Emerging Genetic and Environmental Risk Factors for Prenatal and Postnatal Depression

Kristin Samuelsen

Master Thesis
(Cand. Psychol.)
Department of Psychology

UNIVERSITY OF OSLO

Autumn 2019

Emerging Genetic and Environmental Risk Factors for Prenatal and Postnatal Depression

2019

Emerging Genetic and Environmental Risk Factors for Prenatal and Postnatal Depression

Kristin Samuelsen

http://www.duo.uio.no/

Print: Reprosentralen, Universitetet i Oslo

Abstract

Author: Kristin Samuelsen. **Title:** Emerging Genetic and Environmental Risk Factors for Prenatal and Postnatal Depression. **Supervisors:** Main supervisor Eivind Ystrøm, and co-supervisors Line C. Gjerde and Espen M. Eilertsen. **Background:** Many women experience depression both during pregnancy (prenatal) and following delivery (postnatal). Although there is some literature on risk factors, there is a lack of studies investigating heritability. Thus, it is largely unknown to what extent genetic and environmental factors contribute to depression at these time points, as well as whether they are similar across timing. Research on these questions may yield important insights into whether depression prior to and following childbirth is the same, similar or distinct constructs. **Research aims:** 1) Estimate the relative importance of genetic and environmental factors for depression during and after pregnancy, and 2) Estimate the genetic and environmental correlation between depression during and after pregnancy, i.e. estimate the extent of genetic innovation. **Sample:** The sample used in this study is a subsample of the prospective, ongoing pregnancy cohort study Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health (N = 64 monozygotic (MZ) twin pairs, 35 dizygotic (DZ) twin pairs, 5540 full sibling (FS) pairs, and 400 half siblings (HS) pairs. **Research design:** A quantitative, extended twin study design, including siblings was applied. **Methods:** Measurement was conducted at week 30 of pregnancy and 6 months following delivery, using SCL-8, an abbreviated version of SCL-90. Univariate and bivariate twin modeling was conducted. **Results:** The relative importance of genes and environment for prenatal depressive symptoms was estimated at 16.2%, and 83.8%, respectively, and at 25.7% and 74.3% postnatally. Estimated correlation between pre and postnatal depressive symptoms was at 1.00 for genetic effects, and .36 for environmental effects. The unstandardized genetic effects for postnatal depressive symptoms were 172% of that of prenatal depressive symptoms, showing a quantitative, but a lack of a qualitative, gene-environment interaction (GxE). That is, the same genetic factors had a stronger impact postnatally. **Conclusions:** The findings indicate that the most important risk factors for pre and postnatal depression are environmental in their nature, yet they appear to be different dependent on the timing. The same genetic factors appear to influence depression at both time points, but to a stronger degree postnatally. This implicates that prevention efforts to depression occurring at this time should be predominantly aimed at reducing environmental stressors of depression specific to each timing.

Preface

There are several people I am grateful to for making the writing and completion of this thesis possible.

The opportunity to write my thesis on MoBa/IToR data was made available to me in the autumn of 2016, when I was hired as a research assistant. I helped out in collecting data, by conducting phone interviews with twins who participated in the study. It feel privileged to have had the opportunity to experience being a part of a research process from data gathering to actual findings. In this regard, I am grateful to FHI for giving me access to the data this thesis is based on, and for all the people I've met there, who gave me a warm welcome. I would also like to thank the participants of MoBa, in particular the twins and siblings contributing to this study. You make a highly appreciated contribution to important research.

Thank you to my wonderful supervisors, Eivind Ystrøm, Line C. Gjerde and Espen M. Eilertsen. All of you have been exceptionally generous with your time, being patient and available when I needed it, long past regular office hours. I appreciate that you all have taken an interest in my work, providing me with complementary and always supportive feedback.

Eivind, a great thanks to you for envisioning the project from beginning to end, and for providing exciting and creative ideas.

Line, a great thanks to you for giving exceptionally thorough, precise and supportive feedback, and answering a multitude of questions.

Espen, the R whisperer, a great thanks to you for helping me with methodological issues and conducting analyses, I definitely could not have done it without you.

At last, a great thanks to my dear family and friends. Thank you for cheering me on and always having faith in me and this project. Some of you have contributed to the work directly by proofreading and giving feedback, all of you have helped indirectly by supporting me, and filled breaks from the work with your exquisite company. Especially thanks to my closest friends from PSI, you are simply the best.

Now I am looking forward to finishing 6 years at University, and continue being curious in future work as a psychologist, and hopefully also in research.

Kristin Samuelsen, October 2019

Oslo

Table of Contents

List of Tables and Figures

1 Introduction

Giving birth is considered a major life event for most women, and it is usually associated with joy. However, many women experience depression or depressive symptoms during pregnancy, or subsequent to giving birth. Pregnancy and delivery are associated with major physical changes, in addition to life changes (Rallis, Skouteris, McCabe, & Milgrom, 2014). Hence, separating symptoms of mental illness from natural consequences of pregnancy, delivery and becoming a mother, may be a difficult task. Depression is a disorder creating personal suffering for the affected mother, as well as constituting a risk for the development and well-being of a newborn (Goodman et al., 2011). It may also affect other family members in a negative manner, such as older children in the family or a significant other.

One way of investigating why people vary on certain behaviors or symptoms, such as depressive symptoms, is to look at contributions from genetic and environmental factors. There is now consensus on the field of psychology on the former controversy regarding the role of genetic and environmental factors in the development of mental disorders and various behavioral traits, known as the *nature-nurture controversy* (Plomin, DeFries, Knopik, & Neiderhiser, 2013). The current view is that genetic and environmental factors both contribute to individual differences in observed traits and illness. Twin studies constitute one way of investigating these factors, due to the unique characteristics of this methodology. A commonly used term is *heritability,* which refers to an estimate of how much of the variation in a trait, such as a specific mental illness, is accounted for by genetic factors (Plomin et al., 2013). This is discussed in further detail under section 3.3.1. Heritability estimates exist for all common mental disorders (Polderman et al., 2015). As all estimates for a given population, heritability estimates vary across samples. The heritability of major depressive disorder has been estimated at 37% in a meta study (Sullivan, Neale, & Kendler, 2000).

There are conflicting views on whether depression occurring during and following pregnancy constitute the same, or distinct, phenomena (O'Hara & Wisner, 2014). Additionally, there are conflicting views on whether depression occurring in a period of time related to childbirth is similar to or distinct from depression occurring at other times (Viktorin et al., 2016). Some hold that these episodes of depression represent distinct disorders, at least partially, as they argue that the major endocrinal, i.e. hormonal, changes related to this specific period play a causal role. Others, on the other hand, hold that depression occurring at these specific time points merely reflects an episode of depression, which is similar to episodes occurring at any other time. Arriving closer to an answer regarding whether mental

disorders represent the same construct may be done by investigating whether they are similar in prevalence, symptom presentation, course, response to treatment, as well as whether they share risk or causal factors (O'Hara & Wisner, 2014). The latter approach, namely, studying their etiology, is the approach utilized in the current study.

In contrast to major depressive disorder in general, a limited amount of research has been conducted on genetic and environmental factors contributing to depression occurring during or following pregnancy, resulting in a lack of knowledge on their relative importance. Hence, the heritability of depression occurring during these specific time periods, as well as potential overlap between these factors, is uncertain. In a long-term perspective, increased knowledge regarding these questions may have important implications for the prevention, detection and treatment of depression occurring in this specific period.

2 Depression

2.1 Conceptual Clarification

A depressive episode may occur at any time over the course of a life, also during or following pregnancy (Kessler, 2003). There are several terms used to specify the timing of the depressive episode, and how they are used vary considerably among studies. *Perinatal*, as well as *neonatal* and *peripartum*, usually refers to the period of gestation and the months, up to the first year, following delivery. The time frames applied also vary considerably among studies. *Prenatal*, *antenatal*, and *prepartum* refers solely to during pregnancy. *Postnatal* and *postpartum* refers solely to after delivery. The terms used in this thesis are *prenatal* depression and *postnatal* depression. Throughout this thesis, depression occurring during the gestation period and the first year postpartum will be collectively referred to as *perinatal* depression, and depression occurring outside of this period will be referred to as *non-perinatal* depression. This is not a scientific or diagnostic distinction, rather a distinction used in order to help separate the depressive episodes, based on the timing of their occurrence.

Both perinatal and non-perinatal depression may occur as part of a bipolar disorder, and/or with psychotic symptoms, however, the focus of the current study is unipolar depression, without occurrence of psychotic symptoms. Furthermore, the focus of this study is depression occurring in relation to pregnancy and delivery. As noted, there is some controversy on the field, as to whether prenatal and postnatal depression, as well as perinatal and non-perinatal depression are one, similar or distinct phenomena (Di Florio & Meltzer-Brody, 2015; O'Hara & Wisner, 2014; Viktorin et al., 2016), as will be discussed in further

detail shortly. Hence, a brief introduction on major depression in general, e.g. non-perinatal depression, is warranted.

2.2 Major Depressive Disorder

2.2.1 Definition and Prevalence

Depression is a common, but potentially severe, type of mood disorder (Feliciano & Renn, 2014). There are several depressive disorders. *Major depressive disorder* (MDD), or simply *major depression* (MD) is widely studied, and are by many considered to have the largest societal impact (Feliciano & Renn, 2014). Depression is also the most studied mental disorder in relation to pregnancy (L. M. Howard et al., 2014) and will therefore be the focus of this thesis. MDD is characterized by the occurrence of at least one *major depressive episode* (MDE), and no history of mania (Feliciano & Renn, 2014). It may occur alone, or in comorbidity with one or several other mental or somatic illnesses. Recurrence is highly common (Feliciano & Renn, 2014). It is usually characterized as mild, moderate or severe, on the basis of its severity (American Psychiatric Association, APA, 2013; Feliciano & Renn, 2014; World Health Organization, WHO, 1992). Severity and duration vary among the affected individuals. The central aspects are the occurrence of low mood or sadness, loss of energy and loss of interest in activities previously considered enjoyable, over a period of at least 2 weeks (American Psychiatric Association, APA, 2013; Feliciano & Renn, 2014; World Health Organization, WHO, 1992). Additionally, it often includes anhedonia, changes in sleep and appetite, agitation or slowing, and feelings of guilt and worthlessness. It is often accompanied by a characteristic cognitive style, which includes pessimism and negative thinking, difficulty with problem-solving, and a lack of initiative. It is also associated with self-harm and suicidal ideation and behavior (Feliciano & Renn, 2014).

MDD are among the most common mental disorders, prevalent among most age groups (Bromet et al., 2011; Feliciano & Renn, 2014; Kessler et al., 2005). Prevalence rates vary across the time frames used to measure them, as well as somewhat across samples. The global point prevalence of MDD across genders, adjusted for methodological differences, has been found to be at 4.7% and to be very similar over time (Ferrari et al., 2013). Prevalence of depression is found to peak during the ages 18-44 (Kessler, 2003). Median age-of-onset has been found to be between age 25 and 34 years (Bromet et al., 2011; Ferrari et al., 2013; Kessler et al., 2005). This is an interesting finding, given that it is concurrent to the age of when most women have children (Kenny et al., 2013; Mathews & Hamilton, 2009).

Lifetime prevalence rates are generally higher than 6 or 12-month or point prevalence rates (often operationalized as current or past month), as they overreach a larger time span. However, they might also be influenced by recall bias, which may contribute to underestimate the numbers somewhat (Kruijshaar et al., 2005; Moffitt et al., 2010). Nevertheless, lifetime prevalence rates of depression range from 14.6% to 20.6% (Bromet et al., 2011; Hasin et al., 2018; Kessler et al., 2005).

The current study focuses, as noted, on depression within a time frame spanning the months of gestation, and the first months following delivery. Hence, the most meaningful prevalence rates are those spanning a shorter time frame, such as 12 months. For depression, 12-month prevalence rates such as 10.4% (Hasin et al., 2018) and 16.6% (Kessler et al., 2005), across genders, have been reported. The prevalence is consistently and globally estimated to be higher among women than men, and the female/male risk ratio is found to be approximately 2:1 (Andrade et al., 2003; Bromet et al., 2011; Feliciano & Renn, 2014; Kessler, 2003; Piccinelli & Wilkinson, 2000).

2.2.2 Etiology

Etiology is a debated topic in the research on depression (Feliciano & Renn, 2014). Most research converges on the understanding that multifactorial models of explanation are most successful in comprehending the *heterogeneity*, i.e. multiple causal factors to the same condition, seen in depression (Hyde, Mezulis, & Abramson, 2008; Kendler, Thornton, & Prescott, 2001; Kessler, 2003; O'Keane, 2000), as they incorporate interactions of psychological, social and biological features. Both risk and protective factors for depression have been identified. Examples of well-established protective factors are coping style and social support (Feliciano & Renn, 2014), as well as certain family-related characteristics, such as a higher *socio-economic status* (SES) (Van de Velde, Bracke, & Levecque, 2010). However, the focus in this thesis is on risk factors.

As noted, twin studies have estimated the heritability of MDD at 37% (Sullivan et al., 2000). It has proven difficult to find consistent evidence for specific genetic factors involved in the etiology of major depression, despite several candidate genes and various polymorphisms, i.e. gene variants, have been suggested to be implicated (Flint & Kendler, 2014; Hasler, Drevets, Manji, & Charney, 2004). Recently, however, a large meta-analysis identified 102 independent genetic variants associated with depressive symptoms (D. M. Howard et al., 2019), using the *genomic association wide study* (GWAS) method, in which the entire genome is analyzed (Plomin et al., 2013). The difficulty of finding specific variants

may be due to the disorder being only low to moderately heritable, yet, it may also be due to heterogeneity in genetic factors contributing to depression. Accordingly, genetic effects contributing to MDD are found to be non-specific, in the sense that they appear to contribute to vulnerability to psychopathology in general, rather than to depression specifically (Kendler et al., 1995; Kuehner, 2017). For instance, MDD and generalized anxiety disorder (GAD) are found to share the exact same genetic vulnerability (Kendler, Neale, Kessler, Heath, & Eaves, 1992). The finding of non-specific genetic factors is a common finding in psychopathology research (Kendler et al., 1995; Kessler, 2003). In addition to being a well-established risk factor for depression (Feliciano & Renn, 2014), the high level of comorbidity between mental disorders may also be viewed as suggestive of this non-specificity (Caspi et al., 2014). Thus, some propose viewing psychiatric symptoms as the result of a general *psychopathology vulnerability* (p) factor, rather than the result of risk for specific disorders (Caspi et al., 2014).

It has been suggested that genetic factors may play a greater role in the etiology of depression in women than in men (Kendler, Gardner, Neale, & Prescott, 2001). The genes that influence risk for the two genders appear correlated, however, not entirely overlapping, as the genetic correlation in liability to depression in women and men have been estimated at between .50 and .65 (Kendler, Gardner, et al., 2001). Genetic factors influencing internalizing and externalizing phenotypes, which are unequally distributed, with the first being more prominent in women, while the latter being more prominent in men, might explain some of the gender difference (Kuehner, 2017).

Furthermore, a myriad of biological pathways are hypothesized, as well as found, to be implicated in depression, particularly for women (Feliciano & Renn, 2014; Hyde et al., 2008). Mentioning of and elaboration on all of the hypothesized pathways exceed the scope of this thesis. Yet, some of them are considered particularly relevant to the current study, as they are closely related to the events of pregnancy and delivery. Examples include cortisol hypersecretion and dysregulation of sleep (Levinson, 2006). Many converge on the understanding that *pathophysiological* phenotypes of depression, i.e. differential sensitivity to different biomarkers such as endocrine or genetic factors, contribute to the heterogeneity of depression (Flint & Kendler, 2014; Kuehner, 2017; Levinson, 2006).

The *hypothalamic-pituitary-adrenal* (HPA)-axis comprises a major part of the neuroendocrine system, which regulates various bodily responses (Feliciano & Renn, 2014). This includes the production and regulation of cortisol, a hormone involved in the body's response to stress (Breedlove & Watson, 2013). Cortisol has been implicated in various types

of psychopathology, also MDD, which is found to be associated with an overabundance of cortisol (Feliciano & Renn, 2014). Furthermore, dysregulation of several other neurotransmitters are found to contribute to major depression. Some of the most commonly implicated neurotransmitters are serotonin and noradrenaline (Feliciano & Renn, 2014). Noradrenaline is involved in action mobilizing, associated with genes such as *catechol-O-methyl-transferase* (COMT) and *mono-amine-oxidase type A* (MAOA). Serotonin is involved in feelings of well-being, associated with *serotonin transporter gene/5-hydroxytryptamine translocator* (5-HTT) (Breedlove & Watson, 2013; Owens & Nemeroff, 1994).

As noted, there might be biological factors contributing to the gender differences in occurrence of depression, one of these being variations in hormonal levels (Feliciano & Renn, 2014; Kuehner, 2017). The gender difference in depression is first apparent in puberty (Hyde et al., 2008; Kessler, 2003). This is theoretically interesting in regards to perinatal depression, as the perinatal period, as well as puberty, involves substantial hormonal changes. Some argue that a subgroup of women are susceptible to normal hormone fluctuations during premenstrual and perinatal periods, as well as during perimenopause (the transition period into menopause) and menopause (Deecher, Andree, Sloan, & Schechter, 2008; Kuehner, 2017). This makes for a more homogenous female phenotype of depression that seems closely related to reproductive events. This appears to be related to the changing levels of ovarian hormones, such as estrogen and progesterone. These influence bodily systems that are involved in major depression, such as the serotonergic and noradrenergic system (Deecher et al., 2008). Furthermore, a blunted cortisol response to stress in periods with high concentrations of estrogen in women might constitute a risk of depression (Kuehner, 2017). Atypical depression, which is associated with mood reactivity, significant weight gain or increase in appetite, hypersomnia, leaden paralysis (heavy feelings in arms or legs) and a long-standing pattern of interpersonal rejection sensitivity (APA, 2013), is characterized by hypoactivation of the HPA-axis (Kuehner, 2017). This is proposed to represent a distinct pathophysiological phenotype, which is particularly common in women (Kuehner, 2017).

Twin studies have estimated that nonshared environment explain 63% of the variance in major depression (Sullivan et al., 2000). Exposure to stress is found to significantly increase the risk of depression (Feliciano & Renn, 2014; Kendler & Gardner, 2010). This may include acute stressors, i.e. experiencing stressful life events, such as experiencing loss or an accident. However, it may also include exposure to more chronic stress, which is stress

persistent over longer time periods, for instance over several years (Bromet et al., 2011; Hammen, 2005).

A commonly applied model of understanding depression, is the *stress-vulnerability model*. This model proposes that psychopathology is the result of interplay between encounters with stress-inducing life experiences, and a level of innate vulnerability to respond to these experiences, such as genetic sensitivity (Ingram & Luxton, 2005). It was first applied to schizophrenia (Nuechterlein & Dawson, 1984), but has subsequently been applied to a range of mental disorders, including depression (Ingram & Luxton, 2005). By extension, support has been found for a *kindling hypothesis*, which holds that the brain becomes increasingly more sensitized to a depressive state with each occurring depressive episode, which implies a progressively diminishing role of environmental stressors (Kendler, Thornton, & Gardner, 2000). Additionally, there appears to be some degree of stress generation in depression, i.e. individuals who are prone to depression appear to actively contribute to increase the risk of experiencing non-random stressors associated with depression, such as interpersonal problems (Liu & Alloy, 2010). By extension, the sensitivity to the increased risk induced by stress appear to be altered, at least partly, by genetic factors (Feliciano & Renn, 2014; Kendler et al., 2010; Tennant, 2002). In depression, as well as in other aspects of human life, there is correlation between the genes and the environment, which refers to the role of genetics in exposure to environments (the nature of nurture) (Plomin et al., 2013). This correlation can be partitioned into three categories; *passive*, *evocative/reactive* and *active* (John, Robins, & Pervin, 2008; Plomin et al., 2013). Passive correlation refers to when children passively inherit family environments from their parents that are correlated with their genetic dispositions. A recent study provides an example of this; maternal prenatal depressive symptoms were found to be associated with offspring early-life psychopathology primarily through intergenerationally shared genetic factors (Hannigan et al., 2018). Evocative correlation occurs when individuals evoke certain responses from their environment because of their dispositions. For example, evidence has been found that internalizing problems in children evoke depressive symptoms in their mothers (McAdams et al., 2015). Active correlation refers to when individuals select and manipulate experiences that are correlated with their genetic dispositions (Plomin et al., 2013). In regards to depression, one such finding is that the level of neuroticism, i.e. negative affectivity, which is a trait notably influenced by genetic factors (De Moor et al., 2015; Jang, Livesley, & Vemon, 1996), is associated with the likelihood of experiencing stressful life events, which in turn

may contribute to development of depressive symptoms (Van Os, Park, & Jones, 2001), thus possibly reflecting an active correlation, i.e. stress generation.

Overall, it appears that interactions between hormone levels and stressors, as well as interactions between genetic vulnerability and hormones, contribute to the observed gender differences in depression (Hyde et al., 2008). Furthermore, findings suggest that environmental stress related to gender and gender roles may exacerbate the effects of a biological susceptibility (Kessler, 2003; Kuehner, 2017). Gender differences in depression will not be elaborated on further, but the described mechanisms may be of importance in understanding perinatal depression.

2.2.3 Consequences

Depression has both individual and societal negative consequences. It is found to be very debilitating to the individual, and negatively impact the quality of life (Feliciano & Renn, 2014). It may affect cognition, such as increase rumination tendencies, and may interfere with the execution of daily activities and routines (Feliciano & Renn, 2014). Furthermore, it may cause disruption of social functioning and interpersonal relationships (Hirschfeld et al., 2000). Depression is also globally and consistently associated with elevated rates of self-harm and suicidal risk (Feliciano & Renn, 2014; Nock et al., 2008). On a societal level, it contributes substantially to poor quality of life and disability (Pincus & Pettit, 2001), and is predicted to be among the leading causes of disability globally by 2030 (Mathers & Loncar, 2006). Thus, it is important to increase the understanding of the illness, to ever amplify precision of treatment and prevention efforts.

2.3 Measurement of Depression - Diagnosis vs. Symptoms

There is growing consensus on the notion that mental disorders appear to exist on a severity continuum from “normal” behavior and mood, rather than distinct categories, i.e. continuous rather than categorical (Goldberg, 2010; Widiger & Gore, 2014). This also applies to depression specifically, as it appears that depression is not a qualitatively distinct form of sadness, rather, similar to “normal” feelings of sadness, however, the difference lies in the severity continuum (Widiger & Gore, 2014). However, an elaboration on the difference in measurement of diagnosis and questionnaires is warranted.

The gold standard for diagnostic assessment is the administration of psychiatric interviews which correspond to the diagnoses provided by the diagnostic frameworks. However, these interviews require time and resources, as they are extensive. Hence, for research purposes, various questionnaires are often used, as in this study.

2.3.1 Diagnostic Classification

There are currently two mainly used diagnostic frameworks for classification of mental disorders. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition, (DSM-5) is developed by the American Psychiatric Association (APA, 2013). The Classification of Mental And Behavioral Disorders, tenth edition, (ICD-10) is developed by World Health Organization (WHO, 1992). The DSM-5 is mostly used in American health care, while the ICD-10 is mostly used in European health care. There are task groups in place to revise and harmonize the classifications in order to achieve a more globally applicable body of research (WHO, 1992). Both frameworks are used in research, although the most widely used is the DSM-5. Hence, this thesis will focus on the classification provided by the DSM-5.

The DSM-5 diagnosis of a major depressive disorder requires the fulfillment of several diagnostic criteria and symptoms (APA, 2013). In addition, there is a specifier for perinatal onset of the depressive episode. This specifier requires the onset to occur during pregnancy, or in the 4 weeks following delivery. The occurrence of *baby blues* (also referred to as *maternity blues* or *postpartum blues*), a relatively mild, self-limiting depressive mood state occurring within the first 2 weeks postpartum, is considered beneath the clinical threshold of major depression (Buttner, O'Hara, & Watson, 2012; L. M. Howard et al., 2014).

2.3.2 Questionnaires/Symptom Checklists

There are many psychometric instruments available for research purposes. These instruments are easier to use continuously, as opposed to categorically, i.e. diagnosis or not, as they allow for counting of symptoms. The instruments typically consist of 10 to several hundred items to be answered. The purpose of having multiple items is being able to ensure measurement precision, by partitioning different aspects of the trait. However, most large, population-based health studies use some form of abbreviated versions of these psychometric instruments, as a way of saving questionnaire space. Questionnaires are often studied in comparison to diagnostic interviews, to assess the validity, i.e. whether they measure what they are intended to measure (Bordens & Abbott, 2002). A more detailed description of the measurement of depression in this study is presented in section 5.2.

2.4 Prenatal Depression

2.4.1 Definition and Prevalence

As noted, prenatal depression is depression occurring during pregnancy, prior to delivery. There is currently a gap in the understanding of the disorder, as there is a lack of large studies systematically reviewing the literature (Bennett, Einarson, Taddio, Koren, & Einarson, 2004).

Prenatal depression is also markedly less studied than postnatal depression. Most of the studies conducted have focused on the second and third trimester, which may affect the findings (Bennett et al., 2004). A consistent finding is that prenatal depression is often misclassified as postnatal depression (APA, 2013).

The lack of extensive research is also evident in the lack of reports of prevalence rates. However, a few large studies have investigated prevalence rates. Bennett and colleagues (2004) found rates of prenatal depression to vary, although not significantly, across trimesters, and found the following average (across studies) prevalence rates for the trimesters to be 7.4%, 12.8% and 12.0%, respectively. Whether prevalence in earlier and later stages of pregnancy are similar or different, vary among studies (Bennett et al., 2004; Gavin et al., 2005). Average prevalence has been estimated at 8.4% across all trimesters (Vesga-Lopez et al., 2008). Studies that have investigated the effects of pregnancy on onset and recurrence of major depression have consistently failed to find significant differences in the rates, compared to non-pregnant controls (Kessler, 2003). Yet again, it is important to note that somatic symptoms of pregnancy, such as fatigue and altered sleep, might be difficult to distinguish from those of depression for the affected individual, as well as for health professionals and researchers (Bennett et al., 2004).

2.4.2 Etiology

The etiology of prenatal depression is not yet fully understood. It might be distinct from or similar to depression occurring at other times, as will be elaborated on in section 2.6.1 and 2.6.2.

The genetic factors involved in prenatal depression are currently not well-understood (Figueiredo, Parada, de Araujo, Silva Jr, & Del-Ben, 2015; Serati, Redaelli, Buoli, & Altamura, 2016). A recent twin study estimated heritability of prenatal depression at 37% (Viktorin et al., 2016). Several studies assess the role of polymorphisms within the *serotonin-transporter-linked polymorphic region* (5-HTTLPRR) (Figueiredo et al., 2015). Other examples are COMT, MAOA and oxytocin receptor gene (OXTR) (Figueiredo et al., 2015). Oxytocin is a hormone contributing particularly to bodily responses allowing for delivery and breastfeeding, as well as other mother-infant-interactions (Breedlove & Watson, 2013).

There are a wide array of hormonal changes related to the perinatal period which may contribute to the occurrence of prenatal depression. Mentioning and elaboration on all of them exceed the scope of this thesis, yet, some are considered particularly relevant to prenatal depression. During gestation, there are several changes to gonadal steroid levels, as well as to

androgens (Bloch, Daly, & Rubinow, 2003). Hormones related to the HPA-axis, for instance cortisol, show a marked increase, although significant associations between this and prenatal depression are not consistently found (Seth, Lewis, & Galbally, 2016). Whether these changes play a causal role in the development of perinatal depression is currently a debated topic, with some arguing that they represent a risk factor for some vulnerable women, whereas some argue that prenatal hormonal changes are protective against depressive symptoms (Bennett et al., 2004; Biaggi, Conroy, Pawlby, & Pariante, 2016).

There appears to be a substantial contribution from environmental factors to the occurrence of prenatal depression. A recent twin study found that environmental factors contributed to 63% of the variance in prenatal depression (Viktorin et al., 2016). Consistent findings on risk factors of prenatal depression include a personal history of depression, current comorbid anxiety, low partner support/relationship problems, life stress, lack of social support, domestic violence, substance abuse and unintended pregnancy (Biaggi et al., 2016; Lancaster et al., 2010; Milgrom et al., 2008; Ryan, Milis, & Misri, 2005; Räisänen et al., 2014).

2.4.3 Consequences

The consequences of prenatal depression are not very well understood (Evans, Heron, Francomb, Oke, & Golding, 2001), yet, a consistent finding is that prenatal depression constitutes a risk factor for postnatal depression (Field, 2011; Milgrom et al., 2008; Silverman et al., 2017).

Many studies have investigated the potential consequences of maternal prenatal depression on the offspring. Several studies have found that women with prenatal depression are at increased risk of several undesirable pregnancy outcomes, such as preterm birth and low birth weight (Grote et al., 2010; Nezvalová-Henriksen et al., 2016; Räisänen et al., 2014). Prenatal depression is associated with problems in the offspring's infancy, most commonly sleep problems and unease (Field, 2011). Furthermore, many studies have found that prenatal depression is associated with negative early-life outcomes for the offspring, such as internalizing and externalizing problems (Field, 2011). Prenatal psychopathology may have an important effect on the uterine environment, which is suggested to have an impact on the developing child (Evans et al., 2001; Fisk & Glover, 1999). There exists some uncertainty about the exact mechanisms, however, it is suggested that neuroplasticity and neurodevelopment of the fetus is affected (Field, 2011). One model of explanation postulates that exposure of the fetus to high maternal levels of cortisol and noradrenaline and low levels

of dopamine, a neurotransmitter involved in reward-motivated behavior, and serotonin, i.e. dysfunction of the HPA-axis of the mother, may subsequently result in effects on the HPA-axis, behavior and cognitive function of the developing fetus (Field, 2011; Sawyer, Zunszain, Dazzan, & Pariante, 2018). However, this may also, at least partially, be due to a shared genetic vulnerability, rather than a result of in-utero exposure to prenatal depression. Indeed, this is recently found in several studies (Gjerde et al., 2017; Hannigan et al., 2018). Additionally, maternal depression occurring at other times during the offspring's development, e.g. such as during the postnatal period, as well as level of severity and chronicity of the depressive symptoms, appear to contribute substantially to the observed associations between prenatal depression and outcomes in offspring (Field, 2010; Gjerde et al., 2017). Examples of other confounding variables are prenatal comorbid anxiety and anger (Field, 2011).

2.5 Postnatal Depression

2.5.1 Definition and Prevalence

Postnatal depression is, as noted, depression occurring after delivery. It is found to be one of the most common complications following birth (Robertson, Grace, Wallington, & Stewart, 2004). More research has been conducted on postnatal than prenatal depression (O'Hara & Wisner, 2014). As noted, there is a lack of consistency across studies regarding what constitutes the postnatal period, and different time frames are used for different purposes (Brummelte & Galea, 2016; O'Hara & McCabe, 2013). Studies increasingly operationalize the postnatal period as lasting up to the first year following delivery (O'Hara, 2009). As noted, there are conflicting views on whether postnatal depression and non-postnatal, e.g. prenatal and non-perinatal, depression are similar or distinct constructs, as it occurs at a special time in the affected woman's life (Di Florio & Meltzer-Brody, 2015; Whiffen, 1992). The literature suggests that postnatal depression does not differ qualitatively from non-postnatal depression (Di Florio & Meltzer-Brody, 2015; Riecher-Rössler & Fallahpour, 2003; Whiffen, 1992). Yet again, somatic changes and symptoms of the postnatal period, such as changes in sleep and weight, may be difficult to separate from depressive symptoms (Di Florio & Meltzer-Brody, 2015; O'Hara & McCabe, 2013).

The average prevalence rates across studies are found to center around 10-15% (Mann, Gilbody, & Adamson, 2010; O'Hara & Swain, 1996). Some studies have found that rates of depression increase substantially during this period (Vesga-Lopez et al., 2008). In contrast, most recent studies have found that there is little evidence of an increased risk compared to

non-postnatal women, rather, it appears that the risk is similar (O'Hara & Wisner, 2014; Silverman et al., 2017). Furthermore, these studies also suggest that the perceived increased risk is a result of postnatal women being a medically captured group. The risk of recurrence is estimated at 25% (Wisner, Parry, & Piontek, 2002), with some evidence suggesting that poor sleep quality is a significant predictor of recurrence (Dørheim, Bjorvatn, & Eberhard-Gran, 2014; Okun et al., 2011).

2.5.2 Etiology

The postnatal period has been hypothesized to be a period of increased risk of depression, as it is closely related to large hormonal changes, as well as with major life changes, which may induce stress (Bloch et al., 2003; O'Hara & Wisner, 2014).

Although there are few heritability estimates, heritability of postnatal depression has been estimated at 40% (Viktorin et al., 2016). Furthermore, genetic factors have been found to explain 38% of the variance in postnatal depressive symptoms following first live birth, as well as 25% of the variance in lifetime major depression occurring postnatally (Treloar, Martin, Bucholz, Madden, & Heath, 1999). Increased familial clustering is consistently found (Forty et al., 2006), and some evidence suggests that it is particularly increased for onsets shortly after delivery (Segman et al., 2009). Several studies point to postnatal depression being associated with a past personal or family history of affective disorders (Figueiredo et al., 2015), especially in first onset depressive episodes occurring postnatally (Kessler, 2003). A recent Swedish prospective population-based study found that the relative risk of postnatal depression in women with a history of depression was more than 20 times higher than for those without such history, as well as that maternal depression history had a modifying effect on pre-and postnatal risk factors (Silverman et al., 2017). Furthermore, there is some evidence of intergenerational transmission of postnatal depression from mothers to daughters (Séjourné, Alba, Onorrus, Goutaudier, & Chabrol, 2011). These findings are suggestive of a heritable component, i.e. shared genetic vulnerability, in the occurrence of the disorder.

Despite extensive attempts at discovering specific genetic risk factors, as several genetic associations can be linked theoretically to an increased risk of postnatal depression (e.g. hormones), the genetic factors involved in postnatal depression remain largely unknown, as results are conflicting and insufficient (Corwin, Kohen, Jarrett, & Stafford, 2010; Skalkidou, Hellgren, Comasco, Sylvén, & Poromaa, 2012). Postnatal depression appears to be linked to MAOA, COMT, 5-HTT and other genetic factors commonly associated with major depression in general, e.g. non-perinatal depression (e Couto et al., 2015; Figueiredo et al.,

2015; Zhang et al., 2014), which strengthens the notion that it is the same disorder as non-postnatal depression. As prenatal depression, it appears linked to oxytocin (Figueiredo et al., 2015). Recently, initial evidence for a distinctive gene expression profile in women considered completely recovered from postnatal depression, was found (Landsman, Aidelman, Smith, Boyko, & Greenberger, 2017). This is thought to contribute to explain onset and the high risk of postnatal depression recurrence (Landsman et al., 2017). Yet, whether this alteration is the cause of depression, or a result of depression, awaits further research.

By extension, there are several proposed neurobiological mechanisms underlying postnatal depression, such as disruptions in reproductive hormones, stress, HPA-axis dysfunction and functional brain changes following the perinatal period (Payne & Maguire, 2018; Skalkidou et al., 2012), which are all highly interrelated.

However, the most extensively studied connections are between endocrine changes and postnatal depression. There are three substantial, sequential changes in the hormonal state of women during the postnatal period (Bloch et al., 2003). First, there are precipitous changes in hormone levels along with delivery. Second, there is a prolonged hypogonadal state, which persists until the reinitiation of ovulation and the menstrual cycle. Third, there is resumption of the normal cyclic ovarian function. The two first changes are thought to contribute to postnatal depression. In support of this, Bloch and colleagues (2003) found that women with a history of postnatal depression displayed a significantly greater mood sensitivity to changes in gonadal steroid levels than controls, suggesting a vulnerable subgroup of women. Various later studies suggest a subtype particularly sensitive to these endocrine changes (Bennett et al., 2004; Deecher et al., 2008).

Furthermore, several studies focus on the associations between oxytocin and postnatal depression (Moura, Canavarro, & Figueiredo-Braga, 2016). Higher levels of oxytocin are hypothesized to protect against postnatal depression, whereas lower levels are hypothesized to increase the risk of depression. In support of this, Ystrøm (2012) found an association between breastfeeding cessation and symptoms of postnatal depression, and depression to be more stable throughout the first six months postpartum in mothers who stopped breastfeeding. Although several studies show protective effects on depressive symptoms, there is a lack of consistent, significant results, and reviews suggest that there might be subtypes of women with postnatal depression more closely related to oxytocin levels (S. Kim et al., 2014; Moura et al., 2016). By extension, increased risk for a subgroup of women particularly vulnerable to hormonal changes, who experience early onset of postnatal depression, i.e. shortly after birth,

concomitant to when the hormonal changes are most pronounced, is suggested (O'Hara & Wisner, 2014). Yet another subgroup of women particularly vulnerable to the hormonal changes of the later stages of the postnatal period, such as weaning from breastfeeding and resumption of menstruation, has also been suggested (Burke, Susser, & Hermann, 2019).

Nonshared environmental factors have been found to explain 75% (Treloar et al., 1999) and 60% of the variance (Viktorin et al., 2016), suggesting that environmental factors have substantial impact on postnatal depression. Risk factors with moderate to strong associations with postnatal depression include a personal or family history of depression, depression and anxiety during pregnancy, neuroticism, low self-esteem, postpartum blues, stressful life events (including childcare-related stressors), poor marital relationship and poor social support findings (Beck, 2001; O'Hara & Wisner, 2014; Robertson et al., 2004). Other important risk factors, however seemingly of smaller importance, are low SES, being single, unwanted pregnancy, obstetrical stressors, difficult infant temperament, (O'Hara & Wisner, 2014) as well as lack of sleep (Dørheim et al., 2014). Taken together, three constellations of risk factors are found to be central; stressful life events, history of psychopathology and poor social support, and these are overlapping with non-postnatal depression (O'Hara & Wisner, 2014; Wisner et al., 2002).

Most conclude that the etiology of postnatal depression does not appear distinct from that of non-postnatal depression, and that there appears to be considerable heterogeneity (O'Hara, 2009; Riecher-Rössler & Fallahpour, 2003; Whiffen, 1992). Many argue that giving birth, with all the biological and psychosocial factors associated with it, appears to act as a major stressor, which, in line with a general vulnerability-stress-model, may trigger onset of disease in vulnerable women, possibly a subtype (Mitchell et al., 2011; Riecher-Rössler & Fallahpour, 2003). Furthermore, initial evidence of specific gene-environment interactions has been found (Figueiredo et al., 2015; Zhang et al., 2014), such as between two polymorphisms of the 5-HTT and SES (Mitchell et al., 2011).

2.5.3 Consequences

Postnatal depression is found to cause personal suffering and diminish functioning in important life aspects of the affected woman (O'Hara & McCabe, 2013), similarly to non-postnatal depression. Additionally, depression occurring after delivery may interfere with maternal caretaking behaviors, such as ability to respond to the infant's basic needs, breastfeeding and dyadic interactions between mother and infant (Field, 2010). Some also suggest that obstetrical consequences, which is associated with both prenatal and postnatal

depression, coupled with mental illness, might contribute to retained gestational weight gain, which in turn represents a risk factor for subsequent cardio metabolic disease (Meltzer-Brody & Stuebe, 2014).

Moreover, several studies have suggested that postnatal depression is associated with behavioral, cognitive and health-related consequences for the child, such as internalizing and externalizing problems and general psychopathology, as well as with problems in child-parent-interactions (Field, 2010; Wisner et al., 2002). However, several more recent studies suggest that the amount of the child's exposure to maternal depression, also outside of the postnatal period, may play a more critical role (Brand & Brennan, 2009; Goodman et al., 2011; Grace, Evindar, & Stewart, 2003). As with prenatal depression, shared genetic vulnerabilities may also contribute to explain these findings, which is also underlined in these studies.

2.6 Synthesis

Findings on depression occurring at various time points have now been presented separately. However, as this study also seeks to answer questions regarding the relationship between risk factors for depression occurring in different settings, it is important to discuss this relationship somewhat. First, the previously separately presented findings on prenatal and postnatal depression are combined and discussed jointly, referred to as perinatal depression. Second, the relationship between perinatal depression and non-perinatal depression is briefly discussed.

2.6.1 Perinatal Depression

Depression is one of the most common complications of the perinatal period (Gavin et al., 2005). Perinatal depressive symptoms are found to affect more than 25% of perinatal women, and major depressive disorder during the perinatal period is found to affect 10-15% (Gavin et al., 2005; Stuart-Parrigon & Stuart, 2014). There exists some uncertainty regarding whether prevalence is similar or changing during the perinatal period, with evidence suggesting that the second and third months after delivery have slightly higher prevalence (Gavin et al., 2005), whereas other findings are contradictory. For instance, in a study of almost 100 000 pregnancies, Ystrom and colleagues (2014) found the same rates of depressive symptoms in the third trimester (9.3%) as six months postnatally (9.5%). In a repeated measurement study, the point prevalence of depression in the first four months of the postnatal period did not differ significantly compared to other time periods during pregnancy and the postnatal period (Eberhard-Gran, Tambs, Opjordsmoen, Skrondal, & Eskild, 2004).

Furthermore, there is a high risk of recurrence, both perinatally and non-perinatally (L. M. Howard et al., 2014; Meltzer-Brody & Stuebe, 2014).

As noted, a consistent finding on the field is that prenatal depression predicts postnatal depression (Underwood, Waldie, D'Souza, Peterson, & Morton, 2016). This is associated with uncertainty in classification, in regards to whether the onset of postnatal depression is truly postnatal, or rather only discovered postnatally. APA (2013) holds that 50% of depressive episodes that are classified as postnatal actually have onsets prior to delivery. If postnatal depression has a prenatal onset, this implicates that it is similar to depression occurring at other times, i.e. non-perinatal depression. On the other hand, some have also found that a substantial percentage of women with high levels of depressive symptoms prenatally show significant reductions in symptom severity postnatally, and stress that this group has not been the focus of research (Heron, O'Connor, Evans, Golding, & Glover, 2004). Prediction may also be caused by the degree of overlap in risk factors for prenatal and postnatal depression (Lancaster et al., 2010; O'Hara & Wisner, 2014).

A familial component of perinatal depression has been suggested, although evidence has been stronger for postnatal depression specifically (Murphy-Eberenz et al., 2006). Some studies suggest that the late stages of pregnancy or the early stages of the postnatal period show greater genetic vulnerability (Figueiredo et al., 2015).

As noted, there are few twin studies investigating heritability of perinatal depression, seemingly only the two referred to in this thesis; Viktorin and colleagues (2016), and Treloar and colleagues (1999), and none of them investigate the correlation between heritability of prenatal and postnatal depression. The most recent study, employing an extended twin design which included siblings, estimated the heritability of perinatal depression at 44%, with the remaining variance being attributable to nonshared environmental factors (Viktorin et al., 2016).

Most studies investigating the influence of genetic factors on perinatal depression utilize a molecular genetic approach (Figueiredo et al., 2015). The most frequently investigated molecular genetic factor for perinatal depression is the 5-HTT gene, which several studies have found positive associations for (Figueiredo et al., 2015). Furthermore, genetic studies of perinatal depression have been found to reinforce a pathophysiological role of the hormonal changes associated with this period (Figueiredo et al., 2015). The genetic factors associated with prenatal and postnatal depression appear to be closely related, although, not uniform (Figueiredo et al., 2015).

The understanding of how pathophysiological pathways contribute to perinatal depression is largely incomplete (Dickens & Pawluski, 2018). However, research on neuroendocrine aspects have been conducted, particularly research on the HPA-axis. The HPA-axis has been found to contribute to perinatal psychopathology directly, as previously discussed, as well as through interactions with other major biological systems (Dickens & Pawluski, 2018; Kammerer, Taylor, & Glover, 2006). This includes estrogen and progesterone, which are hypothesized to be important for perinatal depression (Sawyer et al., 2018). The HPA-axis further undergoes major alterations during pregnancy, largely due to the creation of a placenta, thus, HPA-axis dysregulation is suggested to be predictive of risk for postnatal depression (Glynn, Davis, & Sandman, 2013). A growing body of research on rodents suggests that stress or activation of the HPA-axis prior to or during the prenatal period can be valuable in understanding depression in the postnatal period (Dickens & Pawluski, 2018). Furthermore, the HPA-axis is hypothesized to contribute to prenatal and postnatal depression in distinct ways (Kammerer et al., 2006). During pregnancy, there is a large increase in plasma *corticotrophin releasing hormone* (CRH) and cortisol, which are both involved in the body's stress response, as well as in estrogen and progesterone (Kammerer et al., 2006). A rapid drop in these hormones occur during delivery, and thus, it is suggested that symptoms of prenatal and postnatal depression may be partly distinct, and partially linked to these differences in function of the HPA-axis, in the sense that prenatal depression may be more melancholic, while postnatal depression may be more atypical (Kammerer et al., 2006). Melancholic depression is characterized by loss of appetite and sleep, anxiousness and loss of responsiveness to the environment (Lamers et al., 2013). Atypical depression is, as noted, characterized by the reverse tendencies; overeating, oversleeping, lethargy and reactivity to the social environment. Evidence of a differential role of the HPA-axis in melancholic and atypical depression, not related to pregnancy, has been suggested and found (Lamers et al., 2013). Some women are thus suggested to be genetically more vulnerable to melancholic or atypical depression, and thus, more or less vulnerable to depression at the different stages of the perinatal period (Kammerer et al., 2006). However, evidence is limited, and, importantly, not every depressive episode is compatible with classification into these two systems.

Changes in estrogen levels are, as noted, suggested to be related to the occurrence of depressive episodes (Deecher et al., 2008). The periods that appear to be most closely related to perinatal depression are concurrent with the periods in which estrogen levels are progressively changing (Bloch et al., 2003; Figueiredo et al., 2015). Estrogen may also be an

important trigger for changes in the expression of genes, thereby mediating the increased predisposition to depressive episodes observed during these time periods (Figueiredo et al., 2015).

Several studies find substantial overlap in the risk factors of prenatal and postnatal depression, however, the overlap is not absolute (Lancaster et al., 2010; O'Hara & Wisner, 2014). Importantly, environmental stressors are found to influence the relationship between the genetic factors and perinatal depressive states, and gene-environment interactions are often found (Doornbos et al., 2009; Figueiredo et al., 2015).

There has been some discussion on the field, regarding whether there are several trajectories of perinatal depression, which may be associated with distinct phenotypic subtypes. Some evidence suggests that different perinatal depressive trajectories are associated with somewhat divergent characteristics (Putnam et al., 2017; Wikman et al., 2019). A recent study suggests that as women move from the prenatal to the postnatal period, sociodemographic and lifestyle risk factors appear to be of less importance, and a personal and family history of depression and postnatal depression seems to be of larger importance, in terms of risk of experiencing depression (English et al., 2018). Only a few studies have investigated whether the symptom patterns of prenatal and postnatal depression are similar or distinct, and the results are inconclusive (Kammerer et al., 2009). It is important to stress that women may experience depression prior to and following birth very differently, as child birth is an important biological, social and psychological event, which may impact both symptom severity and presentation (Evans et al., 2001).

2.6.2 Non-perinatal vs. Perinatal Depression

Non-perinatal depression is not the focus of this study, however, as there are conflicting views on whether perinatal depression represents a distinct disorder, as well as a lack of research on heritability of perinatal depression, a brief summary of the relationship is useful, in order to interpret the upcoming results.

Some studies have estimated the prevalence to be higher in perinatal women than in non-pregnant women when controlling for common risk factors (Eberhard-Gran, Eskild, Tambs, Samuelsen, & Opjordsmoen, 2002), whereas most have found non-significant differences (Gavin et al., 2005; L. M. Howard et al., 2014; Kessler, 2003). Again, as noted, identification rates among non-pregnant women might be lower, resulting in a perceived increased rate (L. M. Howard et al., 2014).

The aforementioned Australian twin study found that the genetic correlation between postnatal depressive symptoms following first live birth and lifetime major depression (both in relation to childbirth and depression) was low (.17) (Treloar et al., 1999). The authors suggested that the construct measured may not have been postnatal major depression, possibly rather postnatal dysphoria. More recently, the Swedish twin study estimated heritability of perinatal depression at 54%, while nonshared environmental effects explained the remaining variance (46%). The heritability of non-perinatal depression was estimated at 32%, with the remaining variance being attributable to shared environment (6%) and nonshared environment (62%). Furthermore, they found that 14% of the total variance, or 33% of the genetic variance, in perinatal depression was unique for perinatal depression. This is suggestive of only partially overlapping genetic etiologies for perinatal and non-perinatal depression (Viktorin et al., 2016).

As presented, perinatal depression has been found to be associated with specific genetic factors, e.g. polymorphisms, that overlap with those associated with non-perinatal depression, such as MAOA, 5-HTT and COMT (Doornbos et al., 2009). Perinatal depression is also found to be associated with OXTR, which is thought to be of heightened importance during the perinatal period (Moura et al., 2016).

As noted, risk factors for perinatal depression have been found to be similar to those typically found for non-perinatal depression, such as stressful life events and poor social support (O'Hara & McCabe, 2013; O'Hara & Wisner, 2014). Although, with the suggested exceptions of sensitivity to hormonal changes specific to the perinatal period and possibly differentiating events related to childbirth, such as brain changes following delivery and transition into a new context, i.e. becoming a mother, which are discussed in further detail under section 7.1.2 (Deecher et al., 2008; Duarte-Guterman, Leuner, & Galea, 2019; Hillerer, Jacobs, Fischer, & Aigner, 2014).

Some studies have investigated whether symptom profiles vary between perinatal and non-perinatal depression. As noted, women may experience significant somatic changes often associated with depression in the perinatal period, even if they are not clinically depressed, and thus be mistakenly classified as depressive symptoms (Pereira et al., 2014). By extension, some studies suggest that somatic symptoms, often associated with atypical depression, may not be suitable for diagnosis of depression in the perinatal period, as they may represent normal consequences of the perinatal period (Kammerer et al., 2009; Kuehner, 2017). Some studies have found that symptom profiles appear somewhat distinct, such as sad mood being

less prominent, while psychomotor problems being more prominent (Bernstein et al., 2008). However, other studies have found that the clinical presentations of depressive symptoms in women of childbearing age do not differ in perinatal and non-perinatal depression (Hoertel et al., 2015).

2.6.3 Brief summary

Prenatal and postnatal depression appear fairly similar in prevalence, symptomatology, gross categories of risk factors; stressful life events, history of psychopathology and poor social support (O'Hara & Wisner, 2014). Yet, some risk factors appear specific to each type, such as timing-specific hormonal changes and life changes following delivery. Importantly, prenatal depression is found to predict postnatal depression (Beck, 2001; Gaillard, Le Strat, Mandelbrot, Keïta, & Dubertret, 2014), which may be due to lack of precision in onset identification, as well as other factors. For instance, to what extent relative influence of genetic and environmental factors contribute to this, is currently unanswered. Furthermore, in terms of heritability, which is the focus of this study, the limited research that exists on perinatal depression suggests that it is more heritable than non-perinatal depression. Additionally, initial evidence suggests that postnatal depression appears more heritable than prenatal depression. Whether the genetic factors contributing to depression at each time are similar or distinct, is also unanswered. Thus, in order to answer these questions regarding heritability, an approach capable of integrating and separating genetic and environmental effects is necessary.

3 Behavioral Genetics

The observation that certain traits vary between individuals within a species is not a recent discovery. It has for a long time been noticed that these traits seem familial, in the sense that they may cluster among families. Thus, they are heritable. These observations form the basis of the modern study of heritability (Plomin et al., 2013).

The story of the study of heredity and genetics often begins with the mentioning of Gregor Mendel (1822-1884), who studied inheritance of characteristics in pea plants. He noticed that by crossing individuals with different traits, interactions between the traits appeared to occur. This interaction resulted in traits being transferred somewhat systematically, and he discovered the foundations of what we today know as recessive and dominant inheritance of traits. Several discoveries have since been made, each contributing to the increasingly sophisticated methods of investigation. However, this is outside of the scope of this thesis, and will not be discussed in further detail. Familial similarity has later been

studied and discussed from different points of view. From Freud's time (1856-1939), most theories regarding similarity between parents and offspring, have postulated that this is due to the family environment that parents provide for their children, and explained sibling similarity with this shared environment (Plomin et al., 2013).

From the second half of the 20th century, however, the study of *risk factors*, i.e. characteristics or variables that contribute to increase the risk of mental illness, has grown increasingly popular (Plomin et al., 2013). This approach has also been used to study *protective factors*, i.e. characteristics or variables that contribute to decrease the risk of mental illness (John et al., 2008). A limitation of many traditional observational studies is that the designs do not allow for the disentanglement of the effects of genes, and the effects of the environment. In order to make this possible, it is necessary to utilize genetically informative designs, e.g. designs that *do* allow for this disentanglement, contributing to our ability to explain and differentiate between various phenomena. Alcohol abuse constitutes a classical example in which the consistent finding of a high risk of transmission across generations may be due to environmental effects, yet, it may also be due to genetic effects (McGue, 1999; Plomin et al., 2013; Verhulst, Neale, & Kendler, 2015).

Behavior genetics is a field of research that seeks to assess heritability of various traits and phenomena, by disentangling the genetic and environmental influences, as well as investigating the interplay between these two. *Genetics* refers the study of inheritance provided by the genes coded for in the *deoxyribonucleic acid* (DNA) (Breedlove & Watson, 2013; Plomin et al., 2013). The term *behavior* is here defined in a broad manner, which includes complex phenomena such as disorders and traits. In order to assess the relative importance of genetic and environmental factors on a trait, i.e. *univariate* analysis, similarity between various kinds of relatives are compared to each other. As the effects are not measured directly, rather inferred, they are referred to as *latent* variables. *Multivariate* analysis is also possible, in which it is estimated how much genetic and environmental influences contribute to the association between two or more phenomena, or to the same phenomenon across time (Plomin et al., 2013).

3.1 The Genes and Genetic Effects

The basis of heredity is the DNA molecule (Plomin et al., 2013). A *gene* is a sequence of the DNA, that encodes for the construction of a particular protein, which in turn codes for specific functions within the organism (Breedlove & Watson, 2013). A gene is the most fundamental unit of heredity (Plomin et al., 2013). A *chromosome* is a complex of condensed

strands of DNA and its associated protein molecules (Breedlove & Watson, 2013). The gene's location on a chromosome is referred to as *locus* (Breedlove & Watson, 2013). Individual genes exist in alternative forms, which is referred to as *alleles*. When a trait is referred to as *heritable*, it implies that at least one allele has a measurable effect on the expressed trait. The total genetic potential of an individual is referred to as the *genotype*, which comprehends the entire set of an individual's alleles. On the other hand, *phenotype* refers to the expressed trait, caused by both genotype and environmental influences.

Some disorders are caused by mutation in a single allele, and are thus referred to as *monogenic* or *single gene disorders*. One example is Huntington's disease, in which a singular dominant allele is responsible for the occurrence of the illness (Plomin et al., 2013). However, most phenotypes, such as mental disorders, are believed to be *polygenic* or *complex*, and thus thought to be influenced by several genes, as well as environmental effects. Genetic effects on a phenotype can be partitioned into *additive* (A) and *non-additive* genetic effects. Additive effects simply involve the sum of the contribution of each allele. Non-additive genetic effects involve any genetic influence that is not additive, hence, the genetic effects of one allele is dependent on other alleles. The two most common non-additive genetic effects considered on the field of behavioral genetics, is *dominance effects* or simply *dominance* (D), and *epistasis*. Dominance implies interaction between alleles at the same locus, in which the phenotype produced by the dominant allele is present, regardless of whether one or two copies of the allele exist. Epistasis implies interaction between alleles at different loci, in which the effect of one gene is dependent on that of another (Plomin et al., 2013).

Research on this field often focus on additive genetic effects. This is due to the notion that they reveal clear similarities between parents and offspring, as well as the notion that they have the strongest statistical power (Plomin et al., 2013). Identification of additive genetic effects is the method utilized in the current study, and will therefore be the focus of elaboration.

3.2 The Environment and Environmental Effects

A wide range of environmental factors have been found to contribute to both the development and preservation of mental illness. Some factors, such as low SES, low levels of social support and adverse life events, as well as several aspects of family organization and interaction have been hypothesized and found to increase risk for a wide range of disorders (Beidel, Frueh, & Hersen, 2014). Other factors appear to constitute a risk that is more specific

in nature, e.g. the association between the exposure to body ideals of the western culture and eating disorders (Rikani et al., 2013). *Environment*, in this context, refers to all factors that influence behavior, that are not genetic.

In twin models, environmental influences are divided into two classes, according to their effects on individual differences. Any influence that contributes positively and equally to the observed similarity between relatives, regardless of degree of genetic relatedness, is defined as *common* or *shared environment* (C). This may be factors such as neighborhood, parental education and behavior (Plomin et al., 2013). There has been controversy on the field, regarding shared environment. There is little evidence of shared environmental influences on many commonly studied phenotypes, with modest influences often found to be significant only through childhood and adolescence (Plomin et al., 2013). By extension, shared environment may be viewed as important to the individual, however, with regards to the population, it does not appear to contribute to making systematic differences (Plomin, 2018). Lack of statistical power may partly explain this finding. It may also be partly explained by the fact that twin models only estimate the effects the environment has on covariance, i.e. similarity, not dissimilarity (Turkheimer, 2000). Hence, sharing a household appears to contribute to the similarity of family members during that time, however, it does not persist (Plomin et al., 2013). Furthermore, objectively shared events may not have an equal effect on both siblings, independent of genetic disposition and unique environmental influences. By extension, a useful distinction is therefore between *objectively* and *effectively* shared environmental influences (Kendler & Prescott, 2007), which refer to differences in what is objectively shared, as opposed to what actually contributes to making siblings more or less similar to each other. If additional information is available, such as in extended family or twin studies, the impact of more subtle environmental influences can be examined.

In contrast to shared environment, *nonshared* or *unique environmental effects* (E) is residually inferred through difference between individuals, and includes any proportion of variance in the sample that cannot be attributed to genetic or shared environmental influences. It also includes any measurement error, hence, it can never be zero (Plomin et al., 2013). It may be difficult to identify specific nonshared environmental differences between siblings, and there is some controversy on the field regarding what the E measure actually entails. Research on the actual experiences of the siblings is needed in order to determine this, such as observational studies (Plomin et al., 2013). Previous observational studies suggest that parental reports of the children's environment are of limited use, in terms of assessing

nonshared environment (Plomin et al., 2013). Experiences outside of the family, and how the siblings experience these, also contribute to nonshared environment. Included in E are also perinatal factors, which have been shown to have lasting effects on phenotype (Plomin et al., 2013). Other factors that are also more biological and random in nature, such as nutrition and illness are also included in this measure. Thus, the utilized definition of E is very broad, which is important for interpretation.

3.3 Foundations of Twin Modeling

For simplicity, the focus in this section is on twins, however, the same logic applies to extended twin designs, such as those including siblings (as the current study does). Twin models are, as noted, commonly used to separate relative effects from the genes and environment, and have contributed substantially to this purpose (Plomin et al., 2013). *Monozygotic twins* (MZ), also referred to as *identical twins*, are the result of one fertilized egg separating, yielding two genetically identical embryos (Plomin et al., 2013). *Dizygotic twins* (DZ), also referred to as *fraternal twins*, are the result of fertilization of two separate eggs by two separate sperm cells. The causes of MZ twinning are considered largely unknown, while DZ twinning is found to be influenced by genetic and environmental maternal factors (Hall, 2003). Accordingly, prevalence rates of MZ twinning are found to be fairly constant globally, while prevalence rates of DZ twinning are found to vary across populations (Hall, 2003). MZ twins share on average 100% of their genes, while DZ twins share on average 50% of their genes. When assessing the phenotypic correlations, i.e. similarity on a singular or several traits, between MZ and DZ twins, one can estimate the relative effects of the genes and the environment (Plomin et al., 2013). As elaborated on, A and C are thought to contribute to similarity among siblings. If MZ twins are more similar, on average, than DZ twins, then genetic effects appear to be more important, as C is assumed to be equal across MZ and DZ twins (Plomin et al., 2013). The same logic applies to extended twin designs. Full siblings share on average 50% of their genes, while half siblings (both maternal and paternal) share on average 25%. Siblings can be added to a twin study design, as done in this study, in order to increase statistical power, as well as generalizability (Plomin et al., 2013).

The variance of a phenotype (P) is, as presented, assumed to arise from the combined effects of additive genetic effects (A), non-additive genetic effects (D), shared environment (C) and nonshared environment (E). Hence, the total variance of P can be written as:

$$\mathrm{Var}(P) = \mathrm{Var}\,(A + D + C + E)$$

However, as discussed, twin studies often have limited statistical power, and are therefore often confined to studying only A in terms of genetic effects. Hence, most commonly only A, C and E are included, resulting in P being written as:

$$Var(P) = Var\ (A + C + E)$$

As discussed, twins are assumed to share the family environment to the same extent, and they share genetics according to zygosity. Hence, the expected covariation between these two types of twins can be written as:

$$Cov_{MZ}(P) = Var(A) + Var(C)$$

$$Cov_{DZ}(P) = \frac{1}{2} Var(A) + Var(C)$$

Thus, if MZ twins are more similar than DZ twins on the given phenotype, these formulas imply that this must be accounted for by their genetic material. To what extent genetic influences contribute to the variance of a trait can be expressed as the heritability.

3.3.1 The Heritability Concept

As noted, the *heritability* is a statistic that describes the contribution of genetic variance to the observed variance on a phenotype (Plomin et al., 2013). It is useful for quantifying the relative importance of genes. However, it is important to underline that it is an estimate conducted on a particular sample at a particular time, and is therefore not strictly generalizable between groups, neither to the same group at a different time. Heritability in this sense, is an abstract aggregate statistic. Some misconceptions about how heritability should be interpreted exist, which are discussed more thoroughly shortly, and it is therefore important to clarify what heritability refers to. Heritability is dependent upon the distribution of environmental and genetic factors in a population, in the sense that the more homogenous environmental influences are within a population, the greater the relative contribution of genes become in accounting for phenotypic variance. Thus, if the sample is drawn from a more homogeneous gene pool, the relative measured effect of environment increases. There are two types of heritability commonly referred to in behavioral genetics. *Narrow-sense* and *broad-sense* heritability (Plomin et al., 2013). Narrow-sense heritability (h^2 or a^2) is most commonly used and includes only additive genetic variance (A), while broad-sense heritability (H^2) also include non-additive genetic effects. By using Falconer's formula, one can calculate the approximate estimate of the narrow-sense heritability:

$$h^2 = 2(r_{MZ} - r_{DZ})$$

In this expression, r is the correlation coefficient. The shared environment, also contributing to similarity, is written as c^2. This can be estimated using the following formula:

$$c^2 = r_{MZ}\text{-}h^2$$

The residual variance of the nonshared environment, E, is found by using the following expression:

$$E^2 = 1 - r_{MZ}$$

This rests on the discussed assumption that any variance that is not shared between MZ twins must be accounted for by E.

It is important to underline that heritability describes what *is*, not what *could* or *should* be. Heritability does not imply genetic determinism. However, it points to a *probability*. Neither does it constrain environmental intervention, such as treatments. In the example of Phenylketonuria (PKU), a rare, possibly severe disorder caused by a genetic mutation, genetic discoveries led to important steps regarding dietary adjustments which lessen the effect of the genetic contribution on the phenotype (Plomin et al., 2013). Applying an evolutionary perspective, there are no "good" and "bad" genes. It is well-established that a gene can have effects of both protection and vulnerability. For instance, the same gene is found to have proactive effects against malaria, while increasing the risk of sickle cell anemia (Allison, 1954; Piel et al., 2010). Furthermore, traits are found to be influenced by *pleiotropy*, i.e. when the same genetic factors cause different phenotypes (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), such as the overlap in genetic factors of GAD and MDD, as discussed in section 2.2.2.

Multivariate analyses show that genetic structure is separate from phenotypic structure, in the sense that many different aspects of psychopathology are highly correlated genetically. However, a certain degree of phenotypic similarity is warranted to investigate potential genetic correlation. Additionally, multivariate analyses across age typically find substantial age-to-age genetic correlations (Plomin et al., 2013). These results implicate that genetic factors contribute largely to stability across age, however, environmental factors contribute largely to change across age.

3.4 Statistical Application of Twin Modeling

3.4.1 Structural Equation Models (SEM)

Today, the *structural equation model* (SEM) approach has gained massive popularity in twin research, as it is able to incorporate advanced hypotheses regarding expected correlation between multiple measures. Additionally, it can explicitly compare different models, which

postulate different causal theories, against each other. One way of expressing SEM models is through path analysis of a model, in which a structural model has a set of parameter values. This allows for the calculation of an expected covariance matrix. This is done by minimizing the distance between the observed and expected covariance matrix. The SEM approach is often preferred, compared to other approaches such as multivariate regression or multilevel models, as it is more flexible than more traditional designs (Plomin et al., 2013).

3.4.2 Univariate Analysis

Univariate analysis refers, as noted, to when an analysis is conducted to estimate the relative contributions of genetic and environmental factors to the variance of a singular trait. The analysis can be presented in various ways. One approach is to present a variance-covariance matrix. For an univariate ACE twin model, the variance-covariance matrices for MZ and DZ twins, respectively, would look like this (Plomin et al., 2013):

$$\begin{bmatrix} A+C+E & \\ A+C & A+C+E \end{bmatrix} \qquad \begin{bmatrix} A+C+E & \\ \frac{A}{2}+C & A+C+E \end{bmatrix}$$

The diagonal elements represent the variance of the trait, while the off-diagonal elements represent the covariance between twins in a pair. The only difference of the model is due to DZ twins sharing only half of the A effects, compared to MZ twins.

Another approach is to present a path diagram of the model, illustrated in Figure 1. The identified model is an ACE model, which means that the best fit between the expected and observed matrices is produced by only one set of parameter values (Plomin et al., 2013). The full model, often ACE, will in almost all cases be the best fitting model. However, by dropping parameters, it is possible to assess whether the resulting set of parameter estimates still are able to account for the covariance observed. This is referred to as model trimming. As noted, E can never be zero, as it includes measurement error. However, parameters A and C can be dropped, resulting in nested submodels, such as AE, CE and E models. These models are then directly comparable to the full model. As long as the fit is not significantly worse, simpler models are preferred.

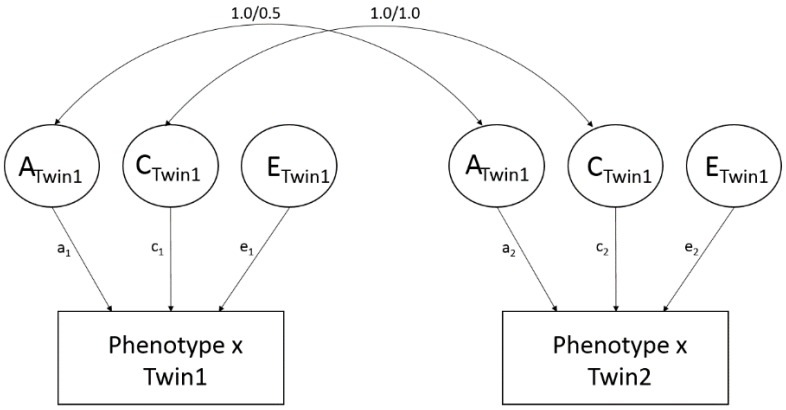

Figure 1. The Classical Univariate ACE Model Depicted as a Path Diagram. Rectangles illustrate observed variables (phenotype x), while circles illustrate latent variables (A, C and E). Single-ended arrows illustrate causal paths (a, c and e), while double-ended arrows illustrate covariance paths. The variance of A, C and E are fixed to 1.0, while a, c and e are estimated based on the variance for the MZ and DZ twins on the measured phenotype. A factors correlate 1.0 for MZ, and 0.5 for DZ twins. The parameter estimates are equal for each twin, and are therefore often simplified by depicting only one twin.

3.4.3 Multivariate Analysis

Multivariate analysis allows, as noted, for investigation of the relative contributions of genetic and environmental factors to the covariance between multiple traits, e.g. estimate the extent to which the same genetic and environmental factors affect different traits, or the same trait across time (Plomin et al., 2013). Bivariate analysis estimate this for two variables. A further utilization made possible by this method is to estimate the genetic correlation between two traits, i.e. examine the extent to which the genetic effects that influence trait X also influence trait Y. The genetic correlation between two traits is completely independent from the heritability of each trait, e.g. the heritability of trait X and Y could be just slightly heritable, yet, the genetic correlation could be high. The genetic correlation is estimated between 0 and 1, 0 thereby implies no association between the genetic effects on trait X and trait Y, while 1 implies that all genetic factors associated with trait X are associated with trait Y.

Multivariate models can be illustrated in the same way as univariate models. For a bivariate ACE twin model, the variance-covariance matrix would look like this (Plomin et al., 2013):

$$\begin{bmatrix} \mathrm{Var}(X_1) & & & \\ \mathrm{Cov}(X_1X_2) & \mathrm{Var}(X_2) & & \\ \mathrm{Cov}(X_1Y_1) & \mathrm{Cov}(X_2Y_1) & \mathrm{Var}(Y_1) & \\ \mathrm{Cov}(X_1Y_2) & \mathrm{Cov}(X_2Y_2) & \mathrm{Cov}(Y_1Y_2) & \mathrm{Var}(Y_2) \end{bmatrix}$$

To utilize this method, use of statistical software designed to manage these data and designs, is necessary. The procedure starts by specifying the model in a script, and provide starting values (which often are more or less informed guesses) for the a, c and e parameters. With the use of optimization tools, the software uses an iterative process to test different values for the parameters from the starting values, until an optimal solution is found that reproduces the observed variance-covariance matrix as closely as possible.

The Cholesky decomposition is a commonly used for multivariate twin models, as it within the same model decomposes variance and covariance into latent factors for several variables. Figure 2 shows a full bivariate ACE model depicted through a path diagram.

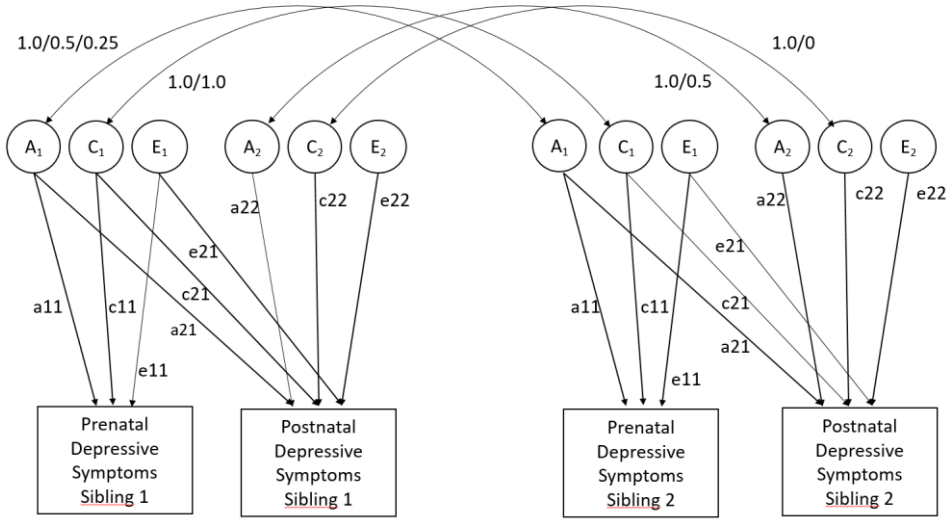

Figure 2. Full Path Diagram for the Classical Bivariate ACE Model. Parameters represent the same constructs as in the univariate model. Causal paths between trait X and trait Y are added in multivariate models.

3.4.4 Statistical Software

The most commonly used software, when working with twin models, is the R software (R Core Team, 2017). The R software has a general statistical purpose, and allows for flexible and powerful statistical operations within several fields. OpenMx (Boker et al., 2011) is an extension package of R, and thus utilizes functions and properties from the R software. It has been developed specifically to facilitate the implementation of multivariate twin and family models into the R software.

3.4.5 Optimization and Fit Function

The process of identifying the best fitting parameter estimates is referred to as *optimization*. When utilizing OpenMx to fit twin models, two standard optimization tools are provided; *maximum-likelihood* (ML) and *full information maximum likelihood* (FIML). ML provides information about the likelihood of a model as a function of the observed data and the model parameters. This likelihood is measures as a log-likelihood (LL). The overall LL should be

maximized by moving the values of the estimated free parameters to minimize the distance between the observed and expected variance-covariance matrices. In comparison, FIML utilizes the raw scores for each twin instead of the observed variance-covariance matrices to obtain the highest likelihood of the data. This also includes cases where there is missing data, which is an advantage. However, both ML and FIML are computationally demanding and sensitive to starting values. Another statistic, the *likelihood-based confidence intervals* (CIs) is utilized to express the amount of certainty to the resulting parameter estimates. CIs are found by moving away from the obtained parameter estimates in both directions, until the *chi-squared* ($\chi 2$) distributed differences in fit is significant. The CIs can be asymmetrical around the estimate, as they are likelihood-based (Rijsdijk & Sham, 2002).

3.4.6 Goodness of Fit

As statistical models may have only subtle differences in their overall goodness of fit, it is important to have an informed method of comparing the models. The statistic Δ-2LL involves the difference (Δ) in -2 times log likelihood between two models, and approaches a $\chi 2$ -square distribution, which allows a check for significant deterioration in $\chi 2$ in two nested submodels. Additionally, the Akaike Information Criterion (AIC), calculated as $\chi 2$ - 2df (the chi-square minus two times the number of degrees of freedom) provides information about the parsimony of models. A lower AIC-value reflects a more parsimonious model and is preferred.

4 Research Objectives

The presented analyses allow for investigation of the genetic and environmental factors contributing to perinatal depression. Investigation of how these are distributed at each time point, as well as correlation between them, makes it possible to assess and compare their etiology. This may represent an important step towards a better understanding of whether prenatal and postnatal depression represent the same construct.

This thesis therefore aims to answer two research objectives:

1) Estimate the relative importance of genetic and environmental factors for depression during and after pregnancy.
2) Estimate the genetic and environmental correlation between depression during pregnancy and after pregnancy, i.e. estimate the extent of genetic innovation.

5 Methods

5.1 Sample

The sample used in this study is a subsample of the Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health (NIPH). MoBa is a prospective, ongoing, pregnancy cohort study (Magnus et al., 2006). It has been granted a license from the Norwegian Data Inspectorate. The material consists largely of questionnaires, however, biological material is also collected. Blood sampling was conducted at the time of recruitment and birth. Several questionnaires have been administered in week 17 and 30 during pregnancy, 6 months postpartum and when the children were age 18 months, 3 years, 5 years, 7 years and 8 years old. Later questionnaires have been administered approximately every second year. The data collected include a wide spectrum of topics, including demographics, health, lifestyle, somatic diseases, learning and language, and is targeted at both children and parents (Magnus et al., 2016). Written informed consent was obtained from all participants upon the time of recruitment.

Recruitment took place between October 1999 and July 2009, at a routine ultrasound examination offered to all pregnant women in Norway, timed at gestational week 17-18. In total, 41% of eligible women participated. The total sample now exceeds 114,500 children, 95,000 mothers and 75,000 fathers (Magnus et al., 2016). The mean age of women participating were in September 2015 40.8 years old. At the same time point, 53% of the women participating were between 40 and 50 years old.

The subsample used in this thesis is part of the Intergenerational Transmission of Risk study (IToR), in which the aim is to gain insight into the causal mechanisms underlying common mental disorders, by studying genetic and environmental modes of transmission of risk for these disorders, intergenerationally. This subsample deviates from the general MoBa sample in the sense that relatedness is more closely identified. For this subsample, not only are the parents separated from the children, but within each generation, full siblings, half siblings and twins (monozygotic and dizygotic) are identified, through the use of registry linkage, genotyping and questionnaires.

The present study utilized data from 64 MZ twin pairs, 35 DZ twin pairs, 5540 full sibling pairs, and 400 half sibling pairs (maternal and paternal) from the parental generation of MoBa siblings. As noted, this study utilizes an extended twin design, which includes siblings. Naturally, only female siblings were included, as the topic of study is perinatal depression.

As the MoBa study does not identify relatedness among the parents participating, relatedness was identified by linking the MoBa cohort to Statistics Norway, which tracks

details about relatedness in the Norwegian population, including plural births. MoBa was linked to the Norwegian Twin Registry (NTR) in order to identify zygosity for the same-sex twins. For those twins who were not registered in NTR, zygosity was determined using a twin questionnaire, which was administered by phone or mail. These questionnaire items have also previously been shown to correctly classify more than 97% of twin pairs (Magnus, Berg, & Nance, 1983). This information was lacking for 16% of the twin pairs, and thus, zygosity of these twins were predicted based on similarity in height, weight, age at menarche, allergies, blood pressure and metabolism. These predictions were obtained by fitting a lasso logistic regression (Hastie & Qian, 2014) to the twin pairs where zygosity was already established. This resulted in correct classification in 87% of the cases.

5.2 Measures

As noted, various questionnaires are often used to assess symptoms of mental illness. One such instrument is Symptom Checklist 90 (SCL-90) (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974). The SCL-90 is one of the most widely used instruments assessing various symptom dimensions of psychological distress, including depression. The SCL-25 is an abbreviated version, developed to focus on depression and anxiety, consisting of respectively fifteen and ten items (Najarian & Davoodi, 2001). It has been found to have acceptable reliability and validity as a measure of psychological distress (Müller, Postert, Beyer, Furniss, & Achtergarde, 2010; Strand, Dalgard, Tambs, & Rognerud, 2003). A further abbreviation of this is the eight item SCL-8. This is the short-form version used in this study, administered at week 30 of gestation, and 6 months postpartum. SCL-8 contains four out of the fifteen items in SCL-25, and has been shown to correlate at .92 with the depression score of the full SCL-25 (Tambs & Røysamb, 2014).

In this study, the focus was on depressive symptoms, and only the items on depression are included in the analyses. These four items were “Worrying too much about things”, “Feeling blue”, “Feeling helpless about the future” and “Feeling everything is an effort”. The participants were asked to what extent a set of statements, i.e. the items, were true for the last 2 weeks. They were asked to respond on a 4- point scale, which included the following responses: 1 (“not bothered”), 2 (“slightly bothered”), 3 (“fairly much bothered”) and 4 (“very much bothered”). The data were treated continuously, rather than as a diagnostic cut-off score. Higher scores indicate more depressive symptoms.

Several responses or no response were coded as missing data. Missing data was treated according to how many items data was missing on. If two or more responses were missing at

one time of measurement, the participants were excluded from further analysis at that time point. If only one response was missing, the missing score was estimated by calculating the average of the collected three responses at that time of measurement.

5.3 Literature Search

Literature search has been conducted continuously during the time spent writing this thesis. The databases Google Scholar and PsychInfo have been the primary sources of literature attainment, limited to articles written in English. The focus of the search has been on discovering reviews and meta-articles, as a meta-perspective on the literature was considered imperative for interpretation of the emerging results. However, also various primary studies have been included where this is found appropriate, either as a result of targeted search, or of it being referenced by articles attained during the primary search.

5.4 Statistical Analyses

5.4.1 Descriptive Analyses

First, descriptive statistical analyses were performed to examine the central tendencies and statistical dispersion, such as means (SD) and score distributions, of the variables, as well as to assess internal consistency, measured by Cronbach's Alpha. The bivariate associations between prenatal and postnatal depression were assessed using Pearson correlation analysis.

5.4.2 Twin Analyses

Second, after inspecting the outcomes of descriptive statistical analyses, biometric analyses were conducted, in order to estimate the genetic and environmental contributions to prenatal and postnatal depressive symptoms, as well as to the covariance between them. In the specification of the biometric analysis, the correlation between A effects among siblings were set to 1 for MZ twins, 0.5 for DZ twins and full siblings, and 0.25 for half siblings, on the basis of the relatedness accounted for in section 3.3. C effects where assumed to be equally shared among all groups of siblings, while E effects were assumed to be unique to the individual.

Several biometric analyses were conducted in order to identify the best-fitting model. A complete ACE model was compared to nested submodels, in order to assess the effect of trimming the model. All models were run using the OpenMx, version 1.0.153. Standard Cholesky models (see Figure 2) were used to estimate genetic and environmental effects to the variance in pre- and postnatal depression, as well as to the covariance between prenatal and postnatal depression. Specifically, qualitative gene-environment interaction was tested by dropping the specific genetic variance component for postnatal depression, rendering a

genetic correlation of unity. Quantitative gene-environment interaction was tested by equalizing the respective genetic effects of the common genetic factor on pre- and postnatal depression.

6 Results

Results of the conducted analyses are presented in this section. First, descriptive results. Second, model fitting results. Some of the results presented here are standardized, as it facilitates interpretation.

6.1 Descriptive Results

In total, a relatively large sample of women participated (N = 12 078). Prenatally, 79% of observations were included in the analysis, whereas 21% of the observations were excluded from analysis. Postnatally, 70.8% of observations were included in the analysis, whereas 29.2% were excluded.

Descriptive statistics and inter-item correlations of the items studied prenatally are presented in Table 1, and postnatally in Table 2. The items are listed in the following order: "Feeling hopeless about the future" (item 1), "Feeling blue" (item 2), "Worrying too much about things" (item 3) and "Feeling everything is an effort" (item 4).

Overall, the symptom severity was low across items, at both time points. Prenatally, means ranged from 1.16-1.46, whereas they ranged from 1.21-1.42 postnatally. The item with the highest means across both time points were "Feeling everything is an effort", which arguably may be somewhat inflated due to general effects of pregnancy and caring for an infant, not directly related to depression. The items were summed to a total score for analysis. Scale statistics of the total scores both prenatally and postnatally are presented in Table 3.

There were moderate positive correlations between all items, both prenatally (ranging from .35-.51) and postnatally (ranging from .39-.54). The highest correlation across both time points was between item "Feeling blue" and item "Feeling hopeless about the future". The moderate correlations indicate that the items are related, i.e. relates to an underlying construct, such as depression, however, they also indicate that the items measure distinct parts of the construct.

Table 1. *Inter-Item Correlation Matrix for Prenatal Depressive Symptoms*

	Mean±SD	*Item 1*	*Item 2*	*Item 3*	*Item 4*

Item 1	1.16 ± .43	*1.00*			
Item 2	1.25 ± .51	.51	1.00		
Item 3	1.36 ± .58	.44	.48	1.00	
Item 4	1.46 ± .62	.34	.43	.35	1.00

Table 2. *Inter-Item Correlation Matrix for Postnatal Depressive Symptoms*

	Mean±SD	*Item 1*	*Item 2*	*Item 3*	*Item 4*
Item 1	1.21 ± .50	1.00			
Item 2	1.25 ± .51	.54	1.00		
Item 3	1.30 ± .55	.50	.50	1.00	
Item 4	1.42 ± .62	.42	.49	.39	1.00

Table 3. *Scale Statistics for Depressive Symptoms Prenatally and Postnatally*

	Mean	Variance	SD
Prenatal Depressive Symptoms	5.23	2.62	1.62
Postnatal Depressive Symptoms	5.19	2.83	1.68

6.1.1 Reliability

Reliability is the proportion of variance in the observed scores due to true scores (Bordens & Abbott, 2002). In order to investigate internal consistency, a Chronbach's Alpha reliability analysis was performed. The results show reliability at an acceptable level, as it ranges within .7 and .8 (Kline, 1999). For prenatal depressive symptoms, the reliability was .74. For postnatal depressive symptoms, the reliability was .77.

6.1.2 Phenotypic Correlation

The total phenotypic correlation between prenatal and postnatal depressive symptoms was .48 (0.46-0.49 with 95% confidence interval), reflecting a moderate correlation. The phenotypic variance denotes all factors for prenatal or postnatal depression in the population (i.e. genetic and environmental factors). The correlation denotes the total overlap between these factors. This is illustrated in Figure 3.

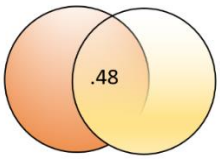

Figure 3. Total Phenotypic Correlation Between Prenatal and Postnatal Depressive Symptoms. Orange circle (left) illustrates the variance of prenatal depression, while the yellow circle (right) illustrates the variance of postnatal depression. The overlap illustrates their correlation (r = .48).

6.2 Model Fitting Results

6.2.1 Twin Model Fitting

To further investigate the relative contributions of genetic and environmental factors, model fitting was conducted. The fit statistics for the modeling are shown in Table 4.

First, a fully saturated ACE model ("ACE") was tested against the data on both pre- and postnatal depressive symptoms, which would allow for both genetic effects, as well as shared and unique environmental effects. The full ACE model constitute the model of reference, to which the fit of the other two models were compared (-2LL = 73461.46, df = 19681, p = -, AIC = 34099.46).

Second, an AE model ("AE") was conducted. This was done to investigate whether or not removing the shared environmental effects (C) had a significant effect on the results. This was not a significantly worse fit, hence, in accordance with the concept of making a model as parsimonious as possible, it was chosen for further analysis ($\chi 2 = 0.82$, $\Delta df = 3$, $p = 0.84$, $\Delta AIC = -5.18$).

Third, a constrained AE model ("AE2") was conducted. to test qualitative gene-environment interaction. In this model, the additive genetic effects unique to postnatal depressive symptoms were constrained to 0. This renders a genetic correlation of unity, and was done in order to investigate the overlap in additive genetic effects to depressive symptoms at each of the time points more closely. This model did not show a significantly worse fit than the previous AE-model ($\chi 2 = 1.56$, $\Delta df = 4$, $p = .82$, $\Delta AIC = -6.44$). Thus, it was the model that portrayed the information provided in the data in the simplest way.

Fourth, a furthermore constrained AE model ("AE3") was conducted to test quantitative gene-environment interaction. In this model, the additive genetic effects for pre- and postnatal depression was constrained to be the same. This model had a worse fit to the

data ($\chi 2 = 8.31$, $\Delta df = 5$, $p = .14$, $\Delta AIC = -1.69$), indicating that in the best fitting model, genetic effects were larger for postnatal than prenatal depression.

Table 4. *Comparison of Model Fits*

Model	-2LL	*df*	P	AIC
ACE	73461.46	19681	-	34099.46
AE	73462.28	19684	0.84	34094.28
AE2	**73463.02**	**19685**	**0.82**	**34093.02**
AE3	73469.77	19686	0.14	34097.77

A full Cholesky decomposition of an ACE model, without parameter estimates, is previously presented in Figure 2. The parameter estimates of the various models are presented in Table 5, including standard error (SE) and confidence intervals (CI). Lastly, the preferred model is presented through a simplified Cholesky decomposition, in Figure 4.

Table 5 *Parameter Estimates of the Models up to Best Fitting Model.*

	ACE			AE			AE2		
Parameter	Estimate	SE	95% CI	Estimate	SE	95% CI	Estimate	SE	95% CI
M pre	5.24	.02	5.20 – 5.27	5.24	.02	5.20 – 5.27	5.24	.02	5.20 – 5.27
M post	5.21	.02	5.17 – 5.24	5.21	.02	5.17 – 5.24	5.21	.02	5.17 – 5.24
a11	.48	.35	-.78 – .78	.68	.06	.55 - .79	.66	.06	.53 - .77
a21	.44	.54	-.96 - .96	.81	.09	.64 - .96	.86	.06	.74 - .97
a22	.28	.35	-.56 - .56	.33	.18	-.57 - .57	-	-	-
c11	.34	.23	-.54 - .54	-	-	-	-	-	-
c21	.49	.28	-.68 - .68	-	-	-	-	-	-
c22	.00	.35	-.37 - .37	-	-	-	-	-	-
e11	1.52	.06	1.43 – 1.59	1.48	.03	1.43 – 1.54	1.49	.03	1.44 – 1.55
e21	.64	.11	.47 – .76	.54	.04	.46 - .63	.52	.04	.45 - .60
e22	1.41	.07	1.31 – 1.46	1.36	0.03	1.30 – 1.42	1.37	.03	1.32 – 1.42

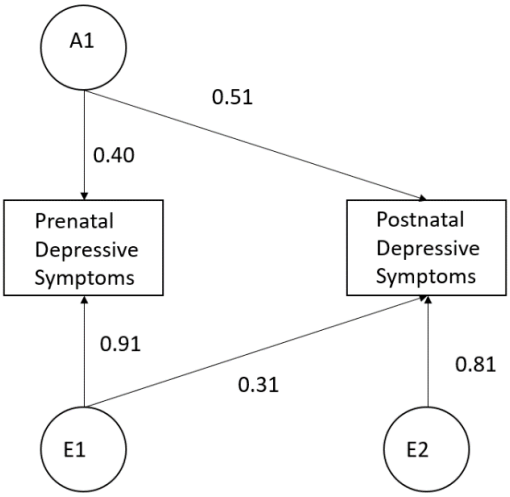

Figure 4. Simplified Cholesky Decomposition of the Resulting AE Model. Path coefficients are standardized.

6.2.2 Genetic and Environmental Factors for Prenatal and Postnatal Depressive Symptoms

Based on the discussed model, the relative importance of genetic and environmental factors for prenatal and postnatal depressive symptoms were estimated. The results are presented separately for pre- and postnatal depressive symptoms, and illustrated in Figure 5.

For prenatal depressive symptoms, the genetic, environmental, and phenotypic variance was 0.43, 2.23, and 2.66, respectively. The relative importance of genetic factors (i.e. the heritability) for prenatal depressive symptoms were 16.2% (95% CI = 10.7 – 22.1), whereas environmental factors were 83.8% (95% CI = 78.0 – 89.3).

For postnatal depressive symptoms, the genetic, environmental and phenotypic variance was 0.75, 2.16, 2.90, respectively. These numbers correspond to 172%, 97%, and 109% of the estimates for prenatal depressive symptoms, respectively. The relative importance of genetic factors (i.e. heritability) for postnatal depressive symptoms were 25.7% (95% CI = 19.2 – 32.2), whereas environmental factors were 74.3% (95% CI = 67.8 – 80.8).

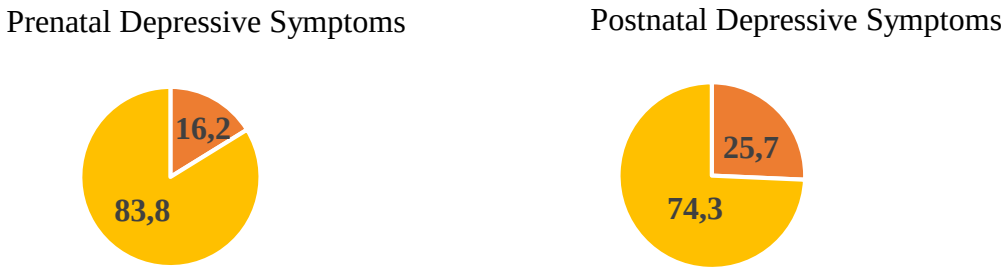

Figure 5. Relative Importance of Genetic and Environmental Factors for Prenatal and Postnatal Depressive Symptoms. Prenatal depressive symptoms are shown to the left. Postnatal depressive symptoms are shown to the right. Genetic effects (A) are illustrated by the orange color, whereas environmental effects (E) are illustrated by the yellow color.

6.2.3 Genetic and Environmental Correlation Between Prenatal and Postnatal Depressive Symptoms

The genetic and environmental correlation between depressive symptoms during and after pregnancy were estimated, in order to assess whether there were unique genetic effects important to postnatal depressive symptoms. The results are presented separately, followed by an illustration in Figure 6.

Genetic effects unique to postnatal depressive symptoms were constrained to zero, resulting in a genetic correlation of 1.00, without significantly poorer fit of the model. This indicates no significant genetic innovation in postnatal depressive symptoms.

The correlation of environmental effects was .35. This indicates that the innovation of environmental effects was substantial.

Figure 6. Overlap of Genetic and Environmental Effects Across Timing. Extent of overlap between genetic effects (green color) and environmental effects (blue color) between prenatal and postnatal depressive symptoms.

6.2.4 Gene-Environment Interactions

The unity of genetic risk factors for prenatal and postnatal depression indicates that the same causal genetic variants have effect prior to and following delivery. This can be conceptualized as a (lack of) *qualitative* gene-environment interaction (Purcell, 2002). The 172% higher genetic variance postnatally compared to prenatally indicates that the same causal genetic

variants have stronger effects postnatally than prenatally. This can be conceptualized as a *quantitative* gene-environment interaction (Purcell, 2002). The consequential increase in heritability was not artifactual, since it could not be explained by a decrease in environmental variance.

7 Discussion

This study sought to assess the heritability of prenatal and postnatal depressive symptoms, as there is some debate as to whether they constitute the same, or different, constructs. The aims were to assess the relative importance of genetic and environmental factors at each time point, as well as investigate the correlation between these two, i.e. whether there were unique genetic effects contributing to postnatal depressive symptoms. This was done by utilizing a bivariate Cholesky model, on a relatively large sample of twins and siblings from the MoBa study. In this section, the results, and potential implications of these, are discussed.

The main findings were that genetic factors were of low importance both prenatally and postnatally, while environmental factors were of high importance. There was no genetic innovation, whereas there was substantial environmental innovation. Furthermore, there was a qualitative gene-environment interaction, in the sense that the same genetic factors were more important following, than prior to, delivery.

7.1 What Can Explain the Association Between Prenatal and Postnatal Depressive Symptoms?

7.1.1 Contributions from Genetic and Environmental Factors for Depressive Symptoms Preceding and Following Delivery

As presented, the twin results of this study showed that the genetic effects for prenatal depressive symptoms explained 16.2% (95% CI = 10.7%–22.1%) of the variance. This is lower than the genetic contributions estimated in the recent Swedish twin study which estimated heritability of prenatal depression at 37% (95% CI=27% - 47%) (Viktorin et al., 2016), despite both using an extended twin design including siblings. This may be due to various reasons. One, the measurement instrument and timing of measurement varied. This study measured symptoms across two particular weeks of the perinatal period, while the Swedish study measured symptoms across the whole perinatal period up to 12 months following delivery. Stable risk factors, such as genetic effects, become more prominent with aggregation of observations across time (Torvik, Gustavson, et al., 2018). Two, while all pregnant women were eligible for our sample, the Swedish study required that the depression was under some form of treatment, possibly censoring environmental variance in the

population (Torvik, Ystrom, et al., 2018). Three, while designs relying on siblings to a great extent estimate narrow sense heritability (i.e. additive genetic factors), the classical twin design, relying to a great extent on MZ twins, also capture non-additive genetic effects, approximating broad sense heritability (Plomin et al., 2013). A pure twin design may have yielded different results, however, given the relatively small number of twins included in the study, statistical power would have been insufficient. Taken together, the existing evidence on risk factors of prenatal depression suggests a heritable component (Serati et al., 2016), although, of unknown importance, and appears to be less important than in postnatal depression.

Environmental factors contributed to explain 83.8% (95% CI = 78 – 89.3%) of the variance in prenatal depressive symptoms in this study. The finding that environmental factors are of larger importance than genetic factors to prenatal depression is in line with the recent Swedish twin study, reporting E effects explaining 63% of the variance (95% CI = 51–73%) (Viktorin et al., 2016). In both studies, environmental factors were limited to nonshared environmental effects, whereas shared environmental effects were not significant. The findings of low impact of shared environment is not uncommon in twin research, as it does not appear to contribute significantly to variance in traits in larger samples (Turkheimer, 2000). These studies employed a sibling design, which, as noted, may allow for a more accurate generalization to the population, however, also entails a less controlled sample. As non-twin siblings and half siblings differ more in shared environmental factors than twins do, such as age, living situation, social group, etc., it logically follows that the shared environmental factors may be lower than what is found in regular twin studies, and unique environmental factors may be higher. As noted, E always includes measurement errors, and thus, it may be somewhat inflated. Furthermore, the finding that nonshared environmental effects are high is common in research on major depression in general (Sullivan et al., 2000). As previously discussed, existing research suggests that there are several important environmental risk factors relevant to the prenatal period, such as low partner support, life stress, lack of social support, domestic violence, substance abuse and unintended pregnancy (Biaggi et al., 2016; Leigh & Milgrom, 2008). These are examples of factors that twins and siblings may reasonably vary on, independent of each other, i.e. they may contribute to the nonshared environmental variance.

For postnatal depressive symptoms, the relative importance of genetic factors (i.e. heritability) was 25.7% (95% CI = 19.2%–32.2%). This is in line with the earliest twin study

available, which found that genetic factors explained 25% (CIs not reported) of the variance in postnatal depression (Treloar et al., 1999). It is, however, lower than the most recent one, which found that genetic factors explained 40% (95% CI = 31%-49%) of the variance (Viktorin et al., 2016). Heritability is, as noted a characteristic of the population studied, not of the phenotype in itself. Hence, these differences in estimates could be due to the reasons aforementioned for prenatal depression, to differences in the population (e.g. secular trends in health care or partner support), or due to randomness under the same sampling distributions. Aforementioned differences between the studies may also have influenced the difference in results. Taken together, existing literature on postnatal depression suggests a heritable component, however, the exact nature and extent of this heritability is unknown (e Couto et al., 2015; Figueiredo et al., 2015).

The environmental factors explained 74.3% (95% CI = 67.8–80.8%) of the variance in postnatal depressive symptoms in this study. As noted, nonshared environmental factors have been found to explain 75% (CIs not reported) (Treloar et al., 1999) and 60% (95% CI = 51%–69%) (Viktorin et al., 2016) of the variance in postnatal depression, and thus, this study appears to be in line with the previous research in the sense that nonshared environmental effects appear to be of great importance. Several important risk factors to postnatal depression have, as presented, been suggested in the literature. Many of the risk factors are shared with depression occurring at other times such as low social support, stressful life events, neuroticism and low self-esteem (Eberhard-Gran et al., 2002; O'Hara & McCabe, 2013; O'Hara & Wisner, 2014), whereas some, as discussed, may be more ingenious and particularly relevant to the postnatal period, such as childcare-related stressors, lack of sleep, and postpartum blues (Beck, 2001; Brummelte & Galea, 2016; O'Hara & Wisner, 2014). These are factors that may reasonably vary among twins, and thus, may contribute to the nonshared environmental factors contributing to variance.

The finding that the genetic variance of postnatal depressive symptoms was 172% of the corresponding estimate of prenatal depression indicates, as presented, a quantitative gene-environment interaction, i.e. that the same genes have different impact prior to and following delivery (Plomin, DeFries, & Loehlin, 1977). This finding indicates that the same genes are involved across time, however, they appear to exert a stronger effect postnatally than prenatally. This is an important finding in terms of how the genes and environment interact. More generally, it is important to yet again underline that although effects of genes and environment are separated in terms of behavioral genetics studies, they are by no means

independent of each other. There are various ways in which this may come into play. There exists a degree of heritability in virtually every trait studied, as well as in life events (Kandler, Bleidorn, Riemann, Angleitner, & Spinath, 2012; Kendler & Baker, 2007; Plomin et al., 2013). Thus, there is considerable interaction between genes (G) and environment (E), often abbreviated *GxE interaction*. GxE refers to when the effect of the environment on a phenotype is dependent upon genotype, or, that the effect of a genotype on a phenotype is dependent upon the environment. This is in line with general vulnerability-stress models, which, as noted, postulate that individuals with genetically increased risk for psychopathology are particularly sensitive to the effects of stressful environments (Plomin et al., 2013). Various studies have shown that environmental factors can activate and inhibit effects of the genetic predispositions of individuals (Burkhouse, Gibb, Coles, Knopik, & McGeary, 2011; Kim-Cohen et al., 2006; Plomin et al., 2013). This may apply to this study as well. Environmental factors might thus contribute to both increase and reduce the risk of experiencing perinatal depressive symptoms. Furthermore, the contexts of which the women live in, is different from the prenatal to the postnatal period, providing distinct environmental stressors, such as new responsibilities and routines (Leigh & Milgrom, 2008). This may influence the genotypic contribution to the phenotype of depression in distinct ways. For instance, the finding that there is a reciprocal relationship between postnatal depression and parenting stress, i.e. the level of stress within the parent-child system, is an example of how different environmental risk factors can contribute to depression postnatally than prenatally, even though other risk factors are found to be substantially interrelated (Leigh & Milgrom, 2008).

7.1.2 Contributions to Stability and Change in Risk Factors for Depressive Symptoms Preceding and Following Delivery

The phenotypic correlation between pre- and postnatal depression was estimated at .48. This is lower than the temporal stability using patient registry data in Norway. Torvik, Gustavson and colleagues (2018) found the two-, four-, and six-year stability of diagnoses to be .75, .60, and .47, respectively. However, when using clinical interviews on a population based sample, Torvik and colleagues (2017) found the five-year stability to be .33. It could be that diagnoses in a registry is more dependent data due to factors related to the clinician. It could also be that diagnoses to a lesser extent capture total variance in risk factors for depression, inflating the estimated correlation across time.

As noted, a general tendency is that genetic factors are found to contribute to measured stability over time, whereas nonshared environmental factors are found to

contribute to change (Plomin et al., 2013). As presented, the genetic effects unique to postnatal depressive symptoms were constrained to zero, resulting in a genetic correlation of 1.00, without significantly poorer fit of the model. This implies that the genetic factors are the same, i.e. genetically prenatal and postnatal depressive symptoms are at unity. Alternatively, this can be expressed as zero genetic innovation in postnatal depressive symptoms. This appears contradictory to earlier findings of overlapping, but not uniform, genetic factors across the perinatal period (Figueiredo et al., 2015). This finding can be seen as a rejection of a hypothesis on qualitative gene-environment interaction. As discussed, according to the best-fitting model the genetic variance was 172% postnatally than that of prenatal depressive symptoms is indicative of a quantitative gene-environment interaction across time points, i.e. prior to and following delivery. In other words, the genetic factors were stable across time, however, their influence increased.

The genetic correlation at unity does not have to be causal genetic variants coding for genetic risk only within the organism. The genetic correlation between pre and postnatal depression could be due to common factors conceptualized as measured "environmental" factors in non-genetically informative studies. The point being, that exposure to environmental factors contributing to depression appear to, as discussed in the introductory sections, occur non-randomly, i.e. it is influenced by genetic factors (Kendler & Baker, 2007), as discussed in the introductory sections, it is influenced by correlation between genes and environment (Plomin et al., 2013). Heritability estimates for a wide array of environmental factors have been conducted (Kendler & Baker, 2007). Stable heritable personality traits, such as neuroticism and introversion (Jang et al., 1996; John et al., 2008), could be common factors for prenatal and postnatal depression. Partner selection and relationship conflicts, also related to genetic factors and personality (John et al., 2008; Kandler et al., 2012), could represent active and evocative gene-environment mechanisms, respectively, driving the high observed genetic correlation. The large categories of risk presented earlier, overlapping between both prenatal and postnatal depression, as well as between perinatal and non-perinatal depression (stressful life events, history of psychopathology and poor social support) consist of contributions from both genetic and environmental factors with considerable correlation (Kendler & Baker, 2007). Regardless, the point is that a high genetic correlation does not imply that there are not common factors that can be intervened on.

The correlation of environmental effects was .35 in the postnatal measurement of depressive symptoms. This indicates substantial environmental innovation. In other words,

the stressors contributing to depressive symptoms appear endogenous to the postnatal period. In a recent twin study, the environmental correlation of MDD was found at .36 over a period of 4 years in an adult sample comparable to the sample studied in this thesis, although it included both genders (Torvik, Gustavson, et al., 2018). One could therefore argue that the transition from pregnancy to becoming a mother appears comparable to several years, in terms of extent of uniqueness of the environmental factors contributing to the depressive symptoms. Accordingly, the transition to motherhood is associated with significant emotionality and distress, even in women not experiencing psychopathology of clinical value (Rallis et al., 2014). It may involve considerable changes in lifestyle and routines, e.g. disruption, as well as introducing major, possibly additional, responsibilities (Duarte-Guterman et al., 2019; Leahy-Warren, McCarthy, & Corcoran, 2012; Rallis et al., 2014). For multiparous women, i.e. having given birth more than once, giving birth to a new baby might put a strain on resources available to care for the infant's siblings, as well as other tasks. Additionally, various somatic and hormonal changes are occurring concomitantly. Some therefore advocate for a broader definition of perinatal distress rather than simply depression and anxiety (Rallis et al., 2014). What is more, if prenatal depression in itself, or the risk factors thereof, directly caused postnatal depression, we would expect that the genetic and environmental correlations to be equal. The current findings indicate less room for such an interpretation of the factors for stability in perinatal depression. Although, there is some room, since only an environmental correlation of zero rules out such an interpretation. However, if the stability in perinatal depression was solely due to mediating factors, we would also expect the genetic and environmental correlations to be the same. The current findings then also limit the room for putative mediating factor that can be intervened on during this period. It could be that the observed gene-environment interaction is a better place to lay interventions than using an additive mediation model.

As discussed in the introductory sections, some propose a subgroup of women who are particularly vulnerable to the mood effects of hormonal changes (Bloch et al., 2003), as various hormonal factors and hormonal changes are associated with perinatal and non-perinatal depression in women (Kendler, Gardner, et al., 2001; Kendler et al., 2010; Kuehner, 2017). *Reproductive depression* is proposed as an overreaching subtype of depression, in which depressive symptoms are occurring concomitant with reproductive events, such as in the perinatal period (Stuart-Parrigon & Stuart, 2014), which may have contributed to observed depressive symptoms. Furthermore, dysregulation of the HPA-axis is, as noted, suggested to

have a depressogenic, as well as differentiating, effect, preceding and following delivery, which may contribute to depression at both times (Dickens & Pawluski, 2018; Kammerer et al., 2006).

By extension, hormones and neurotransmitters are found to potentially affect neuroplasticity, which is linked to the perinatal period (Figueiredo et al., 2015). Some research suggests that there are significant structural and functional brain changes related to the perinatal period, both during and following gestation (Brunton & Russell, 2008; P. Kim et al., 2010). Some of these appear transient, whereas others appear to have long-lasting effects (Hoekzema et al., 2017). These long-lasting effects appear to affect how the woman's brain responds to challenges later in life, such as hormones, diet and stress, long after the reproductive event (Duarte-Guterman et al., 2019). These changes are predominantly found to facilitate maternal behavior, however, they are also proposed to increase the risk of psychopathology, such as perinatal depression (Brunton & Russell, 2008; Duarte-Guterman et al., 2019). Evidence is more solid in animal studies, such as on rodents, however, also increasing in human mothers (Macbeth & Luine, 2010). One example is that it is suggested that the changes in hormonal levels throughout the ovarian cycle modulate neuronal excitability through effects on $GABA_A$ receptors, and that this constitutes an increased risk of postnatal depression (Brunton & Russell, 2008; Maguire & Mody, 2008). As discussed, GABA dysregulation is suggested as a potential contributing factor to late-onset postnatal depression in particular (Burke et al., 2019). Furthermore, pregnancy is associated with transient cognitive impairments, particularly in terms of memory and executive functions, and these impacts appear to be exacerbated by multiparity (Duarte-Guterman et al., 2019). By extension, a speculation in this regard is that there may be something about pregnancy and childbirth (i.e. "by design") that bring forth changes that are perceived as illness, which may intrinsically be evolutionary features that facilitate change in behavior, as a consequence of the event of reproduction. For example, there has been put forth theories on how aspects of depression is more a "feature" than a "bug" in human affect processing (Durisko, Mulsant, & Andrews, 2015). The combined finding of same genes, but larger genetic effects postpartum could indicate that "normal" aspects of genetic risk for depression is applied to a greater extent in this specific context.

There is also some evidence that perinatal sleep changes contribute to mood states (Dørheim et al., 2014; Okun et al., 2011). It is hypothesized that chronic sleep deprivation mediates the link between baby blues and postnatal depression, i.e. for most women, mood

improves in parallel with a gradual reduction in sleep disturbances, whereas for other women who continue to experience these disturbances, negative mood may develop into a depressive episode (Ross, Murray, & Steiner, 2005). However, evidence is limited.

Recently, an antidepressant medication for the treatment of postnatal depression was approved for the first time (Frieder, Fersh, Hainline, & Deligiannidis, 2019). An exhaustive elaboration on antidepressant medication, and selective serotonin reuptake inhibitors (SSRIs) in particular, exceeds the scope of this thesis, however, this study proposes that the genetic factors are at unity. Thus, possibly prompting questions regarding the foundations of a medication targeting solely *postnatal* depressive symptoms, as prenatal depressive symptoms appear influenced by the same genetic factors.

It is also important to underline the findings in relation to depression and women in general, also including non-perinatal depression. As discussed, there is a peak in depressive episodes which coincide with the reproductive period. Furthermore, challenges to depression in general, i.e. non-perinatal depression, such as recurrence, stress-vulnerability, possible kindling, and gender differences in depression may influence the occurrence of perinatal depression, regardless of pregnancy and childbirth per se.

7.2 Implications

This study suggests that the same genetic factors are important for depressive symptoms occurring both prenatally and postnatally, whereas the environmental factors are to a great degree changing. The genetic factors appear to be of limited importance to perinatal depressive symptoms, however, of larger importance postnatally than prenatally. This calls for a further investigation into what might exacerbate the effects of the same genetic factors following childbirth. Some possible mechanisms have been suggested here. As noted, there is consistent evidence that the environmental factors are heritable to various degrees, thus, environmental factors may contribute to this finding of increased heritability postnatally. Although prevention and treatment has not been the focus of this study, the results yield implications regarding these aspects. Some of the factors presented here, such as comorbid psychopathology, stressful life events, low social and partner support may contribute to the increase of heritability, while concurrently being factors very eligible for intervention. Factors such as hormonal changes and personality traits, which arguably may be influenced to a stronger degree by genetic factors, may be more difficult to intervene on, however, the genetic factors appear to be of substantially less importance than environmental factors throughout the perinatal period. These findings implicate that the focus of prevention and treatment

should be on reducing the impact of environmental stressors occurring throughout both pregnancy and following delivery, as they appear largely endogenous to each time point. Some specific stressors have been discussed and proposed here, such as transient hormonal changes, sleep disruption and parenting stress.

Several studies underline that the treatment literature for perinatal depression is incomplete, and stress the importance of continued research (Meltzer-Brody et al., 2018; Stuart-Parrigon & Stuart, 2014; Underwood et al., 2016). The context of childbirth may warrant therapeutic needs that differ from those seen in non-perinatal periods, such as accommodation of medication, as well as acknowledging the emerging relationship with the infant (Di Florio & Meltzer-Brody, 2015). As noted, there is some evidence of different perinatal depression trajectories, which may further underline the need for tailored treatment (Putnam et al., 2017; Wikman et al., 2019).

7.3 Methodological Considerations

7.3.1 Reliability

The results showed acceptable reliability at both time points (.75 and .78, respectively), which strengthens the notion that indeed one underlying construct such as depression contributes to the observed results. It is generally accepted that Cronbach's alpha should be at least .7 to ensure the quality of the measurement (Kline, 1999). However, a reliability level of 1 may be undesirable, as it implies that only one construct has been measured. Such as in the case of depression, the presence of both cognitive and affective symptoms appear to contribute to the depressive clinical picture as separate, although correlated, constructs. Thus, a somewhat lower Cronbach's alpha may therefore in fact be a more appropriate measure.

7.3.2 Assumptions of the Twin Method

There are some key assumptions and premises of the twin method which may limit the findings of this study. One assumption is the *equal-environment assumption*, which postulates that the shared environmental factors are equally similar across MZ and DZ pairs. Some controversy remains around this, as some hold that MZ twins are treated more similarly by their environment than DZ twins. However, it is not considered a violation of the equal-environments assumption if the similarities are caused by more similar genotype, and the equal-environments assumption has strong empirical support (Kendler, Neale, Kessler, Heath, & Eaves, 1993; Plomin et al., 2013).

Furthermore, generalizability of twins has been discussed more broadly. There are some important differences between twins and singletons, equal across zygosity, such as lower birthweight, and some delays of cognitive skills, such as verbal ability and IQ (Plomin et al., 2013). However, these differences are generally found to be due to postnatal environment rather than prematurity. In aspects more relevant to this study, such as personality and psychopathology, twins and singletons do not appear to differ significantly (Plomin et al., 2013). This study also included siblings in the analyses, which makes the results here less prone to these possible limitations.

Additionally, the aspect of *assortative mating*, i.e. non-random mating needs to be considered. This refers to the notion that selection of partners occurs non-randomly. There are estimates of correlation between partners on various traits, such as physical traits, intelligence and education (Plomin et al., 2013). In the twin method, positive assortative mating can contribute to correlation between DZ twins, as well as siblings, as assortative mating increases similarity between first-degree relatives (Plomin et al., 2013). Thus, the difference between MZ and DZ twins, which forms the basis of estimating heritability, may be reduced, and consequently contribute to underestimation of heritability.

7.4 Strengths and Limitations

7.4.1 Strengths

There are several strengths to this study. One obvious strength is the relatively large sample size. By extension, the sample included siblings of various relatedness, allowing for a more generalizable heritability assessment. Furthermore, recruitment was very broad, and measurement was conducted prospectively, which allowed for measurement that is not vulnerable to recall bias.

7.4.2 Limitations

There are some limitations to this study. First, the sample may have influenced the results. There may be traits to the women who choose to participate, and continue their participation, in a longitudinal study such as MoBa, that are systematically different from the general population, i.e. selection bias. Yet, as noted, the respondent rate is relatively high and the recruitment broad, potential bias appears to be of limited importance (Nilsen et al., 2009). Furthermore, the questionnaires deployed in these studies are quite early on in the follow-up period, at least for the women participating for the first time, and therefore may suffer less from drop out than questionnaires conducted at a later time point of the MoBa study.

The symptom severity was overall low, across items and across measurement times. The symptom levels being lower is expected in epidemiological studies, particularly compared to clinical studies, nonetheless, this constitutes a limitation to interpretation. As noted, the item with the highest means across both time points were "Feeling everything is an effort". This may arguably may be somewhat inflated due to general effects of pregnancy and caring for an infant, perhaps not directly related to depression.

The measurement method may have influenced the results. It is important to repeat that the measurement method, SCL-8, utilized in this study, measures symptoms, and not a diagnosis, despite demonstrating high reliability and validity. The data collected is continuous, and no clinical cut-off score is utilized, such as in a diagnostic interview. Furthermore, type of depression was not specified. The depressive symptoms observed may be part of recurrent depressive disorder, or non-unipolar depression, i.e. bipolar disorder, which may have influenced the estimates. Also, the timing of measurement, week 30 of pregnancy and 6 months postpartum, may have influenced the responses. Week 30 is well into the third trimester, and may therefore bring about bodily changes which cause symptoms that appear similar to depression, such as fatigue, difficulty sleeping and mood changes (Davis, 1996). Similarly, the timing of the second measurement, 6 months postpartum, may also have influenced the responses. As noted, higher heritability is suggested earlier in the postnatal period. Earlier measurement may allow for a higher prevalence and severity of depressive symptoms. On the other hand, measurement very early in the postnatal period could have led to misclassification of the more transient state of baby blues as depression. At 6 months postpartum, the infant is at an age where it is more active, thereby demanding more of its mother, and hence, depressive symptoms may become more pronounced (Leahy-Warren et al., 2012; Leigh & Milgrom, 2008).

By extension, symptoms of depression is only examined in relation to pregnancy and giving birth. As noted, depression is most prevalent among women of reproductive age. In MoBa, women are recruited solely in effect of being pregnant, hence, there is no readily comparable control group to study depression unrelated to the perinatal period. Whether depressive symptoms occurring in the studied sample would have occurred independently of pregnancy and delivery is therefore difficult to answer. There may be factors in the lives of women that occur at this stage unrelated to pregnancy, which may overlap with a period of childbirth.

Addressing some central limitations of the literature is also warranted. It should be noted that various measures of depression are used, both regarding prenatal and postnatal depression, as well as perinatal depression. The criteria vary among studies, as well as whether depressive symptoms are measured continuously or categorically. Furthermore, there are various definitions of the time frame of depression occurring at these time points.

7.4.3 Conclusion

This study sought to investigate whether prenatal and postnatal depression was the same or distinct phenomena. To answer this, the heritability of depressive symptoms occurring at both time points was investigated. Thus, the aims were to assess the relative importance of genetic and environmental factors at each time point, as well as investigating the correlation between these two, i.e. whether there were unique genetic effects contributing to postnatal depressive symptoms. The main findings were that genetic factors were of low importance both prenatally and postnatally, while environmental factors were of high importance, which is in line with research on major depression in general. There was no genetic innovation, whereas there was a large degree of environmental innovation. Furthermore, there was a quantitative gene-environment interaction, in the sense that the same genetic factors were more important following, than prior to, delivery.

In conclusion, perinatal depression specifically, as major depression generally, appears ingenious to the current context in which people find themselves in at various points in time. This suggests that prevention efforts should be closely related to reducing the occurrence and effects of environmental stressors experienced at each stage of the perinatal period, i.e. during pregnancy and following delivery. As perinatal women already constitute a medically captured group, there are opportunities for preventing, detecting and treating perinatal depression.

7.5 Directions for Future Research

Based on the findings of this study, and the discussed implications of these, there are several suggestions for future research on this topic. This study proposes that genetic factors are of some importance to perinatal depression, whereas environmental factors are of substantial importance, and that these change from pregnancy to after delivery. Several risk factors are identified, as discussed, however, a more thorough understanding of how genetic and environmental factors contribute to depression occurring at these times, is lacking. Further research into the etiology of perinatal depression therefore appears necessary. Data regarding other circumstances which may be relevant to the display of depressive symptoms, such as

health status, role of partner, socio-economic status, etc., are readily available in MoBa. Especially in light of the results, discovering a large proportion of depressive symptoms being caused by environmental factors, as well as an increase in importance of the same genetic factors across the perinatal period, it would be of interest to see future studies examine these associations more closely. The finding that these factors seem mostly unique to each timing may contribute to this task being difficult. However, the finding that perinatal depression is mostly influenced by environmental factors allows for more readily available prevention efforts than genetic findings. A more comprehensive understanding of the etiology of perinatal depression appears crucial to correct treatment, as well as prevention.

8 References

Allison, A. C. (1954). Protection Afforded by Sickle-Cell Trait Against Subtertian Malarial Infection. *British medical journal, 1*(4857), 290-294.

American Psychiatric Association. (APA, 2013). *Diagnostic and Statistical Manual of Mental Disorders (5th ed.).* Arlington VA: Author.

Andrade, L., Caraveo-Anduaga, J. J., Berglund, P., Bijl, R. V., Dragomericka, E., Kohn, R., . . . Wittchen, H. J. I. J. M. P. R. (2003). The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *12*. doi:10.1002/mpr.138

Beck, C. T. (2001). Predictors of Postpartum Depression: An Update. *Nursing research, 50*(5), 275-285.

Beidel, D. C., Frueh, B. C., & Hersen, M. (2014). *Adult Psychopathology and Diagnosis* (7th ed.). Hoboken, NJ: John Wiley & Sons Inc.

Bennett, H. A., Einarson, A., Taddio, A., Koren, G., & Einarson, T. R. (2004). Prevalence of Depression During Pregnancy: Systematic Review. *Obstetrics & Gynecology, 103*(4), 698-709.

Bernstein, I. H., Rush, A. J., Yonkers, K., Carmody, T. J., Woo, A., McConnell, K., & Trivedi, M. H. (2008). Symptom Features of Postpartum Depression: Are They Distinct? *Depression and anxiety, 25*(1), 20-26.

Biaggi, A., Conroy, S., Pawlby, S., & Pariante, C. M. (2016). Identifying the Women at Risk of Antenatal Anxiety and Depression: a Systematic Review. *Journal of Affective Disorders, 191*, 62-77.

Bloch, M., Daly, R. C., & Rubinow, D. R. (2003). Endocrine Factors in the Etiology of Postpartum Depression. *Comprehensive psychiatry, 44*(3), 234-246.

Boker, S., Neale, M., Maes, H., Wilde, M., Spiegel, M., Brick, T., . . . Bates, T. (2011). OpenMx: An Open Source Extended Structural Equation Modeling Framework. *Psychometrika, 76*(2), 306-317.

Bordens, K. S., & Abbott, B. B. (2002). *Research Design and Methods: A Process Approach* (5th ed.). New York: McGraw-Hill.

Brand, S. R., & Brennan, P. A. (2009). Impact of Antenatal and Postpartum Maternal Mental Illness: How Are The Children? *Clinical obstetrics & gynecology, 52*(3), 441-455.

Breedlove, S. M., & Watson, N. V. (2013). *Biological Psychology: An Introduction to Behavioral, Cognitive, and Clinical Neuroscience*. Sunderland: Sinauer Associates.

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., De Girolamo, G., . . . Iwata, N. (2011). Cross-National Epidemiology of DSM-IV Major Depressive Episode. *BMC medicine, 9*(1), 90.

Brummelte, S., & Galea, L. A. M. (2016). Postpartum Depression: Etiology, Treatment and Consequences for Maternal Care. *Hormones & behavior, 77*, 153-166.

Brunton, P., & Russell, J. A. (2008). The Expectant Brain: Adapting for Motherhood. *Nature Reviews Neuroscience, 9*(1), 11–25.

Burke, C. S., Susser, L. C., & Hermann, A. D. (2019). GABA A Dysregulation as an Explanatory Model for Late-Onset Postpartum Depression Associated with Weaning and Resumption of Menstruation. *Archives of Women's Mental Health, 22*(1), 55-63.

Burkhouse, K. L., Gibb, B. E., Coles, M. E., Knopik, V. S., & McGeary, J. E. (2011). Serotonin Transporter Genotype Moderates the Link Between Children's Reports of Overprotective Parenting and Their Behavioral Inhibition. *Journal of Abnormal Child Psychology, 39*(6), 783-790.

Buttner, M. M., O'Hara, M. W., & Watson, D. (2012). The Structure of Women's Mood in the Early Postpartum. *Assessment, 19*(2), 247-256.

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., . . . Poulton, R. (2014). The P Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clinical Psychological Science, 2*(2), 119-137.

Corwin, E. J., Kohen, R., Jarrett, M., & Stafford, B. (2010). The Heritability of Postpartum Depression. *Biological research for nursing, 12*(1), 73-83.

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Identification of Risk Loci with Shared Effects on Five Major Psychiatric Disorders: a Genome-Wide Analysis. *The Lancet, 381*(9875), 1371-1379.

Davis, D. C. (1996). The Discomforts of Pregnancy. *Journal of Obstetric, Gynecologic & Neonatal Nursing, 25*(1), 73-81.

De Moor, M. H. M., Van Den Berg, S. M., Verweij, K. J. H., Krueger, R. F., Luciano, M., Vasquez, A. A., . . . Amin, N. (2015). Meta-Analysis of Genome-Wide Association Studies for Neuroticism, and the Polygenic Association Wwith Major Depressive Disorder. *JAMA Psychiatry, 72*(7), 642-650.

Deecher, D., Andree, T. H., Sloan, D., & Schechter, L. E. (2008). From Menarche to Menopause: Exploring the Underlying Biology of Depression in Women Experiencing Hormonal Changes. *Psychoneuroendocrinology, 33*(1), 3-17.

Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenhuth, E. H., & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): A Self-Report Symptom Inventory. *Behavioral Science, 19*(1), 1-15. doi:10.1002/bs.3830190102 4808738

Di Florio, A., & Meltzer-Brody, S. (2015). Is Postpartum Depression a Distinct Disorder? *Current Psychiatry Reports, 17*(10), 76.

Dickens, M. J., & Pawluski, J. L. (2018). The HPA Axis During the Perinatal Period: Implications for Perinatal Depression. *Endocrinology, 159*(11), 3737-3746.

Doornbos, B., Dijck-Brouwer, D. A. J., Kema, I. P., Tanke, M. A. C., van Goor, S. A., Muskiet, F. A. J., & Korf, J. (2009). The Development of Peripartum Depressive Symptoms is Associated with Gene Polymorphisms of MAOA, 5-HTT and COMT. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 33*(7), 1250-1254.

Duarte-Guterman, P., Leuner, B., & Galea, L. A. M. (2019). The Long and Short Term Effects of Motherhood on the Brain. *Frontiers in Neuroendocrinology, 53*. doi:10.1016/j.yfrne.2019.02.004

Durisko, Z., Mulsant, B. H., & Andrews, P. W. (2015). An Adaptationist Perspective on the Etiology of Depression. *Journal of Affective Disorders, 172*, 315-323.

Dørheim, S. K., Bjorvatn, B., & Eberhard-Gran, M. (2014). Can Insomnia in Pregnancy Predict Postpartum Depression? A Longitudinal, Population-Based Study. *PLOS ONE, 9*(4), e94674. doi:10.1371/journal.pone.0094674

e Couto, T. C., Brancaglion, M. Y. M., Alvim-Soares, A., Moreira, L., Garcia, F. D., Nicolato, R., . . . Corrêa, H. (2015). Postpartum Depression: A Systematic Review of the Genetics Involved. *World journal of psychiatry, 5*(1), 103-111.

Eberhard-Gran, M., Tambs, K., Opjordsmoen, S., Skrondal, A., & Eskild, A. (2004). Depression During Pregnancy and After Delivery: A Repeated Measurement Study. *Journal of Psychosomatic Obstetrics & Gynecology, 25*(1), 15-21.

Eberhard-Gran, M., Eskild, A., Tambs, K., Samuelsen, S. O., & Opjordsmoen, S. (2002). Depression in Postpartum and Non-Postpartum Women: Prevalence and Risk Factors. *Acta Psychiatrica Scandinavica, 106*(6), 426-433.

English, S., Steele, A., Williams, A., Blacklay, J., Sorinola, O., Wernisch, L., & Grammatopoulos, D. K. (2018). Modelling of Psychosocial and Lifestyle Predictors of Peripartum Depressive Symptoms Associated With Distinct Risk Trajectories: A Prospective Cohort Study. *Scientific reports, 8*(1), 12799.

Evans, J., Heron, J., Francomb, H., Oke, S., & Golding, J. (2001). Cohort Study of Depressed Mood During Pregnancy and After Childbirth. *The BMJ, 323*(7307), 257-260.

Feliciano, L., & Renn, B. N. (2014). Mood Disorders: Depressive Disorders. In D. C. Beidel, B. C. Frueh, & M. Hersen (Eds.), *Adult Psychopathology and Diagnosis* (7th ed.). Hoboken: John Wiley & Sons Inc; US.

Ferrari, A. J., Somerville, A. J., Baxter, A. J., Norman, R., Patten, S. B., Vos, T., & Whiteford, H. A. (2013). Global Variation in the Prevalence and Incidence of Major Depressive Disorder: A Systematic Review of the Epidemiological Literature. *Psychological Medicine, 43*(3), 471-481. doi:10.1017/S0033291712001511 22831756

Field, T. (2010). Postpartum Depression Effects on Early Interactions, Parenting, and Safety Practices: A Review. *Infant behavior & development, 33*(1), 1-6.

Field, T. (2011). Prenatal Depression Effects on Early Development: A Review. *Infant behavior & development, 34*(1), 1-14.

Figueiredo, F. P., Parada, A. P., de Araujo, L. F., Silva Jr, W. A., & Del-Ben, C. M. (2015). The Influence of Genetic Factors on Peripartum Depression: A Systematic Review. *Journal of Affective Disorders, 172*, 265-273.

Fisk, N. M., & Glover, V. (1999). Association Between Maternal Anxiety in Pregnancy and Increased Uterine Artery Resistance Index: Cohort Based Study. *The BMJ, 318*(7177), 153-157.

Flint, J., & Kendler, K. S. (2014). The Genetics of Major Depression. *Neuron, 81*(3), 484-503.

Forty, L., Jones, L., Macgregor, S., Caesar, S., Cooper, C., Hough, A., . . . McGuffin, P. (2006). Familiality of Postpartum Depression in Unipolar Disorder: Results of a Family Study. *American Journal of Psychiatry, 163*(9), 1549-1553.

Frieder, A., Fersh, M., Hainline, R., & Deligiannidis, K. M. (2019). Pharmacotherapy of Postpartum Depression: Current Approaches and Novel Drug Development. *CNS drugs, 33*(3), 265-282.

Gaillard, A., Le Strat, Y., Mandelbrot, L., Keïta, H., & Dubertret, C. (2014). Predictors of Postpartum Depression: Prospective Study of 264 Women Followed During Pregnancy and Postpartum. *Psychiatry research, 215*(2), 341-346.

Gavin, N. I., Gaynes, B. N., Lohr, K. N., Meltzer-Brody, S., Gartlehner, G., & Swinson, T. (2005). Perinatal Depression: A Systematic Review of Prevalence and Incidence. *Obstetrics & Gynecology, 106*(5), 1071-1083.

Gjerde, L. C., Eilertsen, E. M., Reichborn-Kjennerud, T., McAdams, T. A., Zachrisson, H. D., Zambrana, I. M., . . . Ystrom, E. (2017). Maternal Perinatal and Concurrent Depressive Symptoms and Child Behavior Problems: A Sibling Comparison Study. *Journal of Child Psychology and Psychiatry, 58*(7), 779-786. doi:10.1111/jcpp.12704

Glynn, L. M., Davis, E. P., & Sandman, C. A. (2013). New Insights Into the Role of Perinatal HPA-Axis Dysregulation in Postpartum Depression. *Neuropeptides, 47*(6), 363-370.

Goldberg, D. (2010). Should Our Major Classifications of Mental Disorders be Revised? *The British Journal of Psychiatry, 196*(4), 255-256.

Goodman, S. H., Rouse, M. H., Connell, A. M., Broth, M. R., Hall, C. M., & Heyward, D. (2011). Maternal Depression and Child Psychopathology: A Meta-Analytic Review. *Clinical child & family psychology review, 14*(1), 1-27.

Grace, S. L., Evindar, A., & Stewart, D. E. (2003). The Effect of Postpartum Depression on Child Cognitive Development and Behavior: A Review and Critical Analysis of the Literature. *Archives of Women's Mental Health, 6*(4), 263-274.

Grote, N. K., Bridge, J. A., Gavin, A. R., Melville, J. L., Iyengar, S., & Katon, W. J. (2010). A Meta-Analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction. *Archives of general psychiatry, 67*(10), 1012-1024.

Hall, J. G. (2003). Twinning. *The Lancet, 362*(9385), 735-743.

Hammen, C. (2005). Stress and Depression. *Annual review of clinical psychology, 1*, 293-319.

Hannigan, L. J., Eilertsen, E. M., Gjerde, L. C., Reichborn-Kjennerud, T., Eley, T. C., Rijsdijk, F. V., . . . McAdams, T. A. (2018). Maternal Prenatal Depressive Symptoms and Risk for Early-Life Psychopathology in Offspring: Genetic Analyses in the Norwegian Mother and Child Birth Cohort Study. *The Lancet Psychiatry, 5*(10), 808-815.

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers. *JAMA Psychiatry, 75*(4), 336-346. doi:10.1001/jamapsychiatry.2017.4602 %J JAMA Psychiatry

Hasler, G., Drevets, W. C., Manji, H. K., & Charney, D. S. (2004). Discovering Endophenotypes for Major Depression. *Neuropsychopharmacology, 29*(10), 1765-1781.

Hastie, T., & Qian, J. (2014). Glmnet vignette. Retrieved from: http://www.web.stanford.edu/~hastie/Papers/Glmnet_Vignette.pdf.

Heron, J., O'Connor, T. G., Evans, J., Golding, J., & Glover, V. (2004). The Course of Anxiety and Depression Through Pregnancy and the Postpartum in a Community Sample. *Journal of Affective Disorders, 80*(1), 65-73.

Hillerer, K. M., Jacobs, V. R., Fischer, T., & Aigner, L. (2014). The Maternal Brain: An Organ With Peripartal Plasticity. *Neural plasticity*, 20.

Hirschfeld, R., Montgomery, S. A., Keller, M. B., Kasper, S., Schatzberg, A. F., Möller, H.-J., . . . Versiani, M. (2000). Social Functioning in Depression: A Review. *The Journal of clinical psychiatry, 61*(4), 268-275.

Hoekzema, E., Barba-Müller, E., Pozzobon, C., Picado, M., Lucco, F., García-García, D., . . . Crone, E. A. (2017). Pregnancy Leads to Long-Lasting Changes in Human Brain Structure. *Nature Neuroscience, 20*(2), 287–296.

Hoertel, N., López, S., Peyre, H., Wall, M. M., González-Pinto, A., Limosin, F., & Blanco, C. (2015). Are Symptom Features of Depression During Pregnancy, the Postpartum Period and Outside the Peripartum Period Distinct? Results from a Nationally Representative Sample Using Item Response Theory (IRT). *Depression and anxiety, 32*(2), 129-140.

Howard, D. M., Adams, M. J., Clarke, T.-K., Hafferty, J. D., Gibson, J., Shirali, M., . . . Major Depressive Disorder Working Group of the Psychiatric Genomics, C. (2019). Genome-Wide Meta-Analysis of Depression Identifies 102 Independent Variants and Highlights the Importance of the Prefrontal Brain Regions. *Nature Neuroscience, 22*(3), 343-352. doi:10.1038/s41593-018-0326-7

Howard, L. M., Molyneaux, E., Dennis, C.-L., Rochat, T., Stein, A., & Milgrom, J. (2014). Non-Psychotic Mental Disorders in the Perinatal Period. *The Lancet, 384*(9956), 1775-1788.

Hyde, J. S., Mezulis, A. H., & Abramson, L. Y. (2008). The ABCs of Depression: Integrating Affective, Biological, and Cognitive Models to Explain the Emergence of the Gender Difference in Depression. *Psychological review, 115*(2), 291-313.

Ingram, R. E., & Luxton, D. D. (2005). *Development of Psychopathology: A Vulnerability-Stress Perspective* (1st ed.). Thousand Oaks: SAGE Publications.

Jang, K. L., Livesley, J. W., & Vemon, P. A. (1996). Heritability of the Big Five Personality Dimensions and Their Facets: A Twin Study. *Journal of personality, 64*(3), 577-592.

John, O. P., Robins, R. W., & Pervin, L. A. (2008). *Handbook of Personality: Theory and research* (3rd ed. Vol. 3). New York: Guilford Press.

Kammerer, M., Marks, M. N., Pinard, C., Taylor, A., von Castelberg, B., Kunzli, H., & Glover, V. (2009). Symptoms Associated with the DSM IV Diagnosis of Depression in Pregnancy and Post Partum. *Archives of Women's Mental Health, 12*(3), 135–141. doi:10.1007/s00737-009-0062-9 19337702

Kammerer, M., Taylor, A., & Glover, V. (2006). The HPA Axis and Perinatal Depression: A Hypothesis. *Archives of Women's Mental Health, 9*(4), 187-196.

Kandler, C., Bleidorn, W., Riemann, R., Angleitner, A., & Spinath, F. M. (2012). Life Events as Environmental States and Genetic Traits and the Role of Personality: A Longitudinal Twin Study. *Behavior genetics, 42*(1), 57-72.

Kendler, K. S., & Baker, J. H. (2007). Genetic Influences on Measures of the Environment: A Systematic Review. *Psychological Medicine, 37*(5), 615-626.

Kendler, K. S., & Gardner, C. O. (2010). Dependent Stressful Life Events and Prior Depressive Episodes in the Prediction of Major Depression: the Problem of Causal Inference in Psychiatric Epidemiology. *Archives of general psychiatry, 67*(11), 1120-1127.

Kendler, K. S., Gardner, C. O., Neale, M. C., & Prescott, C. A. (2001). Genetic Risk Factors for Major Depression in Men and Women: Similar or Different Heritabilities and Same or Partly Distinct Genes? *Psychological Medicine, 31*(4), 605-616.

Kendler, K. S., Kessler, R. C., Walters, E. E., MacLean, C., Neale, M. C., Heath, A. C., & Eaves, L. J. (2010). Stressful Life events, Genetic Liability, and Onset of an Episode of Major Depression in Women. *Focus, 8*(3), 459-470.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992). Major Depression and Generalized Anxiety Disorder: Same Genes,(Partly) Different Environments? *Archives of general psychiatry, 49*(9), 716-722.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). A Test of the Equal-Environment Assumption in Twin Studies of Psychiatric Illness. *Behavior genetics, 23*(1), 21-27.

Kendler, K. S., & Prescott, C. A. (2007). *Genes, Environment, and Psychopathology: Understanding the Causes of Psychiatric and Substance Use Disorders*. New York: Guilford Press.

Kendler, K. S., Thornton, L. M., & Gardner, C. O. (2000). Stressful Life Events and Previous Episodes in the Etiology of Major Depression in Women: An Evaluation of the "Kindling" Hypothesis. *American Journal of Psychiatry, 157*(8), 1243-1251.

Kendler, K. S., Thornton, L. M., & Prescott, C. A. (2001). Gender Differences in the Rates of Exposure to Stressful Life Events and Sensitivity to their Depressogenic Effects. *American Journal of Psychiatry, 158*(4), 587-593.

Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of general psychiatry, 52*(5), 374-383.

Kenny, L. C., Lavender, T., McNamee, R., O'Neill, S. M., Mills, T., & Khashan, A. S. (2013). Advanced Maternal Age and Adverse Pregnancy Outcome: Evidence from a Large Contemporary Cohort. *PLOS ONE, 8*(2), e56583.

Kessler, R. C. (2003). Epidemiology of Women and Depression. *Journal of Affective Disorders, 74*(1), 5-13. doi:10.1016/S0165-0327%2802%2900426-3 12646294

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry, 62*(6), 593-602. doi:10.1001/archpsyc.62.6.593 %J Archives of General Psychiatry

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., & Moffitt, T. E. (2006). MAOA, Maltreatment, and Gene–Environment Interaction Predicting Children's Mental Health: New Evidence and a Meta-Analysis. *Molecular Psychiatry, 11*(10), 903-913.

Kim, P., Leckman, J. F., Mayes, L. C., Feldman, R., Wang, X., & Swain, J. E. (2010). The Plasticity of Human Maternal Brain: Longitudinal Changes in Brain Anatomy During the Early Postpartum Period. *Behavioral neuroscience, 124*(5), 695-700.

Kim, S., Soeken, T. A., Cromer, S. J., Martinez, S. R., Hardy, L. R., & Strathearn, L. (2014). Oxytocin and Postpartum Depression: Delivering on What's Known and What's Not. *Brain research, 1580*, 219-232. doi:10.1016/j.brainres.2013.11.009

Kline, P. (1999). *The Handbook of Psychological Testing* (2nd ed.). London: Routledge.

Kruijshaar, M. E., Barendregt, J., Vos, T., de Graaf, R., Spijker, J., & Andrews, G. (2005). Lifetime Prevalence Estimates of Major Depression: An Indirect Estimation Method and a Quantification of Recall Bias. *European Journal of Epidemiology, 20*(1), 103-111. doi:10.1007/s10654-004-1009-0

Kuehner, C. (2017). Why is Depression More Common Among Women than Among Men? *The Lancet Psychiatry, 4*(2), 146-158.

Lamers, F., Vogelzangs, N., Merikangas, K., De Jonge, P., Beekman, A., & Penninx, B. (2013). Evidence for a Differential Role of HPA-Axis Function, Inflammation and Metabolic Syndrome in Melancholic Versus Atypical Depression. *Molecular Psychiatry, 18*(6), 692–699.

Lancaster, C. A., Gold, K. J., Flynn, H. A., Yoo, H., Marcus, S. M., & Davis, M. M. (2010). Risk Factors for Depressive Symptoms During Pregnancy: A Systematic Review. *American journal of obstetrics & gynecology, 202*(1), 5-14.

Landsman, A., Aidelman, R., Smith, Y., Boyko, M., & Greenberger, C. (2017). Distinctive Gene Expression Profile in Women with History of Postpartum Depression. *Genomics, 109*(1), 1-8.

Leahy-Warren, P., McCarthy, G., & Corcoran, P. J. J. o. c. n. (2012). First-time mothers: social support, maternal parental self-efficacy and postnatal depression. *21*(3-4), 388-397.

Leigh, B., & Milgrom, J. (2008). Risk Factors for Antenatal Depression, Postnatal Depression and Parenting Stress. *BMC psychiatry, 8*(1), 24.

Levinson, D. F. (2006). The Genetics of Depression: A Review. *Biological psychiatry, 60*(2), 84-92.

Liu, R. T., & Alloy, L. B. (2010). Stress Generation in Depression: A Systematic Review of the Empirical Literature and Recommendations for Future Study. *Clinical Psychology Review, 30*(5), 582-593.

Macbeth, A. H., & Luine, V. N. (2010). Changes in Anxiety and Cognition due to Reproductive Experience: A Review of Data from Rodent and Human Mothers. *Neuroscience & Biobehavioral Reviews, 34*(3), 452-467.

Magnus, P., Berg, K., & Nance, W. E. (1983). Predicting Zygosity in Norwegian Twin Pairs born 1915–1960. *Clinical Genetics, 24*(2), 103-112.

Magnus, P., Birke, C., Vejrup, K., Haugan, A., Alsaker, E., Daltveit, A. K., . . . Knudsen, G. P. (2016). Cohort Profile Update: the Norwegian Mother and Child Cohort Study (MoBa). *International journal of epidemiology, 45*(2), 382-388.

Magnus, P., Group, T. M. S., Irgens, L. M., Group, T. M. S., Haug, K., Group, T. M. S., . . . Group, T. M. S. (2006). Cohort Profile: The Norwegian Mother and Child Cohort Study (MoBa). *International journal of epidemiology, 35*(5), 1146-1150. doi:10.1093/ije/dyl170 %J International Journal of Epidemiology

Maguire, J., & Mody, I. (2008). GABAAR Plasticity During Pregnancy: Relevance to Postpartum Depression. *Neuron, 59*(2), 207-213.

Mann, R., Gilbody, S., & Adamson, J. (2010). Prevalence and Incidence of Postnatal Depression: What Can Systematic Reviews Tell Us? *Archives of Women's Mental Health, 13*(4), 295-305.

Mathers, C. D., & Loncar, D. (2006). Projections of Global Mortality and Burden of Disease from 2002 to 2030. *PLoS medicine, 3*(11), e442.

Mathews, T. J., & Hamilton, B. E. (2009). Delayed Childbearing; More Women are Having Their First Child Later in Life. *NCHS Data Brief, 21*, 1-8.

McAdams, T. A., Rijsdijk, F., Neiderhiser, J. M., Narusyte, J., Shaw, D., Natsuaki, M., . . . Leve, L. (2015). The Relationship Between Parental Depressive Symptoms and Offspring Psychopathology: Evidence from a Children-Of-Twins Study and an Adoption Study. *Psychological Medicine, 45*(12), 2583-2594.

McGue, M. (1999). The Behavioral Genetics of Alcoholism. *Current Directions in Psychological Science, 8*(4), 109-115.

Meltzer-Brody, S., Howard, L. M., Bergink, V., Vigod, S., Jones, I., Munk-Olsen, T., . . . Milgrom, J. (2018). Postpartum Psychiatric Disorders. *Nature reviews, 4*, 18022.

Meltzer-Brody, S., & Stuebe, A. (2014). The Long-Term Psychiatric and Medical Prognosis of Perinatal Mental Illness. *Best Practice & Research: Clinical Obstetrics & Gynaecology, 28*(1), 49-60.

Milgrom, J., Gemmill, A. W., Bilszta, J. L., Hayes, B., Barnett, B., Brooks, J., . . . Buist, A. (2008). Antenatal Risk Factors for Postnatal Depression: a Large Prospective Study. *Journal of Affective Disorders, 108*(1-2), 147-157.

Mitchell, C., Notterman, D., Brooks-Gunn, J., Hobcraft, J., Garfinkel, I., Jaeger, K., . . . McLanahan, S. (2011). Role of Mother's Genes and Environment in Postpartum Depression. *Proceedings of the National Academy of Sciences, 108*(20), 8189-8193.

Moffitt, T. E., Caspi, A., Taylor, A., Kokaua, J., Milne, B. J., Polanczyk, G., & Poulton, R. (2010). How Common Are Common Mental Disorders? Evidence that Lifetime Prevalence Rates are Doubled by Prospective Versus Retrospective Ascertainment. *Psychological Medicine, 40*(6), 899-909.

Moura, D., Canavarro, M. C., & Figueiredo-Braga, M. (2016). Oxytocin and Depression in the Perinatal Period—a Systematic Review. *Archives of Women's Mental Health, 19*(4), 561-570. doi:10.1007/s00737-016-0643-3

Murphy-Eberenz, K., Zandi, P. P., March, D., Crowe, R. R., Scheftner, W. A., Alexander, M., . . . DePaulo Jr, J. R. (2006). Is Perinatal Depression Familial? *Journal of Affective Disorders, 90*(1), 49-55.

Müller, J. M., Postert, C., Beyer, T., Furniss, T., & Achtergarde, S. (2010). Comparison of Eleven Short Versions of the Symptom Checklist 90-Revised (SCL-90-R) for Use in the Assessment of General Psychopathology. *Journal of Psychopathology AND Behavioral Assessment, 32*(2), 246-254.

Najarian, B., & Davoodi, I. (2001). Construction and Validation of a Short Form of the SCL-90-r (SCL-25). *Journal of Psychology, 5*(2), 136-149.

Nezvalová-Henriksen, K., Spigset, O., Brandlistuen, R. E., Ystrom, E., Koren, G., & Nordeng, H. (2016). Effect of Prenatal Selective Serotonin Reuptake Inhibitor (SSRI) Exposure on Birthweight and Gestational Age: A Sibling-Controlled Cohort Study. *International journal of epidemiology, 45*(6), 2018-2029.

Nilsen, R. M., Vollset, S. E., Gjessing, H. K., Skjaerven, R., Melve, K. K., Schreuder, P., . . . Magnus, P. (2009). Self-Selection and Bias in a Large Prospective Pregnancy Cohort in Norway. *Paediatric and Perinatal Epidemiology, 23*(6), 597-608.

Nock, M. K., Borges, G., Bromet, E. J., Cha, C. B., Kessler, R. C., & Lee, S. (2008). Suicide and Suicidal Behavior. *Epidemiologic reviews, 30*(1), 133-154.

Nuechterlein, K. H., & Dawson, M. E. (1984). A Heuristic Vulnerability/Stress Model of Schizophrenic Episodes. *Schizophrenia bulletin, 10*(2), 300.

O'Hara, M. W. (2009). Postpartum Depression: What We Know. *Journal of clinical psychology, 65*(12), 1258-1269.

O'Hara, M. W., & McCabe, J. E. (2013). Postpartum Depression: Current Status and Future Directions. *Annual review of clinical psychology, 9*, 379-407.

O'Hara, M. W., & Swain, A. M. (1996). Rates and Risk of Postpartum Depression - A Meta-Analysis. *International Review of Psychiatry, 8*(1), 37-54. doi:10.3109/09540269609037816

O'Hara, M. W., & Wisner, K. L. (2014). Perinatal Mental Illness: Definition, Description and Aetiology. *Research Clinical Obstetrics & Gynaecology, 28*(1), 3-12.

O'Keane, V. (2000). Evolving Model of Depression as an Expression of Multiple Interacting Risk Factors. *The British Journal of Psychiatry, 177*(6), 482-483.

Okun, M. L., Luther, J., Prather, A. A., Perel, J. M., Wisniewski, S., & Wisner, K. L. (2011). Changes in Sleep Quality, but not Hormones Predict Time to Postpartum Depression Recurrence. *Journal of Affective Disorders, 130*(3), 378-384. doi:10.1016/j.jad.2010.07.015

Owens, M. J., & Nemeroff, C. B. (1994). Role of Serotonin in the Pathophysiology of Depression: Focus on the Serotonin Transporter. *Clinical chemistry, 40*(2), 288-295.

Payne, J. L., & Maguire, J. (2018). Pathophysiological Mechanisms Implicated in Postpartum Depression. *Frontiers in Neuroendocrinology, 52*, 165-180.

Pereira, A. T., Marques, M., Soares, M. J., Maia, B. R., Bos, S., Valente, J., . . . Macedo, A. (2014). Profile of Depressive Symptoms in Women in the Perinatal and Outside the Perinatal Period: Similar or Not? *Journal of Affective Disorders, 166*, 71-78.

Piccinelli, M., & Wilkinson, G. (2000). Gender Differences in Depression: Critical Review. *The British Journal of Psychiatry, 177*(6), 486-492.

Piel, F. B., Patil, A. P., Howes, R. E., Nyangiri, O. A., Gething, P. W., Williams, T. N., . . . Hay, S. I. (2010). Global Distribution of the Sickle Cell Gene and Geographical Confirmation of the Malaria Hypothesis. *Nature communications, 1*, 104.

Pincus, H. A., & Pettit, A. R. (2001). The Societal Costs of Chronic Major Depression. *Journal of Clinical Psychiatry, 62*, 5-9.

Plomin, R. (2018). *Blueprint: How DNA Makes Us Who We Are*. London: Penguin Books Ltd.

Plomin, R., DeFries, J. C., Knopik, V. S., & Neiderhiser, J. N. (2013). *Behavioral Genetics* (6th Ed.). New York: Worth Publishers.

Plomin, R., DeFries, J. C., & Loehlin, J. (1977). Genotype-Environment Interaction and Correlation in the Analysis of Human Behavior. *Psychological bulletin, 84*(2), 309-322.

Polderman, T. J. C., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M., & Posthuma, D. (2015). Meta-Analysis of the Heritability of Human Traits Based on Fifty Years of Twin Studies. *Nature Genetics, 47,* 702–709. doi:10.1038/ng.3285

Purcell, S. (2002). Variance Components Models for Gene–Environment Interaction in Twin Analysis. *Twin Research and Human Genetics, 5*(6), 554-571.

Putnam, K. T., Wilcox, M., Robertson-Blackmore, E., Sharkey, K., Bergink, V., Munk-Olsen, T., . . . Newport, J. (2017). Clinical Phenotypes of Perinatal Depression and Time of Symptom Onset: Analysis of Data from an International Consortium. *The Lancet Psychiatry, 4*(6), 477-485.

R Core Team. (2017). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna Austria. Retrieved from: https://www.R-project.org/.

Rallis, S., Skouteris, H., McCabe, M., & Milgrom, J. (2014). The Transition to Motherhood: Towards a Broader Understanding of Perinatal Distress. *Women and Birth, 27*(1), 68-71. doi:10.1016/j.wombi.2013.12.004

Riecher-Rössler, A., & Fallahpour, M. H. (2003). Postpartum Depression: Do We Still Need this Diagnostic Term? *Acta Psychiatrica Scandinavica, 108*(s418), 51-56.

Rijsdijk, F. V., & Sham, P. C. (2002). Analytic Approaches to Twin Data Using Structural Equation Models. *Briefings in bioinformatics, 3*(2), 119-133.

Rikani, A. A., Choudhry, Z., Choudhry, A. M., Ikram, H., Asghar, M. W., Kajal, D., . . . Mobassarah, N. J. (2013). A Critique of the Literature on Etiology of Eating Disorders. *Annals of neurosciences, 20*(4), 157–161.

Robertson, E., Grace, S., Wallington, T., & Stewart, D. E. (2004). Antenatal Risk Factors for Postpartum Depression: A Synthesis of Recent Literature. *General hospital psychiatry, 26*(4), 289-295.

Ross, L. E., Murray, B. J., & Steiner, M. (2005). Sleep and Perinatal Mood Disorders: A Critical Review. *Journal of psychiatry & neuroscience, 30*(4), 247–256.

Ryan, D., Milis, L., & Misri, N. (2005). Depression During Pregnancy. *Canadian Family Physician, 51*(8), 1087-1093.

Räisänen, S., Lehto, S. M., Nielsen, H. S., Gissler, M., Kramer, M. R., & Heinonen, S. (2014). Risk Factors for and Perinatal Outcomes of Major Depression During

Pregnancy: a Population-Based Analysis During 2002–2010 in Finland. *BMJ open, 4*(11), e004883.

Sawyer, K. M., Zunszain, P. A., Dazzan, P., & Pariante, C. M. (2018). Intergenerational Transmission of Depression: Clinical Observations and Molecular Mechanisms. *Molecular Psychiatry, 24*(8), 1157-1177.

Segman, R. H., Goltser-Dubner, T., Weiner, I., Canetti, L., Galili-Weisstub, E., Milwidsky, A., . . . Hochner-Celnikier, D. (2009). Blood Mononuclear Cell Gene Expression Signature of Postpartum Depression. *Molecular Psychiatry, 15*, 93–100. doi:10.1038/mp.2009.65

Séjourné, N., Alba, J., Onorrus, M., Goutaudier, N., & Chabrol, H. (2011). Intergenerational Transmission of Postpartum Depression. *Journal of Reproductive & Infant Psychology, 29*(2), 115-124.

Serati, M., Redaelli, M., Buoli, M., & Altamura, A. (2016). Perinatal Major Depression Biomarkers: A Systematic Review. *Journal of Affective Disorders, 193*, 391-404.

Seth, S., Lewis, A. J., & Galbally, M. (2016). Perinatal Maternal Depression and Cortisol Function in Pregnancy and the Postpartum Period: A Systematic Literature Review. *BMC Pregnancy & Childbirth, 16*(1), 124. doi:10.1186/s12884-016-0915-y

Silverman, M. E., Reichenberg, A., Savitz, D. A., Cnattingius, S., Lichtenstein, P., Hultman, C. M., . . . Sandin, S. (2017). The Risk Factors for Postpartum Depression: A Population-Based Study. *Depression & anxiety, 34*(2), 178-187.

Skalkidou, A., Hellgren, C., Comasco, E., Sylvén, S., & Poromaa, I. S. (2012). Biological Aspects of Postpartum Depression. *Womens Health, 8*(6), 659-672. doi:10.2217/whe.12.55

Strand, B. H., Dalgard, O. S., Tambs, K., & Rognerud, M. (2003). Measuring the Mental Health Status of the Norwegian Population: A Comparison of the Instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nordic journal of psychiatry, 57*(2), 113-118.

Stuart-Parrigon, K., & Stuart, S. (2014). Perinatal Depression: An Update and Overview. *Current Psychiatry Reports, 16*(9), 468.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *American Journal of Psychiatry, 157*(10), 1552-1562.

Tambs, K., & Røysamb, E. (2014). Selection of Questions to Short-Form Versions of Original Psychometric Instruments in MoBa. *Norsk epidemiologi, 24*(1-2), 195-201.

Tennant, C. (2002). Life Events, Stress and Depression: A Review of Recent Findings. *Australian & New Zealand Journal of Psychiatry, 36*(2), 173-182.

Torvik, F. A., Gustavson, K., Ystrom, E., Rosenström, T. H., Gillespie, N., Reichborn-Kjennerud, T., & Kendler, K. S. (2018). Continuity of Genetic and Environmental Influences on Clinically Assessed Major Depression from Ages 18 to 45. *Psychological Medicine*, 1-9.

Torvik, F. A., Rosenström, T. H., Ystrom, E., Tambs, K., Røysamb, E., Czajkowski, N., . . . Reichborn-Kjennerud, T. (2017). Stability and Change in Etiological Factors for Alcohol Use Disorder and Major Depression. *Journal of Abnormal Psychology, 126*(6), 812-822.

Torvik, F. A., Ystrom, E., Gustavson, K., Rosenström, T. H., Bramness, J. G., Gillespie, N., . . . Reichborn-Kjennerud, T. (2018). Diagnostic and Genetic Overlap of Three Common Mental Disorders in Structured Interviews and Health Registries. *Acta Psychiatrica Scandinavica, 137*(1), 54-64.

Treloar, S. A., Martin, N. G., Bucholz, K. K., Madden, P. A. F., & Heath, A. C. (1999). Genetic Influences on Post-Natal Depressive Symptoms: Findings from an Australian Twin Sample. *Psychological Medicine, 29*(3), 645-654.

Turkheimer, E. (2000). Three Laws of Behavior Genetics and What They Mean. *Current Directions in Psychological Science, 9*(5), 160-164.

Underwood, L., Waldie, K., D'Souza, S., Peterson, E. R., & Morton, S. (2016). A Review of Longitudinal Studies on Antenatal and Postnatal Depression. *Archives of Women's Mental Health, 19*(5), 711-720.

Van de Velde, S., Bracke, P., & Levecque, K. J. S. S. M. (2010). Gender differences in depression in 23 European countries. Cross-national variation in the gender gap in depression. *71*. doi:10.1016/j.socscimed.2010.03.035

Van Os, J., Park, S., & Jones, P. B. (2001). Neuroticism, Life Events and Mental Health: Evidence for Person-Environment Correlation. *The British Journal of Psychiatry, 178*(S40), 72-77.

Verhulst, B., Neale, M. C., & Kendler, K. S. (2015). The Heritability of Alcohol Use Disorders: A Meta-Analysis of Twin and Adoption Studies. *Psychological Medicine, 45*(5), 1061-1072.

Vesga-Lopez, O., Blanco, C., Keyes, K., Olfson, M., Grant, B. F., & Hasin, D. S. (2008). Psychiatric Disorders in Pregnant and Postpartum Women in the United States. *Archives of general psychiatry, 65*(7), 805-815.

Viktorin, A., Meltzer-Brody, S., Kuja-Halkola, R., Sullivan, P. F., Landen, M., Lichtenstein, P., & Magnusson, P. K. E. (2016). Heritability of Perinatal Depression and Genetic Overlap with Nonperinatal Depression. *The American Journal of Psychiatry, 173*(2), 158-165. doi:10.1176/appi.ajp.2015.15010085 26337037

Whiffen, V. E. (1992). Is Postpartum Depression a Distinct Diagnosis? *Clinical Psychology Review, 12*(5), 485-508. doi:10.1016/0272-7358(92)90068-J

Widiger, T. A., & Gore, W. L. (2014). Mental Disorders as Discrete Clinical Conditions: Dimensional Versus Categorical Classification. In D. C. Beidel, B. C. Frueh, & M. Hersen (Eds.), *Adult Psychopathology and Diagnosis* (7th ed.). Hoboken, NJ: John Wiley & Sons Inc; US.

Wikman, A., Axfors, C., Iliadis, S. I., Cox, J., Fransson, E., & Skalkidou, A. (2019). Characteristics of Women with Different Perinatal Depression Trajectories. *Journal of neuroscience research*, 1-16.

Wisner, K. L., Parry, B. L., & Piontek, C. M. (2002). Postpartum Depression. *New England Journal of Medicine, 347*(3), 194-199.

World Health Organization. (WHO, 1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: Author.

Ystrøm, E. (2012). Breastfeeding Cessation and Symptoms of Anxiety and Depression: A Longitudinal Cohort Study. *BMC Pregnancy & Childbirth, 12*(1), 12-36.

Ystrøm, E., Reichborn-Kjennerud, T., Tambs, K., Magnus, P., Torgersen, A. M., & Gustavson, K. (2014). Multiple Births and Maternal Mental Health from Pregnancy to 5 Years After Birth: A Longitudinal Population-Based Cohort Study. *Norsk epidemiologi, 24*(1-2), 203-208.

Zhang, X., Wang, L., Huang, F., Li, J., Xiong, L., Xue, H., & Zhang, Y. (2014). Gene–Environment Interaction in Postpartum Depression: A Chinese Clinical Study. *Journal of Affective Disorders, 165*, 208-212.

Appendix