating women were also administered the Swedish universities Scale of Personality at gestational week 32 [116], as well as the Depression Self-Rating Scale (DSRS) [176] at six months postpartum.

One hundred eight pregnant women who had an EPDS score higher than or equal to 13 at gestational week 32 (9.4%) were excluded from further analyses in order to avoid bias due to a possible depressive state effect on personality assessment measures. In total, 1037 women were included in the study.

Study II

Between December 2011 and March 2012, as well as between June and August 2012, women who had already given their consent to participate in the BASIC-project, were asked to participate in the present study at pregnancy week 36. They were instructed to complete a self-administered structured questionnaire containing questions on personal history, sociodemographic and pregnancy related data as well as the Swedish validated version of the EPDS at the 36th week of pregnancy and at six weeks after delivery. At both times, study subjects were also asked to collect evening salivary samples at home, for cortisol measurement, by using a kit sent by post along with detailed instructions.

Initially, 365 pregnant women from the BASIC cohort were invited. Two hundred eighty four study subjects agreed to participate and sent in an evening salivary sample during pregnancy, and of those, 243 women also provided a salivary sample six weeks after delivery. A valid cortisol sample, accompanied by a completed EPDS questionnaire, was available for 268 study subjects prenatally and 181 postpartum.

In order to assess differences in cortisol levels in more homogeneous groups, three groups of study participants were compared: i) healthy women, ii) women with depressive symptoms prior to or during the current pregnancy but not postpartum, and iii) women with postpartum depressive symptoms, regardless of symptom onset.
Study III

This study was undertaken as a part of the BASIC-project and the Uppsala Biobank of Pregnant Women, where blood samples are collected in conjunction with the routine ultrasound screening at pregnancy week 17. Eligible for inclusion in the Biobank were women being (1) 18 years or older, (2) Swedish-speaking, and (3) without blood-borne disease (Human Immunodeficiency Virus, Hepatitis B and C). Invitation to participate in the Biobank was done randomly, when a research nurse was available. Written informed consent was obtained and a plasma sample was collected. Participation rate was 70% and it is estimated that the Biobank covers approximately half of the pregnant population in Uppsala County. The sample was centrifuged within two hours and stored at −70°C.

A self-administered structured questionnaire containing questions on personal history, sociodemographic and pregnancy related data as well as the Swedish validated version of the EPDS was filled in pregnancy week 17 and 32, as well as at six weeks postpartum. CRH levels were analyzed in maternal blood samples.

To account for the increased placental mass in multiple pregnancies [177], the 21 twin pregnancies in the study sample were excluded from further analyses. Data on EPDS scores in pregnancy week 17 and 32 and at six weeks postpartum, as well as a valid CRH measurement were available for 536 women scoring lower than 12 in the pregnancy week 32 EPDS questionnaire. One woman with an abnormally high level of CRH (and EPDS score of 27 at six weeks postpartum) was considered as outlier and was therefore also excluded. Finally, 535 women were included in the analyses.

Study IV

Study IV was conducted as a sub-study of a larger project within the BASIC-cohort, which examined the role of several stress-regulatory genes, in terms of SNPs, in peripartum depression (Comasco et al., manuscript). Self-administered structured questionnaires were sent to study participants, containing the Swedish validated version of the EPDS at six weeks postpartum and questions on personal history, sociodemographic and pregnancy related variables at pregnancy week 17 and 32 and at six weeks postpartum as well as the Swedish universities Scale of Personality at pregnancy week 32. Moreover, blood samples for genetic analyses were collected at some point between pregnancy week 17 and 8 weeks postpartum. In total, 771 women were included in this study.
Psychometric measures

The Edinburgh Postnatal Depression Scale (EPDS)

The Edinburgh Postnatal Depression Scale is an internationally used, validated, 10-item self-reported questionnaire, designed as a screening tool to identify depressive symptoms in the peripartum period [175]. The EPDS consists of 10 statements, each with four possible answers (0-3 points per answer) that can generate a total score between 0 and 30 points. An example of the Swedish version of the EPDS is provided in Table 4 (Appendix).

Different cut-off values have been suggested for perinatal depression screening. The 10-points threshold has often been used for biological research purposes [178, 179]. A cut-off of 12 points is often used to screen for postpartum depression in clinical settings in Sweden [180]. The 12-points cut-off provides sensitivity between 72% [181] and 77% [182] and specificity between 88% [181] and 92.5% [182]. According to the latest NICE guidelines, the EPDS had good pooled sensitivity (Se=0.68, 95% CI 0.66 – 0.71) and excellent pooled specificity (Sp=0.92, 95% CI 0.92 – 0.93) for a cut-off of 13 points postpartum [183]. Moreover, a cut-off of 13 points in pregnancy had a sensitivity of 77% and specificity of 94% in a Swedish validation study [184].

In Study I, to define women with significant depressive symptoms, the cut-off was set at 13 points in pregnancy and at 12 points postpartum. In Study II, a cut-off of 10 points was used pre- and postnatally. In Studies III and IV, the 12-points threshold was used in pregnancy and postpartum. The Swedish version of the EPDS used in all studies has been validated in pregnant and postpartum populations in Sweden [180, 184].

The Swedish universities Scale of Personality (SSP)

The Swedish universities Scale of Personality was administered for the evaluation of personality traits at pregnancy week 32 [116] in Studies I and IV. The SSP is a self-rating questionnaire, based on the Karolinska Scales of Personality (KSP) [185], which was rationally developed with the aim of assessing vulnerability for psychopathology. SSP has been developed to assess personality traits and does not intend to evaluate depressive symptoms. Compared to KSP, SSP has a reduced number of items and an improved psychometric quality with better face validity, higher internal consistency and better response differentiation [116]. The SSP contains 91 statements (e.g. “I'm the kind of person who is excessively sensitive and easily hurt”) and the participants rated each item on a scale from 1 to 4, where 1 equals “does not apply at all” and 4 equals “applies completely”. The items form 13 scales or traits. For each scale, the SSP scores are transformed into normative T scores with means of 50 and standard deviations of 10 based on a Swedish gender-stratified non-patient sample [116]. Following
factor analysis, these scales are usually grouped into three major factors: neuroticism (somatic trait anxiety, psychic trait anxiety, stress susceptibility, lack of assertiveness, embitterment, mistrust), aggressiveness (trait irritability, verbal trait aggression, physical trait aggression, inverted value of social desirability) and extraversion (impulsiveness, adventure seeking, inverted value of detachment) [116]. The SSP questionnaire used in the studies is provided in Table 5 (Appendix).

**Stressful Life Events (Rosengren Scale)**

For the assessment of stressful life events, a ten-item scale developed by Rosengren et al. [186] was used in all studies. The scale was administered to study participants via a web-based questionnaire at six weeks postpartum. It referred to events during the past 12 months and an index with range 0 – 10 was created. The following were considered as significant stressful life events: serious illness in family member, serious concern about family member, death of family member, divorce or separation, involuntary change of residence, involuntary change of work, feelings of redundancy, feelings of insecurity at work, serious financial trouble, and legal prosecution.

**The Depression Self-Rating Scale (DSRS)**

The Depression Self-Rating Scale was designed to cover the DSM-IV A-criterion for a major depressive disorder in a self-rating form. This scale was used in Study I and was administered at six months postpartum. It has been tested in patients with incapacitating pain syndromes and agreement between self-rated and clinical expert-rated diagnoses was very good (kappa=0.87). Sensitivity and specificity were high (0.94 and 0.96, respectively). Women fulfilling the DSM-IV A-criterion for depression were considered as cases [176].

**Biochemical Analyses**

**Salivary Cortisol**

In Study II, study subjects received written instructions to take a sample of saliva between 20:00 and 22:00 hours, using Salimetrics-tubes (Electra-Box, Diagnostica AB, Sweden). Participants were instructed to refrain from any food intake, consumption of beverages, tobacco products or oral use of foreign bodies (i.e. chewing gum, toothpick or toothbrush) one hour before sampling [187]. Moreover, they were asked to report the presence of illness, oral lesions and whether they had received dental care a few days before sampling. After placing a cotton roll sublingually for at least two minutes, women stored the samples in refrigerator overnight. Thereafter, the samples were mailed back to the laboratory unfrozen, since cortisol concentrations
are stable during extended periods without freezing, even when exposed to varying temperature and movement [188]. After centrifugation at 1000 g for 10 minutes, samples were stored in -18°C prior to further analysis. Salivary free cortisol concentrations were assessed using competitive enzyme-linked immunosorbent assay (ELISA) (Salivary Cortisol Enzyme Immunoassay Kit, Salimetrics, Electra-Box, Diagnostica AB, Sweden) at the department of Laboratory Medicine at Uppsala University Hospital. The intra-assay and inter-assay coefficients of variance were 8% and 11%, respectively. All samples were run in the same assay.

Corticotropin-releasing hormone

In Study III, CRH was analyzed with radioimmunoassay (RIA), using a Corticotropin Releasing Factor (CRF) (Human, Rat Mouse, Canine, Feline) RIA Kit with a 10-1280 pg/ml range from Phoenix Pharmaceuticals, Inc. (Burlingame, CA, USA). 100 µl of pure and undiluted plasma samples were pipetted in polystyrene tubes. Controls, standards and reagents were diluted and used according to the kit’s protocol. Incubation times and temperatures were 21 h at 4°C for rabbit anti-CRH antibody, 24 h at 4°C for 125I-CRH tracer solution and 90 minutes at room temperature for goat anti-rabbit antibody and normal rabbit serum. Tubes were subsequently centrifuged at 3500 rpm for 15 min at 4°C. The supernatant was carefully poured off so that only a pellet was left. Samples were analyzed using a WIZARD automatic gamma counter from Perkin-Elmer (Waltham, MA, USA). A standard curve was automatically generated by plotting the standard sample concentration against the 125I-CRH binding relative to the maximum binding (B/Bmax) in that particular sample. Bmax was calculated by subtracting the counts per minute (cpm) value of a non-specific binding control from the cpm value of a total binding sample, in which all 125I-CRH was bound to the available antibody. Subsequently, CRH concentration in the tested samples was automatically derived from the standard curve. The intra-assay variability in the first 100 cases was 1.7%. Due to this low variability, it was decided to test the remainder of the samples in mono. In total, eight RIAs were performed, and positive controls from normal pregnancies were analyzed in each RIA to assess the inter-assay variability (inter-assay variability 3.0%). In order to nullify the effect of inter-assay variability on our final results, samples from every group were present in each RIA.

Genetic analyses

As mentioned above, study IV was undertaken as part of a larger study where several candidate genes involved in the HPA-axis were selected for genotyping analyses. DNA was isolated from blood using the silica-based Kleargene DNA extraction method. The eighteen candidate genes selected
for the larger study were: the arginine vasopressin receptor 1B (AVPR1B); corticotropin releasing hormone (CRH); corticotropin releasing hormone binding protein (CRHBP); corticotropin releasing hormone receptor 1 (CRHRI); corticotropin releasing hormone receptor 2 (CRHR2); cytochrome P450, family 17, subfamily A, polypeptide 1 (CYP17A1); cytochrome P450, family 21, subfamily A, polypeptide 2 (CYP21A2); FK506 binding protein 5 (FKBP5); hydroxysteroid (11-beta) dehydrogenase 1 (HSD11B1); hydroxysteroid (11-beta) dehydrogenase 2 (HSD11B2); hydroxysteroid (17-beta) dehydrogenase 2 (HSD17B2); hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 (HSD3B1); hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2 (HSD3B2); melanocortin 2 receptor (MC2R); nuclear receptor subfamily 3, group C, member 2 (mineralocorticoid receptor) (NR3C2); nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor) (NR3C1); proopiomelanocortin (POMC); and serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 6 (SERPINA6) gene.

Data on these genes were obtained from HapMap database for a region spanning ± 100bp each gene, and haplotype-tag SNPs were selected using Haploview 4.2 (minimum minor allele frequency of 0.1; \( r^2 \geq 0.8 \), pairwise tagging only). Candidate markers from previous association studies were also considered. Genotyping was performed using the Kbioscience Allele-Specific Polymorphism assay (KASP) based on competitive allele-specific polymerase chain reaction (PCR) and bi-allelic scoring of the SNP (KBio-science®). No-template control samples were included to enable the detection of contamination or non-specific amplification.

The association to postpartum depressive symptoms was examined for 120 SNPs, after the exclusion of those not in Hardy-Weinberg Equilibrium \((N=5)\) as well as those with genotyping call rate < 97\% \((N=1)\) or minor allele frequency < 1\% \((N=1)\). Linkage disequilibrium \((r^2 \text{ and } D')\) and potential haplotype blocks were estimated with the expectation-maximization (EM) algorithm using SNP & Variation Suite 8.4.1 (GoldenHelix®).

Statistical Analyses

The IBM SPSS versions 20 and 22 (SPSS Inc., Chicago, IL) and the Stata version 14 (Stata CorpLP, Texas, USA) were used for data analyses. Statistical significance was set at a \(p\)-value of < 0.05, if not stated otherwise.

The main statistical tests used in Studies I-IV are listed below.
Factor analysis [Study I]

Factor analysis for personality traits was performed with varimax rotation in order to identify factors with Eigenvalues > 1. Principal axis factoring was used as extraction method and the limit for factor loading was set at > 0.45.

Mann-Whitney U-test [Studies I, II, III, IV]

Mann-Whitney U-test was used to account for non-normality when examining groups where values were not normally distributed. It was applied when comparing: scores of personality factors and traits among depressed and non-depressed women (Study I), cortisol levels in relation to self-reported depressive symptoms during pregnancy and postpartum as well as to various population characteristics (Study II), CRH levels in relation to various population characteristics (Study III) and EPDS in relation to genotypes and population characteristics (Study IV).

Spearman’s rank correlation coefficient [Studies I, II]

Spearman’s rho (r) was used to assess the correlation between EPDS scores and the score of each of the three personality factors as well as between EPDS scores and peripartum cortisol levels.

Regression models [Studies I, II, III, IV]

In Study I, binary logistic regression analyses were performed, with EPDS score as the dependent variable. Personality factors were introduced in the models as dichotomous independent variables grouped as the highest quartile versus the two lowest quartiles, in order to reduce misclassification. Several possible confounders were also inserted in the models. In another model, backward stepwise logistic regression was performed for all 13 personality traits (dichotomized as the highest quartile versus the rest) and dependent variable as stated above. Statistically significant traits were identified for further analyses and introduced in another model, along with possible confounders. Similar analyses were done with DSRS as the dependent variable.

In Study II, the dichotomized postpartum EPDS score was inserted in the regression model as the dependent variable and cortisol levels (dichotomized at the median) as the independent variable. In a final step, possible confounding factors were also introduced in the model.

In Study III, the dichotomized postpartum EPDS score was used as the dependent variable and log transformed CRH levels as the independent variable. Possible confounding factors were also introduced in the model. In further sub-analyses, study subjects with preterm birth (< 37 gestational weeks) (N=15) and with newborns characterized as small for gestational age (SGA) (> 2 standard deviations under the mean birth weight for newborns of
same sex, born during the same gestational week, according to the national birth weight curves used in clinical practice in Sweden [189]) (N=4) were excluded from the study population, due to the possible correlation between CRH levels and gestational length as well as suboptimal fetal growth [190-192]. Moreover, women on corticosteroids (N=12) were also excluded to account for a potential medication effect on the HPA-axis. Thereafter, the analyses were repeated.

Linear regression models were constructed in Study IV with the natural logarithm of the EPDS score as the dependent variable and the rs12565406 SNP (GG vs. TG/TT), neuroticism score, interaction between rs12565406 and neuroticism as well as various potential confounders as independent variables, introduced successively in the models.

Pearson Chi-square or Fisher’s exact test [Studies I, III, IV]
Pearson χ² test is used to discover whether there is a relationship between two categorical variables. Fisher’s exact test is a similar test, employed when sample sizes are small. These tests were applied wherever dichotomous variables were compared such as population characteristics, EPDS and neuroticism scores and genotypes.

Path analysis [Study IV]
Path analysis using structural equation modeling (SEM) was applied to examine the relationship among the independent and dependent variables in Study IV, based on a conceptual model constructed to investigate the potential mediatory role of neuroticism in the association between the rs12565406 SNP and postpartum depression (Figure 2, Results). Variables included in the model were selected based on their observed associations with neuroticism and EPDS scores in our material. Standardized path coefficients were calculated. To indicate the variance of the examined variables accounted for by the factors, squared multiple correlation coefficients (R²) were also calculated. As indicators of goodness-of-fit, standardized root mean square residual (SRMR), comparative fit index (CFI), Tucker-Lewis index (TLI) and root mean square error of approximation (RMSEA) were used.

Ethical approval and study consent
The Regional Ethical Review Board in Uppsala approved the study protocol (Dnr 2009/171). Written informed consent was obtained from all women participating in the study, after being informed about the course and aim of the study. The study was performed in accordance with the latest version of the Declaration of Helsinki.
Results

Study I

Significant depressive symptoms were reported by 8.5% (83/975) and 8.5% (80/936) of women at six weeks and six months after delivery, respectively. According to the DSRS, 4.9% (20/408) met the criteria for major depression at six months postpartum. The factor analysis confirmed the expected three-factor model in our population. The 13 traits were grouped into the personality factors neuroticism, aggressiveness and sensation-seeking (for details see Study I, Table 1). The only difference from the study by Gustavsson et al. [116] was that the trait “detachment” in our model was included in the neuroticism factor, and not in the sensation-seeking (extraversion) factor as in the original study.

Women with depressive symptoms at six weeks and six months postpartum had higher scores on neuroticism, while women with depressive symptoms at six months postpartum also had higher scores on aggressiveness (Mann-Whitney U-test derived p-value < 0.05).

Binary logistic regression models showed that high levels of neuroticism were associated with postpartum depressive symptoms at six weeks and six months, even after adjustment for possible confounders. On the personality trait level, a positive association between somatic and psychic trait anxiety and depressive symptoms at six weeks postpartum was noted, while mistrust was associated with depressive symptoms at six months postpartum, after adjustment for confounders (Table 1).
Table 1. Logistic regression derived Odds Ratios (OR) and 95% Confidence Intervals (CI) for self-reported depression (EPDS ≥ 12) in relation to personality factors and traits

<table>
<thead>
<tr>
<th></th>
<th>6 weeks postpartum</th>
<th>6 months postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroticism</td>
<td>5.0 (2.2-11.5)*</td>
<td>7.9 (3.1-20.0)*</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>0.8 (0.3-2.0)</td>
<td>0.6 (0.2-1.6)</td>
</tr>
<tr>
<td>Sensation Seeking</td>
<td>1.1 (0.5-2.7)</td>
<td>1.2 (0.4-3.0)</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroticism</td>
<td>3.4 (1.8-6.5)*</td>
<td>3.9 (1.9-7.9)*</td>
</tr>
<tr>
<td>Previous depression</td>
<td>1.8 (1.0-3.3)</td>
<td>1.9 (1.0-3.8)</td>
</tr>
<tr>
<td>Low education</td>
<td>0.8 (0.4-1.6)</td>
<td>0.3 (0.1-0.8)*</td>
</tr>
<tr>
<td>No breastfeeding</td>
<td>1.2 (0.4-3.4)</td>
<td>3.8 (1.9-7.8)*</td>
</tr>
<tr>
<td>Poor partner support</td>
<td>1.2 (0.7-2.2)</td>
<td>1.9 (1.0-3.7)</td>
</tr>
<tr>
<td>Poor sleep</td>
<td>2.2 (1.2-4.1)*</td>
<td>4.0 (2.1-7.7)*</td>
</tr>
<tr>
<td>Stressful life events</td>
<td>1.6 (0.8-2.9)</td>
<td>2.0 (1.0-4.2)</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychic trait anxiety</td>
<td>1.9 (1.1-3.1)*</td>
<td>not included*</td>
</tr>
<tr>
<td>Somatic trait anxiety</td>
<td>2.1 (1.2-3.5)*</td>
<td>not included*</td>
</tr>
<tr>
<td>Stress susceptibility</td>
<td>not included*</td>
<td>1.7 (1.0-2.9)</td>
</tr>
<tr>
<td>Mistrust</td>
<td>not included*</td>
<td>1.9 (1.1-3.4)*</td>
</tr>
<tr>
<td>Previous depression</td>
<td>1.6 (0.9-2.6)</td>
<td>1.9 (1.1-3.2)*</td>
</tr>
<tr>
<td>Low education</td>
<td>0.9 (0.5-1.6)</td>
<td>0.4 (0.2-0.9)*</td>
</tr>
<tr>
<td>No breastfeeding</td>
<td>1.5 (0.7-3.7)</td>
<td>2.7 (1.6-4.7)*</td>
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<tr>
<td>Poor partner support</td>
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<td>1.4 (0.9-2.4)</td>
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<tr>
<td>Poor sleep</td>
<td>2.0 (1.2-3.4)*</td>
<td>2.7 (1.6-4.4)*</td>
</tr>
<tr>
<td>Stressful life events</td>
<td>1.2 (0.8-2.1)</td>
<td>1.7 (1.0-3.0)*</td>
</tr>
</tbody>
</table>

*aPersonality factors dichotomized as the highest quartile vs the two lowest
bPersonality traits dichotomized as the highest quartile vs all others
cA backward stepwise logistic regression with all personality traits produced two different sets of significant personality traits to be included in the multivariate analyses, one for six weeks and one for six months postpartum

The analyses were repeated using the DSRS as outcome variable with very similar results. Finally, EPDS score (0-12) at gestational week 32 was introduced as a continuous variable in the models, with minimal alterations in the results.

**Study II**

At gestational week 36, 18.3% (49/268) of the study subjects reported significant depressive symptoms (EPDS ≥ 10). The respective prevalence at six weeks after delivery was 18.2% (33/181).
In the total sample, women with self-reported postpartum depressive symptoms had significantly higher evening cortisol both in gestational week 36 (median cortisol 4.3 nmol/L vs. 3.8 nmol/L), and postpartum (median cortisol 1.19 nmol/L vs. 0.89 nmol/L) (Mann-Whitney U-test derived \( p < 0.05 \)). These associations were significant even when using an EPDS cut-off of 12 points. However, the number of individuals with significant depressive symptoms postpartum was then reduced to 9.6% at gestational week 36 and 11.5% at six weeks postpartum.

Moreover, as illustrated in Figure 1 below, study participants with postpartum depressive symptoms had significantly higher postpartum median cortisol levels compared to both women with depressive symptoms prenatally and controls (Kruskal-Wallis derived \( p \)-values 0.019 and 0.004, respectively).

*Figure 1. Median evening salivary cortisol values in pregnancy week 36 and postpartum week 6 among healthy controls, women with self-reported depressive symptoms before and/or during pregnancy (but not postpartum) and women with self-reported depressive symptoms postpartum*

*Kruskal-Wallis test derived \( p \)-values \( p < 0.05 \)

^Not postpartum

For illustrative purposes, cases with cortisol > 8 nmol/L at pregnancy week 36 \( (N = 12) \) and postpartum week 6 \( (N = 5) \) are not shown in the figure
In late pregnancy, a similar association between depressive symptoms and cortisol levels in the three subgroups was initially observed. However, because the week of sample collection and the elapsed time between awakening and cortisol sampling in the evening had a significant association with cortisol levels in the univariate analyses in late pregnancy, an analysis of covariance (ANCOVA) model was performed to control for these variables. After adjustment, the association between depressive symptoms and cortisol levels in late pregnancy did not remain significant.

A logistic regression model with postpartum EPDS scores as the dependent variable and dichotomized postpartum cortisol as the independent variable showed a positive association between cortisol levels and depressive symptoms (Odds Ratio [OR] = 4.1; 95% CI 1.7 – 9.7). This association remained significant even after controlling for history of depression, use of tobacco, partner support, breastfeeding, stressful life events and sleep problems as possible confounders (adjusted OR = 4.5; 95% CI 1.5 – 14.1).

In the postpartum period, EPDS scores were significantly and positively correlated with salivary cortisol levels (Spearman’s r=0.166, p < 0.05). No significant correlation was observed between cortisol levels in pregnancy week 36 and EPDS scores in late pregnancy and postpartum.

Finally, a significant expected decrease in cortisol values from late pregnancy to postpartum was observed, within all three subgroups (Wilcoxon Signed Ranks Test, p-value < 0.001). However, neither the absolute nor the percentage decrease in cortisol levels was different between the three groups (after adjusting for the week of sample collection and for the elapsed time between awakening and cortisol sampling in the evening in late pregnancy, ANCOVA).

**Study III**

The CRH median value was 60 pg/ml (sample minimum 24.4 pg/ml, maximum 139 pg/ml). The proportion of women scoring 12 or more points on the EPDS at six weeks postpartum was 44/535 (8.2%). Log transformed CRH levels were significantly higher among women with 12 or more points on postpartum EPDS, compared to controls (mean log CRH 4.19 vs. 4.08, respectively, independent samples t-test derived p=0.033).

As illustrated in Table 2 below, a binary logistic regression model with dichotomized postpartum EPDS score as the dependent variable and log transformed CRH concentration as the independent variable showed a positive association between CRH levels in gestational week 17 and self-reported postpartum depressive symptoms. This association remained significant even after adjustment for confounders.
Table 2. Logistic regression derived Odds Ratios (OR) and 95% Confidence Intervals (CI) for self-reported exclusively postpartum depressive symptoms in relation to log transformed corticotropin-releasing hormone (CRH) levels

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>CRH (log)*</td>
<td>1.11 1.01 – 1.22</td>
<td>1.12 1.01 – 1.25</td>
<td>1.13 1.02 – 1.26</td>
</tr>
<tr>
<td>Age</td>
<td>1.07 0.99 – 1.14</td>
<td>1.07 0.99 – 1.15</td>
<td></td>
</tr>
<tr>
<td>History of depression</td>
<td>1.39 0.56 – 3.45</td>
<td>1.27 0.50 – 3.25</td>
<td></td>
</tr>
<tr>
<td>Coexisting medical conditions a</td>
<td>2.29 1.15 – 4.56</td>
<td>2.10 1.03 – 4.28</td>
<td></td>
</tr>
<tr>
<td>CRH sampling day</td>
<td>1.54 0.80 – 2.96</td>
<td>1.73 0.87 – 3.43</td>
<td></td>
</tr>
<tr>
<td>SSRI b</td>
<td>1.26 0.22 – 7.18</td>
<td>1.64 0.28 – 9.57</td>
<td></td>
</tr>
<tr>
<td>Sleep problems c</td>
<td>5.18 1.35 – 19.9</td>
<td>2.39 0.93 – 6.14</td>
<td></td>
</tr>
<tr>
<td>Stressful life events d</td>
<td>1.70 0.52 – 5.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=535 N=475 N=468

*per 0.1 unit increase in log CRH
aMigraine, hypertension, diabetes, thyroid dysfunction, allergy, irritable bowel syndrome, significant alcohol consumption or chronic pain (during pregnancy)
bSelective Serotonin Reuptake Inhibitors
cDifficulties in falling back to sleep after waking up in the night
dRefer to past 12 months. Cut-off 2/3 events
eExclusive or non-exclusive vs. none

In further sub-analyses, the exclusion of women with preterm birth and newborns small for gestational age as well as study subjects who used inhalation corticosteroids during pregnancy did not change the significant association between CRH levels and postpartum depressive symptoms. Furthermore, adjusting for body mass index and nicotine use during pregnancy did not alter the results.

Study IV

The single nucleotide polymorphism rs12565406 in the HSD11B1 gene was the SNP with a statistically significant association with postpartum depressive symptoms (after correction for multiple comparisons) in a larger sample (Comasco et al., manuscript) and was therefore chosen for the present study.

Out of 769 study participants with available genotypic data, 650 (84.5%) were homozygous for the major allele (GG), 7 (0.9%) were homozygous for the minor allele (TT), and 112 (14.6%) were heterozygous (TG), providing a minor allele frequency of 0.08, consistent with Hardy-Weinberg equilibrium.
Sixty-five women (8.6%) reported significant depressive symptoms at six weeks postpartum (EPDS ≥ 12).

Women who were homozygous for the major allele (GG) presented with higher postpartum EPDS score than T carriers (Mann-Whitney U-test, \( p=0.022 \)). Study subjects with EPDS ≥ 12 had higher scores on neuroticism compared to controls (Mann-Whitney U-test derived \( p<0.001 \)). Moreover, a positive association between high neuroticism score (dichotomized at median) and the GG genotype of the SNP (Pearson Chi-Square \( p<0.001 \)) was observed. No association was observed between the GG genotype and history of depression.

Table 3 presents the results of the linear regression models. An association was observed between the rs12565406 GG genotype and depressive symptoms. When neuroticism was introduced in the model, it was positively associated with EPDS whereas the association between the GG genotype and EPDS became borderline significant. Furthermore, results were not changed after adjusting for possible confounders. Finally, results were unaltered after the introduction of the interaction term between SNP and neuroticism in the model, with the interaction term itself not being associated to EPDS score (data not presented in the table).

Table 3. Linear regression derived standardized coefficients for the association between the genetic variant rs12565406, neuroticism and possible confounders and postpartum EPDS score (log transformed)

<table>
<thead>
<tr>
<th></th>
<th>( \beta )</th>
<th>( p )-value</th>
<th>( \beta )</th>
<th>( p )-value</th>
<th>( \beta )</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs12565406 (TG/TT vs. GG)</td>
<td>0.094</td>
<td>0.01</td>
<td>0.064</td>
<td>0.063</td>
<td>0.066</td>
<td>0.050</td>
</tr>
<tr>
<td>Neuroticism score</td>
<td>0.340</td>
<td>0.001</td>
<td>0.267</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression history(^2)</td>
<td>0.105</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stressful Life Events(^3)</td>
<td>0.065</td>
<td>0.058</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Breastfeeding(^4)</td>
<td>0.036</td>
<td>0.280</td>
<td></td>
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<tr>
<td>Poor sleep(^5)</td>
<td>0.219</td>
<td>0.001</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Smoking(^6)</td>
<td>-0.002</td>
<td>0.959</td>
<td></td>
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</table>

\(^1\)Standardized coefficients
\(^2\)Absence vs. presence of previous self-reported depressive episode
\(^3\)Reported at six weeks postpartum, referring to past 12 months. Cut-off 2/3 events
\(^4\)Exclusive or non-exclusive vs. none
\(^5\)Referring to six weeks postpartum, reported at the same time-point, > 6 hours/night vs. ≤ 6 hours/night
\(^6\)Pregnancy and/or postpartum
The path analysis revealed that neuroticism had a mediatory role in the association between the SNP and PPD (EPDS score) (Figures 2 and 3). The percentage of the variance ($R^2$) of EPDS and neuroticism explained by the model was 21% and 13%, respectively. The direct association between the SNP and EPDS score was borderline significant ($0.1 > p > 0.05$). A minor proportion of the neuroticism effect on EPDS was mediated by stressful life events and sleep. Moreover, 69% of the effect of the rs12565406 on PPD was direct and 31% was mediated by neuroticism. Goodness-of-fit indices indicated a good fit of data to the proposed model (SRMR < 0.08, CFI and TLI > 0.90, the lower bound of the 90% confidence intervals of RMSEA < 0.05).
Figure 2. Path diagram (conceptual model) illustrating the relationships among rs12565406, Edinburgh Postnatal Depression Scale (EPDS) scores (PPD) and related variables.

The rs12565406 was inserted in the model grouped as homozygous for the major allele vs. homozygous for the minor allele and heterozygous. Log transformed neuroticism and EPDS scores were used as continuous variables. Sleep hours (longest period of undisturbed sleep during night in hours) and stressful life events (number of events) were inserted as continuous variables. All other variables were introduced in the model as dichotomous variables (education: college/university vs. primary/high school degree, depression history: absence vs. presence of self-reported previous depressive episode, smoking in pregnancy and/or postpartum: no vs. yes, breastfeeding: exclusive or non-exclusive vs. none).
Figure 3. Path diagram (final model) illustrating the relationships and respective standardized path coefficients among rs12565406, Edinburgh Postnatal Depression Scale (EPDS) scores (PPD) and related variables.

Continuous arrows indicate significant associations ($p < 0.05$) and the intermittent arrow indicates a borderline significant association ($0.05 > p > 0.1$). Squared multiple correlation coefficients ($R^2$) are reported to demonstrate the percentage of the variance that is explained by the model for neuroticism, PPD (EPDS score), stressful life events, and sleep hours. Sleep hours indicate the longest period of undisturbed night sleep during the last weeks.
Discussion

Methodological considerations

Strengths of the studies

The studies included in this thesis have several strengths. All studies were based on the BASIC-project, which has a population-based design and provides availability of prospectively collected information on numerous background characteristics and possible confounding factors that have been obtained on an individual level. Thus, risk of recall bias is minimized. Additionally, an important strength is the sample size of the BASIC-project, being among the largest in this research field. In study I, personality was assessed before delivery and only individuals without depressive symptoms at the time of personality assessment were included in the analyses, to avoid bias due to a possible depressive state effect on personality assessment. In Study II, cortisol levels were assessed in different subgroups of depressed and non-depressed study subjects in pregnancy and postpartum, trying to elucidate HPA-axis function in more distinct groups. Study III assessed CRH levels at an early stage of gestation, which provides data on the risk of developing postpartum depressive symptoms several months before delivery. Moreover, the sample of this study was large compared to similar studies and especially those who assessed non-depressed pregnant women. Study IV is a novel study that attempts to incorporate genetic variants, neuroticism, postpartum depression and other factors in a path analytic model.

Design of studies – General considerations

Studies I, III and IV had a nested case-control design, since participants were primarily assessed on the basis of their outcome and cases and controls were selected from individuals within the same cohort (BASIC) that was followed prospectively, starting at pregnancy week 17. In general, a case-control study compares the characteristics of a group with a particular outcome to a group of individuals without the outcome, to examine whether any factors occurred more or less frequently between cases and controls. In nested case-control studies, the baseline data on exposure is collected before the onset of disease, which reduces the risk of recall bias and uncertainty regarding the temporal sequence between exposure and disease onset.
Study II had a combined nested case-control and cross-sectional design, since the exposure and the outcome were measured at the same point in time, but women with postpartum EPDS as outcome were also compared in terms of their cortisol levels in pregnancy. The repeated measurement of cortisol levels through pregnancy and the postpartum period might have been more informative since it would allow a more thorough cortisol monitoring and permit the identification of more precise cortisol secretion patterns in depressed and non-depressed pregnant and newly delivered women. However, for practical reasons and to avoid compromising participation rates and compliance, it was finally decided to sample women only twice throughout the study course. Additionally, the recruitment of more women would have provided us with a larger study sample and possibly had reduced possible type II error. In fact, the study was conducted during two different time periods (winter and summer) in an attempt to increase the study sample, after initially recruiting women between December 2011 and March 2012, but also to account for seasonality effect on depressive symptoms [193].

A single measurement of CRH levels was performed in study III. To increase our understanding of the HPA-axis function in postpartum depression, multiple blood samples during pregnancy would have allowed us to also analyze CRH trajectories. Nevertheless, this procedure would require extra hospital visits for the women, who were already contacted and sampled in various ways, multiple times during pregnancy. Thus, it would compromise the participation rate in the particular study.

In study IV, a path analytic model was constructed to explore the role of neuroticism and other population characteristics in the association between the studied SNP and postpartum depressive symptoms. However, this model did not embrace a substantial part of factors believed to contribute in PPD, such as hormonal measures, which is in line with the fact that approximately one fifth of the percentage of variance of PPD was explained by our model. Inclusion of CRH or cortisol levels would have added to our understanding of mechanisms underlying PPD. However, since this was not the primary goal of these studies, data on hormonal parameters was only available for a minority of women, not providing us with sufficient power to perform the analyses. Moreover, this study investigated one SNP out of 120 HPA-axis related common genetic variants that were examined in a larger study. A GWAS study would have been more comprehensive but for this approach a much larger sample size would have been necessary. Thus, study results should be interpreted with caution and await further confirmation through larger sample sizes since effect sizes for common genetic variants are typically small [158].

In general, one of the most common biases in case-control studies is recall bias. However, most of the self-reporting information gathered from women participating in the present studies regarded parameters closely related to pregnancy and the postpartum period. Therefore, recall bias cannot be considered as a significant source of bias in our studies. The same applies for
another common source of bias in this type of studies, namely observer bias, which should be considered as nearly non-existing, since instruments used to utilize the outcome were of self-assessment type.

Participation bias
The BASIC-project has a population-based design since nearly all pregnant women in Uppsala County at a given time point are being asked to participate. As described in the Materials and Methods section, non-Swedish speakers, women younger than 18 and those with severely pathologic pregnancies as well as protected identity have not been included in the studies. The overall participation rate in the BASIC-project is 22%. Moreover, pregnant women with a higher age, with higher education and primiparas are slightly over represented among study participants, compared to the general population. Indeed, most of these findings are in line with previous studies on non-participation [194]. In addition, by excluding women who cannot communicate in Swedish, the study sample contains more women born in Sweden, in comparison to the background population. It should be noted that the high educational level of study participants could be partly explained both by the under representation of women with foreign background in the sample and by the generally high educational level of the population within Uppsala County, compared to Sweden in general. Regarding depression scores, it was not feasible to perform an attrition analysis due to lack of relevant data for women not participating in the studies. However, according to previous research, non-participants have higher rates of depressive symptoms [194]. Assuming a similar pattern in our studies, theoretically, inclusion of these individuals would possibly have led to even more robust findings.

These observations should be taken into account in terms of generalizability of the study results, since socioeconomic status may be related to the study’s main outcome. As for the rest of BASIC’s exclusion criteria, they only concern isolated cases and cannot be considered as significant bias sources.

Measurement of outcome
The main outcome in all studies was the occurrence of self-reported depressive symptoms in pregnancy and postpartum. Assessment of this measure was performed with the EPDS, which is a self-reporting psychometric measure, and thus a certain degree of misclassification may occur. However, most probably, any misclassification of depressed and non-depressed subjects would have been non-differential. Considering that an association was established in all studies, a more correct classification of controls and cases would only have strengthened the observed associations. Undoubtedly, a structured psychiatric interview would have been more accurate but also more difficult
to conduct in a research setting, considering the large number of study participants. Indeed, this is a frequently observed limitation among studies in this field [45]. On the other hand, the EPDS scale is validated and widely used and has good sensitivity and specificity [180]. Additionally, in Study I, study results at six months postpartum were validated by the DSRS scale, which is a self-rating instrument based on the DSM-IV criteria for major depression and resembles a clinical psychiatric interview.

It should be mentioned that different EPDS cut-offs were used in the studies. However, as stated in the Materials and Methods section of this thesis, all thresholds used are common in research and/or clinical settings. In Study II, main study results were unaltered even when performing analyses with the 12-points cut-off. However, since this would reduce study power, a lower threshold was finally adopted.

Measurement of exposure

**Study I and IV**

In these studies, the exposure (SSP) and outcome (EPDS) measures were both psychometric measures retrieved from the same informants, which may have introduced a common method bias. Indeed, this type of bias is not uncommon in this research field. However, several procedural remedies were considered to eliminate the risk of bias. Firstly, a temporal separation of measurements was applied. The SSP scale was completed in pregnancy week 32 and EPDS was filled in approximately 14 weeks thereafter, which can be considered as an appropriate time lag. Moreover, psychological separation of measurements was also introduced. The personality questionnaire was completed in pregnancy, when life circumstances were substantially different from those six weeks after partus, at a time of significant life changes due to the arrival of an infant. Additionally, in Study I, the outcome measurement was obtained from two different sources, namely EPDS and DSRS, with the latter closely resembling a clinical psychiatric interview. The use of this scale did not alter study results. Finally, a statistical sensitivity analysis was performed, where the EPDS score of the non-depressed pregnant women was controlled for as a covariate in the models, without altering the results. To totally eliminate the bias risks mentioned above, and to confirm that the personality assessment was unaffected by the unique circumstances that pregnancy and childbirth pose, a personality assessment totally separated from pregnancy and the postpartum period would have been preferable, ideally performed before pregnancy and/or long after the postpartum period. However, for practical and administrative reasons, this was not feasible.

Regarding the risk of misclassification of the exposure, this should also be considered as small, since only women in the upper and lowest quartiles
of neuroticism scores were included in the models, after the exclusion of those with intermediate scores.

Study II
In Study II, evening salivary cortisol levels were measured between 20:00 and 22:00 hours. Different evening time-points have been used in previous studies with some authors setting the time frame for evening measurements at 12 hours after awakening and others sampling study subjects in various time points between 18:00 and 23:00 hours. In the present study, the time frame was chosen to ensure maximum compliance among the participants, taking into consideration the unique and demanding circumstances of the early postpartum period. The fluctuations of cortisol levels during this interval are expected to be small. Moreover, the number of hours from awakening to cortisol sampling was taken into account in the statistical analyses. Women were instructed to take the sample at a “regular” day of their week, in order to eliminate the risk of interference with potential stressful moments [195].

The measurement of cortisol in saliva was the hormone assay of choice due to its obvious practical advantages for the study subjects, compared with other methods of cortisol sampling. Collection of saliva is an easy, non-invasive process that can be performed in home settings. Salivary cortisol is a measure of the free cortisol level and cortisol is active only in the unbound state [196]. This is beneficial especially in pregnant subjects as altered concentrations of CBG may complicate the interpretation of total plasma cortisol during pregnancy [196].

The use of a self-sampling kit performed at home environment should be considered as a study limitation, since it restricted the ability to control for inconsistencies in the sampling procedure. Moreover, the provision of multiple cortisol samples at the same day was advocated [195], since multiple measurements would more precisely depict the HPA-axis activity. However, because multiple sampling and administration of samples in hospital environment would have severely compromised participation rates, single sampling during late pregnancy and postpartum at home was finally adopted in this study.

Study I
Neuroticism
The main finding of this study was a strong association observed between the personality factor neuroticism in non-depressed pregnant women and the occurrence of depressive symptoms at six weeks and six months after delivery, even after controlling for several confounding factors.
The role of neuroticism as a vulnerability factor for postpartum depression has been suggested in previous studies [128, 140, 141]. In our study, women who were depressed at the time of the personality assessment were excluded from further analyses. The reason for this exclusion was that, despite the fact that neuroticism is relatively stable and mostly unaffected by life events [113, 117, 197, 198], a concurrent depressive episode, at the time of personality assessment, might skew personality measurements [117]. Nevertheless, studies that did not take into account this effect, have also reported similar results [129, 130, 142].

It has been suggested by some authors that neuroticism may only reflect a sub-threshold episode of an underlying major affective disorder [199]. On the other hand, other studies consider neuroticism as an intermediate phenotype of depressive disorders [144]. In the present study, neuroticism was associated with depressive symptoms in the postpartum period after the exclusion of study subjects with high EPDS scores during pregnancy, and after adjusting for previous depression as well as depressive symptoms below the EPDS threshold used for screening purposes at the time of personality assessment. These findings suggest that neuroticism per se might contribute to the development of postpartum depressive symptoms, possibly through modulating vulnerability. Individuals with high neuroticism scores might be more vulnerable to stressors occurring in the unique circumstances of the postpartum period, such as lack of sleep and baby care. The non-significant results of other studies [200, 201] may depend on methodological issues, such as personality assessment tools and power issues as well as residual confounding in the complex association between personality and depressive symptoms.

Personality traits

Another finding of this study was that the personality traits somatic and psychic trait anxiety were positively associated to self-reported depressive symptoms at six weeks after delivery, while mistrust was associated with depressive symptoms six months after delivery, even after controlling for confounders.

The literature on the association of specific personality traits to postpartum depression is scarce. Psychic trait anxiety refers to characteristics such as worrying and lacking self-confidence and somatic trait anxiety includes characteristics such as restlessness and tension [116]. In the demanding early period after childbirth, women with these traits might feel overwhelmed and subsequently depressed. Suspiciousness and distrusting of people’s motives characterize individuals scoring high on mistrust. These women may be more suspicious when a diagnostic evaluation or treatment for postpartum depression is suggested to them, and thus their depressive symptoms may last longer [202]. In general, a significant amount of women with depressive symptoms lack the intention of seeking help in the obstetrical setting [203].
Moreover, many women identified through screening methods as cases of PPD eligible for interventions do not accept treatment [204]. One could hypothesize that these attitudes might, at least partly, depend on specific personality traits. However, further studies are needed to investigate this hypothesis.

Study II

According to the results of this study, women with depressive symptoms in the postpartum period present with a dysregulated HPA-axis activity, characterized by higher postpartum evening salivary cortisol levels, compared to healthy controls. This observation was unaltered even when women with postpartum depressive symptomatology were compared to women who experienced depressive symptoms before or during pregnancy but not after delivery.

The pathophysiology of depression in the peripartum period in terms of cortisol secretion patterns has been investigated by several studies and many authors suggest a central role for the HPA-axis. However, study results are often contradictory, possibly due to variations in methods and assessment time-point of cortisol and depressive symptoms. This particular study focused on evening cortisol assessment, due to the scarcity of previous studies on the association between this measure and depressive symptoms during pregnancy and postpartum.

Studies focusing on the postpartum period have suggested an abnormal function of the HPA-axis, with elevated levels of morning salivary cortisol and morning as well as afternoon serum cortisol levels among women with postpartum depressive symptoms, compared to healthy controls [77, 90, 91]. These findings point to a state of HPA-axis alteration that may increase the risk of depressive symptoms postpartum. However, it should be noted that substantial differences exist between these studies and the present work. Thus, findings should be interpreted with caution. Nevertheless, our main results seem to be supported by studies in non-pregnant subjects, which demonstrate that morning salivary cortisol may constitute a biomarker for depressive episodes occurring within the first years following cortisol assessment [205-208]. Notably, the results of some studies on the association between HPA-axis function and PPD point to the opposite direction, as authors report lower cortisol levels among depressed women postpartum [96-98].

In summary, these findings provide evidence that a dysregulated HPA-axis function, sometimes in different directions, can be an important part of the hormonal basis of PPD. As mentioned in the Introduction section of this thesis, depression during pregnancy and the postpartum period may have different pathophysiological mechanisms. With the present study, we attempted to examine hormonal profiles of more homogenous subgroups with 48
depressive symptoms in the peripartum period, in order to elucidate these partly contradictory results. Our findings demonstrate that women with depressive symptoms after delivery have a different cortisol pattern not only from healthy controls but also from women whose depressive symptoms do not extend into the postpartum period. A more precise characterization of cortisol secretion in different peripartum depression subtypes could possibly had been achieved if women were categorized in even more homogenous subgroups including healthy controls, women with exclusively prenatal depressive symptoms, women with de novo PPD and women with depression throughout pregnancy and the postpartum period. This strategy would have accounted for the different trajectories of peripartum depression, suggested by some studies [73]. However, a much larger sample size would have been needed.

The lack of difference in the decrease of cortisol levels, from late pregnancy to postpartum, between the three study subgroups in our study, suggests that elevated postpartum cortisol levels per se, and not the alteration in cortisol levels subsequent to the delivery of placenta, may have a role in postpartum depression. In fact, this pathophysiological pattern has been described in major depression among non-pregnant subjects, since authors have previously suggested a positive association between cortisol levels and major depression [209, 210].

Some studies, focusing on pregnancy, report higher cortisol levels in antenatal depression, a finding that we could not replicate [78, 79, 82]. Once more, substantial differences in gestational week of evaluation of depressive symptoms and cortisol measurement might explain the inconsistent findings. Moreover, cortisol levels exhibit a large inter-individual variation during pregnancy [84] which may also have contributed to this lack of significant findings in our results. In addition, the relatively small sample size of the study can also be considered as a possible explanation.

Study III

In this study, CRH levels of non-depressed pregnant women in gestational week 17 were higher among those who developed depressive symptoms postpartum, compared to healthy controls, even after controlling for several confounders and after performing the analyses in different subgroups of women.

Recent studies, performed in mid-gestation or late pregnancy in smaller sample sizes, have reported an association between high CRH levels [102, 103, 107] and depressive symptoms postpartum. Our results indicate an even earlier dysregulation of the HPA-axis, several weeks prior to the occurrence of postpartum depressive symptoms, and are consistent with the hypothesis that, after delivery, the HPA-axis of depressed women may be differentially temporarily suppressed due to an effect of high circulating levels of CRH
during late pregnancy on adrenal function [65, 69]. Indeed, an abnormal and prolonged elevation of CRH during pregnancy may result in greater residual hypothalamic suppression and HPA-axis hypoactivity in the postpartum period, which can predispose vulnerable individuals for depression with postpartum onset. This hypothesis is supported by experimental studies [65], which showed that the blunted ACTH response to the intravenous administration of ovine CRH in women in the postpartum period was more severe and long lasting in depressed subjects, as compared to euthymic. In the present study, the distinction between prenatal and postpartum depression was considered important since these depression subtypes may depend on different pathophysiological mechanisms. Thus, we excluded women with significant depressive symptoms during pregnancy in order to study a more homogeneous group of individuals with de novo postpartum depressive symptoms. This, as well as differences concerning the psychometric and hormonal assessment tools, might be responsible for the inability of other studies to detect an association between CRH and postpartum depressive symptoms [108, 109].

The present results are further strengthened by the fact that the observed association between CRH and depressive symptoms remained significant even after the exclusion of women with characteristics that could have influenced CRH levels, such as multiple pregnancies, preterm labor, women with newborns small for gestational age and use of corticosteroids. Finally, study results were not affected when adjusting for SSRI treatment. This is important, since women who were on SSRIs and in remission during pregnancy could theoretically have experienced a relapse postpartum, and thus have driven the association between CRH levels and postpartum depressive symptoms, due to the higher levels of CRH in women with SSRI treatment, as demonstrated in a recent study [110].

Study IV

The present study suggested a mediatory role of neuroticism in the association between the GG genotype of the single nucleotide polymorphism rs12565406 in the HSD11B1 gene and postpartum depressive symptoms.

Specifically, in the larger cohort (Comasco et al., manuscript), women homozygous for the G allele had higher risk of postpartum depressive symptoms, compared to carriers of the minor allele T, a finding replicated in the present study that only included approximately half of the larger study’s sample. Furthermore, our results show that the effect of this SNP on postpartum depressive symptoms was mediated by neuroticism.

The 11β-HSD1 enzyme catalyzes conversion of cortisone to cortisol. A previous study has reported an association between another SNP in the same gene, evening salivary cortisol levels and depression in non-pregnant individuals, suggesting that this gene may be implicated in HPA-axis regulation.
and depression susceptibility [211]. Furthermore, several studies [144, 171, 172, 212] have established the genetic basis of neuroticism. Specifically, common genetic variants explain 15% of the variance in neuroticism [172]. Additionally, neuroticism and depression have a shared genetic basis [172, 173] and neuroticism has been linked to hormonal alterations in the HPA-axis [150, 213, 214]. Thus, it seems plausible that HPA-axis related common variants might have a role in the shared genetic background between neuroticism and PPD, which would also be in line with the role of neuroticism as an intermediate phenotype of PPD.

On the other hand, since common genetic variants can only account for a small part of the disease phenotype, the potential involvement of other genetic factors such as rare genetic variants, repeat polymorphisms and indels as well as the role of environment and epigenetics should also be taken into account when assessing the genetic basis of neuroticism and depression [158, 166, 172, 215].

Significance of results in a general context and clinical implications

This thesis intended to investigate the implication of personality and the HPA-axis in the occurrence of depressive symptoms related to pregnancy and postpartum. Underlying mechanisms of depression related to childbirth remain to a great extend incompletely understood and the current screening tools of PPD have been proven, to a large extent, insufficient so far. Neuroticism is a personality factor that can be easily evaluated with self-assessment instruments and may be used in the future for the early identification of women at risk of depressive symptoms after childbirth, with beneficial effects on individual and societal level. Moreover, we believe that the studies included in this thesis substantially contribute to the understanding of the complex hormonal and genetic background of peripartum depression, which is an essential step towards early identification, intervention and hopefully improvement of disease outcomes. In particular, although cortisol and CRH secretion patterns during pregnancy have been discussed by previous studies, our results have elucidated some inconsistencies between previous reports and expanded our knowledge, by implementing large sample sizes and possibly more concise study design. The implication of genetic factors has gained increasing attention during the past few years but the literature focusing on PPD is still scarce. The development of a diagnostic test that would incorporate the factors addressed by this thesis, possibly along with others, is an interesting idea. Hopefully, more studies in the future will validate and expand our results, allowing us to come one step closer to early identification of women at risk of postpartum depression and the application of proper interventions that may benefit depressed women.
Conclusions

The results of this thesis demonstrate that neuroticism was a strong and independent predictive factor of depressive symptoms at six weeks and six months postpartum, concerning women without depressive symptoms during pregnancy. Moreover, the personality traits somatic and psychic trait anxiety were positively associated to self-reported depressive symptoms at six weeks after delivery, while mistrust was associated with depressive symptoms at six months postpartum.

Women with depressive symptoms in the postpartum period presented with a dysregulation in HPA-axis activity that was reflected in elevated evening salivary cortisol levels postpartum.

In non-depressed pregnant women, the development of postpartum depressive symptoms was associated with higher CRH levels in gestational week 17.

Neuroticism had a significant mediating role in the association between the rs12565406 in HSD11B1 gene and postpartum depression, taking into account other factors associated with neuroticism and postpartum depressive symptoms.
Future perspectives

Women’s mental health remains to date largely under researched. Depression is a disabling condition and over 12000 new mothers in Sweden are affected each year. The consequences on quality of life of these women and the societal costs of postpartum depression are large and directly comparable to those of common physical diseases. Despite the increasing knowledge and awareness concerning mental health problems in later years, many episodes of postpartum depression go undiagnosed and untreated, even in developed societies. Considering the complexity of depression associated to childbirth, large projects are required to perform rigorous investigations of the heterogeneity of this condition by identifying biomarkers and genetic factors that may be associated with its different trajectories and underlie the clinical manifestations of postpartum depression. These aspects, combined with psychological and other measures, will give us a further insight into the pathophysiological mechanisms of postpartum depression, increase our understanding of the condition, and facilitate the development of new screening strategies for the identification of women at risk. Associated single nucleotide polymorphisms arising from large genome-wide association studies, gene x protein approaches and proteomics as well as metabolomics patterns are only some of the features that could constitute the future of research in the field.
Introduktion

Peripartumdepression innefattar depressiva episoder som uppstår under graviditet eller de första 4 veckorna efter förlossningen. Upp till 50% av postpartumdepressioner (PPD) debuterar under graviditeten. PPD drabbar 10-15% av alla nyförlösta kvinnor, och är en vanlig orsak till morbiditet relaterad till graviditet och postpartumperioden. PPD kan innebära allvarliga konsekvenser för mamman och barnet, men även för kvinnans partner. I Sverige rekommenderar Socialstyrelsen att man screenar för PPD 6-8 veckor efter förlossningen. Vissa psykosociala och psykologiska insatser i slutet av graviditeten eller efter förlossningen kan minska risken för PPD. Det behövs således ytterligare forskning med fokus på utveckling av metoder som underlättar tidig upptäckt av kvinnor som har en ökad risk för PPD.

Flera riskfaktorer associerade med PPD har beskrivits i litteraturen. Meta-analytiska studier har klassificerat depression och ängest under graviditet, tidigare episoder av depression, neuroticism, svåra livshändelser under graviditet eller postpartum, bristande socialt stöd, låg självkänsla, dåligt partnersstöd och postpartum blues som starka riskfaktorer för PPD. Dessutom har ett antal biologiska faktorer blivit kopplade till förekomst av PPD, nämligen stress och tyreoideahormoner samt immunologiska och inflammatoriska parametrar. Därutöver har den genetiska komponenten i PPD studerats genom genetiska associationsstudier. Denna avhandling behandlar specifika psykologiska, hormonella och genetiska faktorer associerade till PPD.

Vissa studier har identifierat samband mellan neuroticism och depression bland gravida och nyförlösta kvinnor. Andra studier har undersökt en eventuell koppling mellan personlighet och ändrad aktivitet i hypotalamus-hypofys-binjure (HPA-) axeln. Neuroticism beskriver tendensen att erfara negativa känslor och har kopplats till flera psykopatologier, inklusive depression. Neuroticism har traditionellt varit en central del av personlighetsteorier med en väsentlig roll i nästan alla större modeller av personlighet. Personlighet kan definieras som de karakteristiska mönstren av tankar, känslor och beteenden som gör en person unik och förblir ganska oförändrade genom livet.

Fysiologiska endokrina förändringar som sker under graviditet förändrar profilen av flera hormoner, inklusive de som är relaterade till HPA-axeln,

Genetiska faktorer har också blivit studerade i relation till risk för PPD. Under de senaste åren har polymorfsmer (genetiska variationer) i några gener associerats till PPD. Många gener relaterade till HPA-axeln är dock fortfarande dåligt utforskade.

Syfte
Det övergripande syftet med avhandlingen var att undersöka psykologiska, hormonella och genetiska aspekter av PPD i ett stort, populationsbaserat urval av kvinnor i Uppsala, Sverige.

Metoder och Resultat

Delstudie I
Syftet med denna studie var att undersöka hypotesen att vissa personlighetsfaktorer och/eller personlighetsdrag (traits), undersökt hos icke-deprimerade kvinnor i slutet av graviditeten, kan påverka risken för att utveckla depression efter förlössningen. Kvinnor som rekryterades till denna studie fyllde i en webbaserad strukturerad enkät med sociodemografiska och graviditetsrelaterade frågor, samt EPDS, i graviditetsvecka 17 och 32 samt sex veckor och sex månader efter förlössningen. Sex månader postpartum fyllde kvinnorna även i Depression Self Rating Scale (DSRS), ett annat frågeformulär som liknar en psykiatrisk intervju om depresiva symptom. I graviditetsvecka 32 fick kvinnorna fylla i SSP. Kvinnor med depresiva symptom i graviditetsvecka 32 (EPDS ≥ 13 poäng) blev exkluderade från studien för att undvika påverkan av en eventuell samtidig depressiv episod.

**Delstudie II**


**Delstudie III**

Denna studies syfte var att undersöka, hos icke-deprimerade gravida kvinnor, ett eventuellt samband mellan CRH-nivåer i graviditetsvecka 17 och utveckling av depressiva symptom postpartum. En självdimensionerad strukturerad enkät med frågor om sociodemografisk och graviditetsrelaterad data samt EPDS besvarades i graviditetsvecka 17 och 32 samt sex veckor efter förlossningen. CRH-nivåer analyserades i maternellt blod i graviditetsvecka 17. Totalt antal kvinnor som ingick i studien var 535. Dataanalys visade att kvinnor med depressiva symptom postpartum (EPDS ≥ 12), vilka inte var deprimerade under graviditet (EPDS < 12), hade förhöjda CRH-nivåer i blodet redan från graviditetsvecka 17. Resultaten var oförändrade efter exklusion av kvinnor med förtidsbörd och de som födde barn som var små för tiden samt kvinnor som använde kortikosteroide under graviditeten. En påtaglig och långvarig förhöjning av CRH under graviditeten kan leda till mer avsevärd dämpning av hypotalamus som kvarstår längre efter förlossningen och resulterar i postpartumhypoaktivitet av HPA-axel, vilket i sin tur kan predispone dessa personer för PPD.
**Delstudie IV**

Målet med denna studie var att undersöka en möjlig medande roll av neuroticism i associationen mellan en polymorfism (rs12565406) i hydroxysteroid (11-beta) dehydrogenas 1-genen och PPD. Självadministrerade strukturerade enkäter innehållande EPDS (sex veckor postpartum) och frågor om socio-demografiska och graviditetsrelaterade variabler (graviditetsvecka 17 och 32 samt sex veckor postpartum) samt SSP (graviditetsvecka 32) skickades till alla deltagare i studien. Dessutom togs blodprover för genetiska analyser någon gång mellan graviditetsvecka 17 och 8 veckor efter förlossningen. Totalt ingick i denna studie 771 kvinnor. Resultaten visade att det fanns ett samband mellan polymorfismen, neuroticism och depressiva symptom postpartum, och att neuroticism hade en signifikant medande roll i associationen mellan polymorfismen och depressiva symptom postpartum. Med dessa resultat har studien bidragit till kartläggning av den komplexa genetiska och delvis gemensamma bakgrunden av neuroticism och PPD.

**Slutsatser**

Neuroticism är en personlighetsfaktor som lätt kan utvärderas med självskattningsinstrument och användas i framtiden för att tidigt identifiera kvinnor som löper risk för PPD. Dessutom anser vi att studierna har bidragit till förståelsen av den komplexa hormonella och genetiska bakgrunden av peripartumdepression.
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References

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Appendix

Edinburgh Postnatal Depression Scale (EPDS, Swedish version)

Table 4. Example of the EPDS instrument used for depressive symptoms assessment in all studies

<table>
<thead>
<tr>
<th>EPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Var snäll och kryssa för det svar som bäst stämmer med hur Du känt Dig under de senaste 7 dagarna, inte bara hur Du mår idag. Här är ett exempel som redan är ifyllt:</td>
</tr>
<tr>
<td>☐ ja, hela tiden</td>
</tr>
<tr>
<td>☐ nej, inte särskilt ofta</td>
</tr>
</tbody>
</table>

Detta betyder: Jag har känt mig lycklig för det mesta under veckan som gått. Fyll i de andra frågorna på samma sätt!

Under de senaste 7 dagarna:

1. Jag har kunnat skratta och se tillvaron från den ljusa sidan...
   ☐ lika bra som vanligt
   ☐ nästan lika bra som vanligt
   ☐ mycket mindre än vanligt
   ☐ inte alls

2. Jag har glatt mig åt saker som ska hända ...
   ☐ lika mycket som vanligt
   ☐ något mindre än vanligt
   ☐ mycket mindre än vanligt
   ☐ inte alls

3. Jag har lagt skulden på mig själv onödigt mycket när något gått snett...
   ☐ ja, för det mesta
   ☐ ja, ibland
   ☐ inte så ofta
   ☐ nej, aldrig
4. Jag har känt mig rädd och orolig utan egentlig anledning
   □ nej, inte alls
   □ knappast alls
   □ ja, ibland
   □ ja, mycket ofta

5. Jag har känt mig skrämd eller panikslagen utan speciell anledning
   □ ja, mycket ofta
   □ ja, ibland
   □ nej, ganska sällan
   □ nej, inte alls

6. Det har kört ihop sig för mig och blivit för mycket
   □ ja, mesta tiden har jag inte kunnat ta itu med något alls
   □ ja, ibland har jag inte kunnat ta itu med saker lika bra som vanligt
   □ nej, för det mesta har jag kunnat ta itu med saker ganska bra
   □ nej, jag har kunnat ta itu med saker precis som vanligt

7. Jag har känt mig så olycklig att jag har haft svårt att sova
   □ ja, för det mesta
   □ ja, ibland
   □ nej, sällan
   □ nej, aldrig

8. Jag har känt mig leden och nere
   □ ja, för det mesta
   □ ja, rätt ofta
   □ nej, sällan
   □ nej, aldrig

9. Jag har känt mig så olycklig att jag gråtit
   □ ja, nästan jämt
   □ ja, ganska ofta
   □ bara någon gång
   □ aldrig

10. Tankar på att göra mig själv illa har förekommit
    □ ja, rätt ofta
    □ ja, då och då
    □ knappast alls
    □ aldrig
Table 5. Example of the SSP instrument used for personality assessment in studies I and IV

**SSP – The Swedish universities Scale of Personality**

<table>
<thead>
<tr>
<th>Påstående</th>
<th>Svarsalternativ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ganska ofta kommer jag på mig med att helt utan anledning bita ihop käkarna.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>2 Jag har ganska dåligt själförtroende.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>3 Jag har alltför lätt att bli trött och jäktad.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>4 Om jag blir illa behandlad på en restaurang, har jag svårt att säga ifrån.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>5 Jag brukar handla på ögonblickets ingivelse, utan att tänka mig för så noga.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>6 Jag är alltid pigg på att pröva på nyheter.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>7 Jag har lätt för att komma människor nära inpå livet.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>8 Jag är alltid lika artig och behärskad vem jag än pratar med.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>9 Jag har haft det ganska besvärligt här i livet.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>10 Ibland blir jag irriterad bara av att ha folk omkring mig.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>11 När någon är särskilt snäll mot mig blir jag misstänksam.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>12 Jag råkar lätt i gräl med folk som har en annan åsikt än jag.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>13 Den som förolämpar mig eller mina närmaste, kan räkna med bråk.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>14 Jag känner mig ofta rastlös, som om jag ville något utan att veta vad.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>15 Jag hör nog till den sortens människor som är överdrivet känsliga och tar åt mig för det minsta.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>16 Jag kan klara av att bli störd när jag håller på med ett arbete.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>17 Även om jag vet att jag har rätt i en sak har jag ofta mycket svårt att stå på mig.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>18 Jag blir ofta så entusiastisk över nya idéer och förslag att jag glömmer att ta reda på om det finns några nackdelar.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>19 Jag föredrar människor som gör spännande och oväntade saker.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>20 Jag undviker människor som är intresserade av mina personliga förhållanden.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>21 Jag lyssnar alltid lika intresserat, oavsett vem jag pratar med.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>22 Jag tycks aldrig kunna undvika att råka i trassel.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>23 Jag har lätt för att reta upp mig på folk.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>24 Jag brukar vara på min vakt mot sådana som är vänligare än jag väntat mig.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>25 Om någon ryter åt mig, ryter jag tillbaka.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>26 Om jag ertappade någon som stal från mig, skulle jag inte tveka att ta till våld.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>27 Jag känner mig ofta stel och spänd i kroppen.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>28 Jag vågar sällan yttra mig i en diskussion, därför att jag tror att andra tycker mina åsikter inte är värda någonting.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>29 För att få något gjort måste jag förbruka mer krafter än de flesta.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>30 När någon tränger sig före mig i en kö, brukar jag säga ifrån.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>31 Det händer ofta att jag lite förhastat ger mig in på saker.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>32 Jag har nog ett ovanligt stort behov av omväxling.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>33 Jag känner mig besvär för att komma till mig med personliga förtroenden.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>34 Jag ställer alltid upp när någon behöver min hjälp.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>35 Jag har ofta råkat illa ut, trots att det inte varit mitt fel.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>36 Jag blir lätt otålig.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
<tr>
<td>37 Jag tror inte att folk säger hela sanningen till mig.</td>
<td>Stämmer inte alls, stämmer inte särskilt bra, stämmer ganska bra, stämmer precis.</td>
</tr>
</tbody>
</table>
38 Jag har aldrig med flit sagt något för att såra någon.
39 Jag ger alltid igen om någon slår mig.
40 Ibland dunkar hjärta hårt eller slår oregelbundet utan påtaglig anledning.
41 Det tar nog ovanligt lång tid för mig att komma över obehagliga upplevelser.
42 Jag brukar kunna koncentrera mig även om omgivningen är störande.
43 Jag tycker det är obehagligt att säga till om jag fått för lite växel tillbaka.
44 Jag är en person som tar dagen som den kommer.
45 Jag söker mig gärna till ställen där det händer spännande saker.
46 Jag trivs bäst med att hålla människor på ett visst avstånd.
47 Jag har aldrig något emot att man ber mig om en tjänst.
48 Det ser ut som om jag aldrig skulle få någon chans att komma någonstans här i livet.
49 Jag har inte så mycket tålamod.
50 Det är svårt för mig att lita på andra.
51 Jag kan inte låta bli att vara lite snorkig mot folk jag inte tycker om.
52 Jag skulle inte tveka att ta till våld för att försvara mina rättigheter.
53 Jag kan plötsligt börja svettas utan särskild anledning.
54 Jag känner mig ofta osäker när jag träffar folk som jag inte känner så väl.
55 Jag blir lätt stressad när jag uppmanas att skynda på med ett arbete.
56 När någon retas med mig, kommer jag aldrig på något bra svar förrän efteråt.
57 Jag brukar "tala först och tänka sedan".
58 Jag har nästan alltid behov av mera liv och rörelse.
59 Jag föredrar att slippa engagera mig i andra människors problem.
60 Om jag gjort ett misstag så är jag alltid villig att medge det.
61 Jag tycks oftare än andra göra saker som jag sedan får ångra.
62 Jag känner mig ofta otålig när jag måste ställa in i kö.
63 Jag litar inte på att folk i allmänhet talar sanning.
64 När jag blir arg, yttrar jag mig ofta ironiskt eller sarkastiskt.
65 Om någon slår mig, slår jag tillbaka.
66 Jag rycker till häftigt för oväntade ljud.
67 Jag brukar ofta gå och oroa mig även för sådant som andra uppfattar som bagateller.
68 Jag känner mig lugn och säker även om jag ställs inför nya uppgifter.
69 Jag önskar ibland att jag kunde säga rent ut när jag tycker illa om något.
70 När jag ska bestämma mig går det i allmänhet kvickt.
71 Ibland tycker jag om att göra saker bara för spänningskraft.
72 Jag är nog snarare reservad och lite kylig än hjärtlig och varm.
73 Jag är alltid artig även mot otrevliga personer.
74 Det har hänt att jag avundats folk som har haft tur här i livet.
75 Jag blir irriderad av att vänta på omständliga människor.
76 Jag försöker vara på min vakt för att undvika att folk ska utnyttja mig.
77 Om någon kritiserar mig drar jag mig inte för att komma med vassa och spydiga svar.
78 Det händer att jag blir så arg att människor i min omgivning tror att jag ska börja slåss.
79 Ibland får jag en känsla av att inte få tillräckligt med luft för att kunna andas.
80 Jag blir ångslig långt i förväg när jag ska sätta igång med något.
81 Jag tycker att jag orkar mindre än de flesta i min bekantskapskrets.
82 Jag har svårt att hävda mina åsikter.
83 Jag anser mig vara impulsiv.
84 Rörelse, resor, förändring, spänning - det är ett liv för mig.
85 Människor brukar ofta komma till mig med sina bekymmer.
86 Det har hänt att jag tagit till en lögn för att slippa ifrån något jag inte velat göra.
87 Jag känner det ofta som om jag gjort något illa eller orätt.
88 Jag blir ofta irriterad när jag försenas på grund av andras misstag.
89 Jag får ofta en känsla av att vissa människor försöker undvika mig.
90 Jag är bra på att komma med spydiga kommentarer.
91 Om man blir illa behandlad av någon tycker jag att man ska ge igen.
Literature Review of studies on CRH and Peripartum Depression

Table 6. Summary of studies assessing the relationship between corticotropin-releasing hormone and peripartum depressive symptoms

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>AGE (years)</th>
<th>HORMONAL ASSESSMENT TIME</th>
<th>MOOD MEASURE METHOD &amp; TIME</th>
<th>GROUPS</th>
<th>MODALITY-TECHNIQUE</th>
<th>MAIN FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannerfors et al., 2015 [110]</td>
<td>872</td>
<td>30.4</td>
<td>gw18</td>
<td>EPDS (gw17 + 32)</td>
<td>609 HC 609 DEP 207 SSRI</td>
<td>Blood CRH Radioimmunoassay</td>
<td>SSRI group: higher CRH than HC and DEP</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Mean Age</td>
<td>GW (Age)</td>
<td>Clinical Assessment(s)</td>
<td>Blood CRH Assay</td>
<td>Methodology</td>
<td>Findings</td>
</tr>
<tr>
<td>----------------------------</td>
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<td>------------------------</td>
<td>-----------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Hahn-Holbrook et al., 2013</td>
<td>210</td>
<td>28.5</td>
<td>gw 19 + 29 + 37</td>
<td>BDI (gw 29 + ppw8) 39 mild DEP 5 moderate/severe DEP 166 HC</td>
<td>Blood CRH</td>
<td>Radioimmunoassay</td>
<td>PND &amp; pCRH: n.s. Depressive symptoms pp associated with greater increase in pCRH from gw29 to gw37 and higher pCRH in gw37</td>
</tr>
<tr>
<td>Meltzer-Brody et al., 2011</td>
<td>484/391</td>
<td>N/A</td>
<td>gw &lt; 20 + 24-29</td>
<td>CES-D (gw&lt;20 + 24-29) + EPDS (ppw12 + ppm12) 894 HC 284 early pregnancy moderate/severe DEP; 812 HC 268 late pregnancy moderate/severe DEP; 447 HC 37 PPD</td>
<td>Blood CRH (mostly morning samples) Competitive enzyme immunoassay</td>
<td>Pregnancy (gw24-29): negative association between CRH and moderate/severe CES-D score (diminished after adjustment). Higher mid-pregnancy pCRH not associated with PND or PPD</td>
<td></td>
</tr>
<tr>
<td>O'Keane et al., 2011a</td>
<td>65</td>
<td>32.8</td>
<td>gw25 + 36</td>
<td>SCID (inclusion) + HAM-D, EPDS, BDI, BPRS (gw25 + 36) 38 HC 27 DEP</td>
<td>Blood CRH between 1100h and 1500h Radioimmunoassay</td>
<td>PND gw25: positive association with CRH gw25</td>
<td></td>
</tr>
<tr>
<td>O'Keane et al., 2011b</td>
<td>70</td>
<td>33.1</td>
<td>gw 36 + ppd1-6 x 3 days (ppd1 + 3 + 5 or ppd2 + 4 + 6)</td>
<td>SCID + EPDS (gw36) + Blues Questionnaire (postpartum) N/A</td>
<td>Blood CRH between 1100h and 1500h Radioimmunoassay</td>
<td>Positive association between CRH changes before and after partus and Blues scores.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Mean Age</td>
<td>Gestation Period</td>
<td>Depression Measure</td>
<td>CRH Measure</td>
<td>pCRH Measure</td>
<td>Findings</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>----</td>
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<td>------------------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Latendresse and Ruiz, 2010 [217]</td>
<td>85</td>
<td>N/A</td>
<td>gw14-20</td>
<td>CES-D (gw14-20)</td>
<td>Low CRH</td>
<td>Blood pCRH, Radioimmunoassay</td>
<td>No difference in CES-D scores between low and high CRH groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High CRH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(cut-off 15pg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yim et al., 2009 [103]</td>
<td>100</td>
<td>31.2</td>
<td>gw15 + 19 +</td>
<td>CES-D (gw19 +</td>
<td>84 HC</td>
<td>Blood pCRH, Radioimmunoassay</td>
<td>Positive association between pCRH gw25 and EPDS ≥10 pp</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 + 31 + 37</td>
<td>25 + 31 + 37 EPDS (ppw8.7)</td>
<td>16 PPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rich-Edwards et al., 2008 [109]</td>
<td>800</td>
<td>N/A</td>
<td>gw26-28</td>
<td>EPDS (mid-pregnancy + ppm6)</td>
<td>730 HC (pregnancy)</td>
<td>Plasma CRH, Radioimmunoassay</td>
<td>PND: positive association between CRH and EPDS in mid-pregnancy but not postpartum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70 PND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>570 HC (pp)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46 PPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmeelk et al., 1999 [218]</td>
<td>58</td>
<td>17.3</td>
<td>gw9-21</td>
<td>DISC (time of mood measure not specified)</td>
<td>N/A</td>
<td>Morning blood CRH (between 0830h and 0900h) Radioimmunoassay</td>
<td>PND: negative association with CRH</td>
</tr>
<tr>
<td>Susman et al., 1999 [86]</td>
<td>59</td>
<td>17.3</td>
<td>gw9-21</td>
<td>DISC (gw9-21 + gw32-34 + ppw4-5)</td>
<td>N/A</td>
<td>Morning plasma CRH (0830h) Radioimmunoassay</td>
<td>CRH gw9-21: negative association with depression in late pregnancy (gw32-34)</td>
</tr>
<tr>
<td>Smith et al., 1990 [89]</td>
<td>97</td>
<td>26.2</td>
<td>gw28 + gw38 + ppd2 + 3 samples during labor</td>
<td>POMS + MADRS (gw28 + gw38 + ppd2 + ppm3)</td>
<td>36 mood deterioration</td>
<td>CRH blood samples (non-labor samples collected between 0800h and 1000h)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

BDI: Beck Depression Inventory; BPRS: Brief Psychiatric Rating Scale; CES-D: Center for Epidemiological Studies Depression Scale; CRH: Corticotropin-Releasing Hormone; DEP: depressed state; DISC: Diagnostic Interview Schedule for Children; gw: gestational week; EPDS: Edinburgh Postnatal Depression Scale; HAM-D: Hamilton Rating Scale for Depression; HC: healthy controls; MADRS: Montgomery-Åsberg Depression Rating Scale; N/A: not available; n.s.: non significant; pCRH: placental Corticotropin-Releasing Hormone; PND: prenatal depression; POMS: Profile of Mood States-Depression; pp: postpartum; ppd: postpartum day; PPD: postpartum depression; ppm: postpartum month; ppw: postpartum week; SCID: Scheduled Clinical Interview for DSM-IV Axis I Disorders; SSRI: Selective Serotonin Reuptake Inhibitor
Overview of studies

Figure 4. Illustration of the design of studies included in the thesis (DEMO = Demographic data, C1 = Cortisol 1, C2 = Cortisol 2, variables marked as blue indicate main exposure while variables marked as red indicate main outcome in each study)
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