Tiina Taka-Eilola

MENTAL HEALTH PROBLEMS IN THE ADULT OFFSPRING OF ANTEnataly DEPRESSED MOTHERS IN THE NORTHERN FINLAND 1966 BIRTH COHORT; RELATIONSHIP WITH PARENTAL SEVERE MENTAL DISORDER
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Abstract

Maternal depressed mood during pregnancy is common, but studies on the offspring of antenatally depressed mothers, with a long follow-up, are scarce. The aim was to study whether the adult offspring of antenatally depressed mothers are at an elevated risk of psychoses, depression, bipolar disorder, antisocial and borderline personality disorder, and schizotypal and affective traits. Parental severe mental disorder was considered as both a genetic and environmental risk factor for mental disorders.

The data are based on the unselected, prospective, population-based Northern Finland 1966 Birth Cohort of 12,058 live-born children. The data were collected beginning from pregnancy and ending mid-adulthood. The mothers were asked about their mood during pregnancy at the antenatal clinic at 24-28 gestational weeks. Of the mothers, 13.9% rated themselves as depressed (11.8%) or very depressed (2.1%) during pregnancy. Parents’ severe, hospital-treated mental disorders, and the cohort members’ mental disorders were identified mainly by using the Finnish Care Register for Health Care.

In this study, the adult offspring of antenatally depressed mothers had an increased risk of depression, and the male offspring for antisocial personality disorder, compared to cohort members without antenatal depressed mothers. The offspring with both maternal antenatal depressed mood and parental severe mental disorder had a markedly elevated risk of schizophrenia and depression, compared to cohort members without one or both of the risk factors.

This is the first study where the offspring of antenatally depressed mothers were followed till mid-adulthood, also taking into account parental severe mental disorders. Based on the findings, the prevention of and early intervention in antenatal depression, especially in families with severe mental illness, might present an opportunity to reduce the risk of mental disorders in the offspring.

Keywords: affective traits, antenatal, antisocial personality disorder, bipolar disorder, borderline personality disorder, depression, famil*, maternal, mood disorders, offspring, pregnancy, prenatal, psychosis, schizophrenia, schizotypy
Taka-Eilola, Tiina, Mielenterveysongelmat raskausaikana masentuneiden äitien aikuisilla lapsilla Pohjois-Suomen 1966 syntymäkohortissa – yhteys vanhempien vakaviin mielenterveyshäiriöihin.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala
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Tiivistelmä
Äitien raskausajan masennus on yleistä, mutta pitkää seurantatutkimuksia raskausaikana masentuneiden äitien lapsista on vähän. Tutkimuksen tavoitteena oli selvittää raskausaikana masentuneiden äitien aikuisilla jälkeläisillä kohonnut riski sairastua skitsofreniaan, masennukseen, kaksisuuntaiseen mielialahäiriöön, epäosiaaliseen tai epävakaiseen persoonallisuushäiriöön, ja ilmeneekö heillä enemmän skitsotyyppisiä tai affektiivisia piirteitä. Vanhempien vakavien mielenterveyshäiriöiden katsottiin olevan sekä mahdollisia geneettisiä että ympäristöön liittyviä riskitekijöitä jälkeläisten mielenterveyshäiriöille.

Tutkimus perustuu yleisväestöön pohjautuvaan, prospektiiviseen Pohjois-Suomen vuoden 1966 syntymäkohorttiin, johon kuuluu 12 058 elävänä syntynyttä lasta. Kohortin jäseniä on seurattu sikiöaikalta keski-ikään, aina 49 ikävuoteen saakka. Äitien raskaudenaikasta mielialaa tiedusteltiin raskausviikoilla 24-28 neuvolassa. 13.9% äideistä raportoi mielialansa masentuneeksi (11.8%) tai hyvin masentuneeksi (2.1%) raskauksena. Vanhempien vakavien mielenterveydenhäiriöiden katsottiin olevan sekä epäosiaalisia että epävakaa persoonallisuushäiriöön. Kohortin jäsenten mielenterveyshäiriöiden katsottiin olevan sekä epäosiaalisia että epävakaa persoonallisuushäiriöön.

Tutkimuksessa raskausaikana masentuneiden äitien lapsilla havaittiin kohonnut depressioriesiko sekä kohonnut epäosiaalisen persoonallisuushäiriön riski miehillä, verrattuna kohortin jäseniin, joiden äitien mielialaa ei ollut masentunut raskausaikana. Kohortin jäseniä ilmeni myös enemmän vakavia mielenterveyshäiriöitä, kohonnut riski sairastua skitsofreniaan ja depressioon, verrattuna heihin, joilla oli vain yksi tai ei kumpaakaan näistä riskitekijöistä.

Tämä on ensimmäinen tutkimus, jossa raskausaikana masentuneiden äitien lapsia on seurattu keski-ikään saakka, huomioiden myös vanhempien vakavat mielenterveydenhäiriöt. Tutkimuksen tulosten perusteella äidin raskausajan masennunseoksia on suuren tunnistamisen ja hoidon voitaisiin ajatella vähentävän jälkeläisten mielenterveysongelmien riskiä, etenkin perheissä, joissa on vakavia mielenterveysongelmia.

Asiasanat: affektiiviset piirteet, antenaalidepressio, mielialahäiriöt, persoonallisuushäiriöt, psykoosi, skitsofrenia, skitsotyyppiset piirteet, äidin raskausaikainen masennus
In memory of Professor Pirjo Mäki
Acknowledgements

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25.3.2019 Ylivieska

Tiina Taka-Eilola
Vocabulary related to childbirth

Conception

Fertilization and/or implantation of the embryo.

Parity

Number of births for a given woman, counting a multiple birth pregnancy as one. Nullipara = no previous births; primipara = one previous birth to a fetus/child after 20 weeks of gestation; multipara = more than one previous birth; grand multiparity ≥ 5 births.

Antenatal / Prenatal / prepartum

During pregnancy, before birth.

Perinatal / Peripartum

Around labor, shortly before and after delivery. Perinatal period: According to WHO, a period of 22 completed weeks (154 days) of gestation and seven completed days after birth. Often used in a wider context, meaning the whole pregnancy and 3-12 months after delivery.

Postnatal / Postpartum

After delivery. The postnatal period is usually defined as 6 weeks after childbirth.

Neonatal

The first 28 days of life.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine</td>
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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
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<tr>
<td>ADHD</td>
<td>Attention Deficit / Hyperactivity Disorder</td>
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<tr>
<td>ALSPAC</td>
<td>Avon Longitudinal Study of Parents and Children</td>
</tr>
<tr>
<td>ASPD</td>
<td>Antisocial Personality Disorder</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
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<tr>
<td>BDI-II</td>
<td>Beck Depression Inventory, 2nd edition</td>
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<tr>
<td>BDNF</td>
<td>Brain Derived Neurotrophic Factor</td>
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<tr>
<td>BIP2</td>
<td>Bipolarity II Scale</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BPD</td>
<td>Borderline Personality Disorder</td>
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<tr>
<td>CBT</td>
<td>Cognitive Behavioral Therapy</td>
</tr>
<tr>
<td>CES-D</td>
<td>Center for Epidemiologic Studies Depression Scale</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>COMT</td>
<td>Cathecol-O-methyltransferase</td>
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<tr>
<td>CRH</td>
<td>Cortisol releasing hormone</td>
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<tr>
<td>CRHC</td>
<td>Care Register for Health Care</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>EPDS</td>
<td>Edinburgh Postnatal Depression Scale</td>
</tr>
<tr>
<td>ES</td>
<td>Effect size</td>
</tr>
<tr>
<td>FHDR</td>
<td>Finnish Hospital Discharge Register</td>
</tr>
<tr>
<td>FinESSI</td>
<td>Finnish Register-Based Study</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle Stimulating Hormone</td>
</tr>
<tr>
<td>GBD</td>
<td>Global Burden of Disease</td>
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<tr>
<td>GHQ</td>
<td>General Health Questionnaire</td>
</tr>
<tr>
<td>GUSTO</td>
<td>Growing Up in Singapore Towards Healthy Outcomes</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Hamilton Rating Scale for Depression</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamus-Pituitary-Adrenal axis</td>
</tr>
<tr>
<td>HPS</td>
<td>Hypomania Scale</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>IPT</td>
<td>Interpersonal Psychotherapy</td>
</tr>
</tbody>
</table>
IQ    Intelligence Quotient
K10   Kessler Psychological Distress Scale
LBW   Low birth weight
LH    Luteinizing hormone
LAMIC Low and middle income countries
MAO   monoamine oxidase -enzyme
MGMQ  Matthey Generic Mood Questionnaire
MUSP Mater Misericordiae Mothers' Hospital-University of Queensland Study of Pregnancy
NFBC 1966 Northern Finland 1966 Birth Cohort
NICE The National Institute for Health and Care Excellence
OR    Odds Ratio
PANSS Positive and Negative Syndrome Scale
PAS   Physical Anhedonia Scale
PDS   The Pregnancy Depression Scale
PDSS  Postpartum Depression Screening Scale
PER   Perceptual Aberration Scale
PHQ   Patient Health Questionnaire
PREDO The Prediction and Prevention of Preeclampsia Study
PRQ   Pregnancy Risk Questionnaire
REM   Rapid Eye Movement
RR    Risk Ratio
SAS   Social Anhedonia Scale
SCHD  Schizoidia Scale
SCID  The Structured Clinical Interview for DSM-IV
SCL   Hopkins Symptom Checklist -25
SES   Socioeconomic status
SLDCS South London Child Development Study
SNRI  selective serotonin and norepinephrine reuptake inhibitors
SOFAS Social and Occupational Functioning Assessment Scale
SRQ   Self-Reporting Questionnaire;
SSRI  Selective serotonin reuptake inhibitors
WHO  World Health Organization
ZSDS  Zung Depression Scale
List of original papers

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:


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1 Introduction

Maternal depression during pregnancy is common, affecting 10-17% of mothers. It is more common than other pregnancy complications (Accortt & Wong, 2017), and as common as postpartum depression (Evans, Heron, Francomb, Oke, & Golding, 2001; Louise M Howard et al., 2014; Underwood L. D’Souza S., Peterson ER., Morton S., 2016). Antenatal depression has long remained understudied in comparison with postnatal depression, but recently, interest in antenatal mental health has risen in research and clinical practice. Still, of the mothers with antenatal depression, only about 50% get correctly diagnosed and less than 10% get adequate treatment (E. Q. Cox, Sowa, Meltzer-Brody, & Gaynes, 2016). Both the World Psychiatric Association (WPA) (I. Brockington et al., 2011) and the World Health Organization (WHO) (World Health Organization, 2015) have noticed the need for better detection and treatment of perinatal depression and parental severe mental disorders.

Maternal depression during pregnancy affects both the mother and the fetus. The fetal environment has an important role in the origin of mental disorder (O’Donnell & Meaney, 2017; Schlotz & Phillips, 2009). In offspring with prenatal adversities, the cumulation of multiple risk factors in childhood and adolescence results in most detrimental effects (Apter, Bobin, Genet, Gratier, & Devouche, 2017). As knowledge increases about the risks to the offspring of antenatally depressed mothers, the importance of antenatal depression research becomes clearer.

The antenatally depressed mothers are at elevated risk of postpartum depression (Gavin et al., 2005; Underwood L. D’Souza S., Peterson ER., Morton S., 2016) and for periods of depression later in life (Park, Brain, Grunau, Diamond, & Oberlander, 2018). Maternal suicide, which is often preceded by untreated depression (Khalifeh, Hunt, Appleby, & Howard, 2016), is the leading cause of maternal mortality in the UK and Australia (M.-P. Austin, Kildea, & Sullivan, 2007). The offspring of antenatally depressed mothers are found to be an increased risk of perinatal complications, developmental delays, behavioral problems and depression (Field, 2011b; Salvatore Gentile & Fusco, 2017; Dominic T Plant, Pariante, Sharp, & Pawlby, 2015; Stein et al., 2014) but long follow-up studies remain scarce.

Mental disorders tend to aggregate in families (Bridge, Brent, Johnson, & Connolly, 1997) and spouses have similarities in their psychiatric histories (Galbaud du Fort, Bland, Newman, & Boothroyd, 1998). Mothers with a history of personal, familial or spousal mental illness are vulnerable to depression during pregnancy (Coates, Saleeba, & Howe, 2018). Parental mental disorders have been
recognized as a risk factor for a variety of psychiatric disorders in the offspring (K. Dean et al., 2010; Rasic, Hajek, Alda, & Uher, 2014; Reupert, J Maybery, & Kowalenko, 2013). The risk for mental disorders in the offspring related to maternal antenatal depression and severe parental mental disorders is probably mediated by both genetic and environmental factors (Schmitt, Malcho, Hasan, & Falkai, 2014).

The present study is based on the Northern Finland 1966 Birth Cohort (NFBC 1966), which is an unselected, general population-based sample of 12,058 live-born children. The cohort members have been followed for over 40 years, starting from pregnancy. The aim of the study was to examine long-term psychiatric outcomes in the offspring of antenatally depressed mothers, taking parental severe mental disorders into account. Although antenatal stress and mental disorders other than depression, and postnatal depression are closely related to the topic, they are beyond the scope of the current study.
2 Review of the literature

2.1 Parental mental disorder as a risk factor for mental health problems in the offspring

It has been estimated, that 14-23% of children have a parent with mental illness (Reupert et al., 2013). Parental mental disorder has been recognized as a risk factor for a variety of psychiatric disorders in the offspring (K. Dean et al., 2010; Rasic et al., 2014; Reupert et al., 2013). According to a meta-analysis on high-risk studies, the risk of developing severe mental illness (i.e., schizophrenia, bipolar disorder or depression) is 2.5-fold (95% confidence Interval, 95% CI, 2.08–3.06) in the offspring of parents with severe mental illness compared to subjects without parental severe mental disorder (Rasic et al., 2014). When compared to offspring without parental mental disorder, the adult offspring with parental severe mental illness had an elevated risk of schizophrenia (Risk Ratio, RR, 3.94; 95% CI, 2.03-7.63), bipolar disorder (RR 4.04; 95% CI 2.33-7.01), and depression (RR 2.03; 95% CI 1.57-2.61). Of the adult offspring with parental severe mental illness, 55% (RR 1.6; 95% CI 1.46-1.76) had a mental disorder (Rasic et al., 2014).

In a Finnish study by Holma and colleagues (Holma, Melartin, Holma, Paunio, & Isometsä, 2011), 183 patients with depressive disorder self-reported their family history of mental disorders. Of those, 74.9% had a family history of some serious mental disorder, more precisely, 60.7% of mood disorders, 36.6% of alcoholism, and 10.9% of psychotic disorders. During a 5-year follow-up, patients with a family history of mental disorder had attempted suicides four times more often than those without. They also had an elevated risk of developing a comorbid cluster C personality disorder, neuroticism, alcohol dependence, dysthymia, and they had more symptoms of cluster B personality disorders and less time spent in remission than those without a familial history of mental disorder (Holma et al., 2011). In a previous study of the NFBC 1966, family history of psychiatric disorder was associated with worse outcome in psychotic disorders, than in subjects without family history of psychosis (J. Kåkelä, Nordström, Haapea, Jääskeläinen, & Miettunen, 2018; Juha Käkelä et al., 2017). The effect of parental mental disorder on offspring risk of mental disorders seems to be dose-responsive. More severe parental mental disorder vs. milder mental parental disorder, and mental disorder in both parents, in comparison to one parent, results in higher risk of mental disorders in the offspring (C.-M. Cheng et al., 2018; K. Dean et al., 2010).
Mental disorders tend to accumulate in certain families (Kendler, 1990). Psychotic disorders, mood disorders and alcohol use disorder are often represented in the same families with overlap between different diagnostic groups (Holma et al., 2011). The spouses of patients with mental disorder are found to have impaired mental health, especially if they are lacking social support (Idstad, Roysamb, & Tambs, 2011). Spouses are also found to have similarity with each other for psychiatric illnesses. Significant spousal associations for affective disorders, antisocial personality and substance use disorders have been documented (Galbaud du Fort et al., 1998; Galbaud du Fort, Boothroyd, Bland, Newman, & Kakuma, 2002; Marmorstein, Malone, & Iacono, 2004). Spousal similarity for personality and mental disorders may be explained by assortative mating, a selection of mates for particular phenotypes (Dierker, Merikangas, & Szatmari, 1999; Maes et al., 1998). Mental illness may also have bidirectional effects, where the mental disorder in one subject may influence their close one (Maes et al., 1998). There may be also some shared factors, such as age, education, or religion, which is associated with the risk of mental disorders in both spouses (Maes et al., 1998), and possibly also the offspring.

The offspring with both parents having a mental disorder can be supposed to have not only an enhanced genetic loading for psychiatric illness, but also more environmental risk factors, such as intrafamilial social problems in childhood causing a pronounced risk of mental disorders, compared to children whose parents are mentally healthy, or only one of the parents has a mental disorder. In a recent Finnish register-based study (N = 900 603), 2.8% of the general population had both parents affected with a mental disorder, and the risk of attention deficit / hyperactivity disorder (ADHD) was found to be more elevated among offspring of whom both parents had been affected with mental disorder (adjusted OR 3.6, 95% CI 3.3–4.0), than offspring with only a mother (2.2; 2.0–2.3) or father (1.7; 1.6–1.8) affected (Joelsson et al., 2017). In a Danish register-based study (N = 3 391 018), the offspring of whom both parents were affected with schizophrenia or bipolar disorder were studied (Gottesman, Laursen, Bertelsen, & Mortensen, 2010). The cumulative incidence of any mental disorder until the age of 52 years was 67.5% in the offspring of whom both parents had been affected with schizophrenia, and 44.2% in the offspring of whom both parents had been affected with bipolar disorder, as compared with 11.9% of the offspring of parents never admitted for psychiatric diagnosis (Gottesman et al., 2010). Of the total cohort, 0.007% had both parents diagnosed with schizophrenia and 0.004% had both parents diagnosed with bipolar disorder (Gottesman et al., 2010). In the subjects of whom both parents had
been admitted with a diagnosis of schizophrenia, the risk of schizophrenia was 4-fold when compared to those with only one parent admitted, and 32-fold when compared to subjects of whom neither of the parents ever having been admitted. The risk of bipolar disorder was 6-fold in subjects of both parents admitted with a diagnosis of bipolar disorder, when compared to those with one parent admitted, and 52-fold when compared to subjects of parents never admitted for bipolar disorder (Gottesman et al., 2010).

The risk for mental disorders in the offspring related to parental mental disorders is probably mediated by both genetic and environmental factors (Schmitt et al., 2014). This interaction can affect child neurodevelopment, which results in vulnerability for mental disorders (Lesch, 2004; Maes et al., 1998; Owen & O'Donovan, 2017; Schmitt et al., 2014). Nevertheless, parental severe mental disorder affects the offspring also environmentally and psychosocially, at least in childhood and adolescence, when the children share the household with their parents.

2.2 Antenatal depression

Depression is one of the leading global causes of burden of disease (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017), that usually occurs at a young age, and affects women more often than men (R. C. Kessler & Bromet, 2013; Pedersen et al., 2014; Weissman & Olfson, 1995). The global 12-month-prevalence of depression is 3.7% in the general population, 3.9% in men and 7.2% in women (Ferrari et al., 2013), and 5.5% in developed countries (R. C. Kessler & Bromet, 2013). In Finland, the 12-month prevalence of major depression of population aged 30 years or more is 7.8%, with women being at over 2-fold risk (OR 2.33; 95% CI 1.6–3.4), compared to men (Markkula, 2015).

Antenatal depression is a form of clinical depression affecting women during pregnancy, and is an ailment that increases the risk of postpartum depression (Baker, 2015; Underwood L., Waldie K., D’Souza S., Peterson ER., Morton S., 2016; Verreault et al., 2014). It is associated with many other adverse outcomes in the mother, the pregnancy and the child (Field, 2011a; Gentile, 2017a; Stein, 2014). The clinical picture of antenatal depression includes fatigue, anxiety, agitation, ruminating, obsessive and suicidal thoughts, and lack of interest in the fetus (Meltzer-Brody, 2011).

Perinatal mood disorders include symptomatology from mild to severe. The mildest and most usual mood disturbance, the postpartum blues affects 40-85% of
mothers (Sharma, Rai, & Pathak, 2015). It usually occurs during the first week postpartum, with symptoms such as dysphoria, mood lability, crying, anxiety, insomnia, poor appetite, and irritability (Handley, Dunn, Waldron, & Baker, 1980). The postpartum blues usually passes without treatment within ten days postpartum, although it elevates the risk for postpartum depression (Henshaw, 2003; Matti Isokanni, Murray, Jokelainen, Croudace, & Jones, 2004).

More severe mood disturbance, perinatal depression affects at least every tenth women during pregnancy or postnatally (Woody, Ferrari, Siskind, Whiteford, & Harris, 2017). It occurs at least as frequently during pregnancy as after delivery (Underwood, Waldie, D'Souza, Peterson, & Morton, 2017; Woody et al., 2017). Depression during perinatal period can be diagnosed in terms of major depression and specified with pregnancy or postpartum onset diagnostic codes.

Mood disorders during pregnancy and postpartum have been described in scientific literature since the mid-nineteenth century. Louis-Victor Marcé, a psychiatrist from Paris, France, published one of the earliest systematic clinical monographs in 1858, called “Traité de la folie des femmes enceintes, des nouvelles accouchées et des nourrices, et considérations médico-légales qui se rattachent à ce sujet [Treatise on Insanity in Pregnant, Postpartum, and Lactating Women, and Related Medicolegal Considerations]” (Marcé, 1858). Marcé described psychological changes associated with pregnancy by worry, anxiety, fatigue, hopelessness, lack of interest or initiative, obsessive preoccupations, fears arising from previous pregnancies, fear of having an abnormal baby, physical symptoms, insomnia or hypersomnia, excitement, and irritable dysphoria. He even reviewed some contemporary experts’ findings on elevated risk of cognitive impairment in the children of mothers with mental illness during pregnancy and considered genetic and stress factors as potential causes of these impairments. Marcé’s monograph on women’s major perinatal mental illnesses was the leading publication on this topic until the late twentieth century. The importance of Marcé’s work is noticed by the founding of an international Marcé Society, which is devoted to the study on, prevention in, and treatment of psychiatric disorders of women related to childbearing (Trede, Baldessarini, Viguera, & Bottro, 2009).

The scientific interest on perinatal depression rose again in the 20th century, when the elevated risk of psychiatric illness at the puerperium was recognized (Pitt, 1968). The research focus was aimed mainly at postnatal depression, and antenatal depression was recognized in only a few studies. The prevalence of antenatal depression was found to be 6-10%, and of postnatal depression 9-14%, when using screening methods (Cooper, 1988; J. L. Cox, Connor, & Kendell, 1982; Cutrona,
In studies where antenatal depression was identified by a diagnostic interview, the overall prevalence of depression was lower than in screening studies, with a point prevalence of 3.5-6% for major depression (Cutrona, 1983; O'Hara, 1984; Troutman, 1990) and 3-10% for minor depression (O'Hara, 1984; Troutman, 1990), and a cumulative incidence of 10.2% for minor or major depression during pregnancy (Gotlib, 1989) was found. Generally, depression was most prevalent during the third trimester of pregnancy. Only a few mothers had depression during the whole perinatal period (Cooper, 1988; O'Hara, 1984). Antenatal depression was found to explain the variance of about 50% of the postnatal depression cases (Najman 2000; Dean, 1981; Gotlib, 1989; Rees, 1971; Saks, 1985). It was also recognized that mothers may actually be more distressed during pregnancy than postnatally (Elliott, 1983; O'Hara, 1990; Najman 2000). Antenatal depression was found to be associated with bereavement, marital conflicts (Kumar, 1984), lack of social support (O'Hara, 1986), financial difficulties, and a ‘worrier’-kind of personality (J. L. Cox et al., 1982). Compared with fathers and nulliparous women, perinatally depressed mothers more often expressed irritability, fatigability, work inhibition and loss of libido (Rees, 1971). Depressed mothers were also found to express negative feelings towards their babies (Kumar, 1984; O'Hara, 1986).

The research interest in the offspring of antenatally depressed mothers rose in the 1970-'80s. The first study where clinically diagnosed maternal antenatal depression was studied as a risk factor for early adversity in the offspring was the Rochester Longitudinal Study launched in 1970 (N = 262) (Sameroff, Seifer, & Zax, 1982), where maternal antenatal depression rather than schizophrenia or personality disorder was found to have a more significant effect on offspring adversity. In the general Northern Finland 1966 Birth Cohort study (NFBC 1966, N = 12,058), launched in 1965, Professor Rantakallio proved to be a step ahead of her contemporaries when taking maternal antenatal depressed mood into account as a potential risk factor for low birthweight and perinatal mortality in her general population-based longitudinal Northern Finland 1966 Birth Cohort (NFBC 1966, N = 12,058) study launched in 1965 (P Rantakallio, 1969) on which the present study is based.

Antenatal depression has long remained understudied in comparison with postnatal depression, but in recent years, interest in antenatal mental health has risen in research and clinical practice. After the historical studies presented above, dozens of new large studies on antenatal depression have been launched, and many of them are referenced further on in this thesis.
2.2.1 Aetiology of antenatal depression

Depression is a complex condition that occurs as a sum of multiple individual factors. There are many genetic, epigenetic, anatomical, endocrinological and environmental factors, which are common in subjects with depression, and many of those are related to stress responses. Many different pathways may lead to similar symptomatology regarded as depression. These factors, such as the neurotransmitters, environmental stress and antidepressive medication may also affect the fetus when a pregnant woman is stricken with depression.

It has been discussed whether perinatal depression is a distinct medical condition, or a part of the depression continuum. There are findings of different symptomatology in depression during the perinatal period, especially puerperium, from depression at the non-perinatal period. Pitt (1968) found an elevated rate of depression during puerperium, and most of the mothers with puerperal depression had an atypical illness, compared with classic depression during the non-perinatal period. He described the mothers as having a labile mood with prominent anxiety and irritability, feelings of inability to cope, confusion, insomnia, and diurnal variation of symptoms. Later, Dean and Kendell (C. Dean & Kendell, 1981) found women’s admissions to psychiatric hospital to peak postnatally, and 50% of the psychiatric symptoms of those subjects had started during pregnancy. Women with a puerperal major depressive disorder had significantly more psychotic symptoms, lability, disorientation, perplexity and organic impairment compared to controls. Most of those patients had experienced stressful life-events before admission. The findings of atypical symptoms and elevated risk of psychosis at the puerperium were replicated in a study by Brockington and his colleagues (I. F. Brockington, 1988).

Hormonal changes during pregnancy and postnatally

Women experience dramatic fluctuations in hormone levels during the perinatal period. The most significant changes are seen in reproductive and glucocorticoid hormone levels.

Reproductive hormones play an important role in regulation of glucocorticoid hormone levels. In pregnancy, the levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are low, and the serum levels of gonadal steroids (estradiol and progesterone) are markedly increased (Bloch, Daly, & Rubinow, 2003). Estrogen and progesterone induce the function of the hypothalamic-
pituitary-adrenal (HPA)-axis, mostly by hypothalamic corticotropin releasing hormone (CRH) regulation (M. Kammerer, Taylor, & Glover, 2006). The placenta and the amniotic membranes produce high levels of CRH, and the free glucocorticoids increases this production. The placenta produces CRH-binding protein, which attenuates the cortisol production, but during the late third trimester, the CRH-binding protein production decreases causing highly elevated free cortisol levels at the end of pregnancy (Gelman, Flores-Ramos, López-Martínez, Fuentes, & Grajeda, 2015; M. Kammerer et al., 2006). An increase in adrenocorticotropic hormone (ACTH), arginine vasopressin, testosterone, aldosterone, prolactin, inhibin and beta-endorphins can also be measured during pregnancy (Bloch, 2003). Physiological and hormonal stress responses to challenge appear to be attenuated during late pregnancy, possibly due to hypercortisolemia (de Weerth, 2005).

After parturition, the estrogen and progesterone levels fall dramatically before they slowly adapt to physiological levels as the LH and FSH secretion return to their normal pattern. The cortisol level also declines rapidly after delivery, as the placental CRH decreases in the mother’s circulation (Bloch, 2003). The secretion of hypophyseal CRH remains suppressed for up to 12 weeks postnatally due to hypertrophy of adrenal cortex and decreased estrogen levels (Gelman, 2015; Magiakou et al., 1996). The levels of oxytocin and prolactin are elevated during lactation (Bloch et al., 2005), and oxytocin inhibits ACTH-secretion (Gelman, 2015). Thus, the antenatal hypercortisolemia rapidly changes into hypocortisolemia, and the function of the HPA-axis slowly reverts to normal during the postnatal period. The regulation of thyroid hormones is also altered during the perinatal period, but the levels of free triiodothyronine (T3) and thyroxine (T4) remain stable (Bloch, 2003).

Antenatally depressed women may be especially sensitive to changes in reproductive hormonal changes (Serati, Redaelli, Buoli, & Altamura, 2016). The prevalence of antenatal depression is the highest at the third trimester of pregnancy, when estrogen-, progesterone- and cortisol-levels are at their highest. (Stuebe, 2018).

**Monoamines**

According to the monoamine theory, the decreased activity of monoaminergic neurons, which are mostly responsible for motivation, work memory, sexual drive, appetite, attention and behavior, are associated with the etiology of depression. These monoamine neurotransmitters include norepinephrine, serotonin (5-
hydroxytryptamine, 5-HT) and dopamine. The decrease in monoaminergic activation may be due to the lack of 5-HT precursor tryptophan, the overactivated neurotransmitter reuptake by transporter proteins, the increased inactivation by the monoamine oxidase -enzyme (MAO), or the decreased monoamine receptor activity (Jesulola, 2018). Overactivation of the MAO-A-enzyme is associated with depression and aggression (Alia-Klein, 2008). Drugs which increase monoamine activity by blocking the MAO-A (MAO inhibitors, such as moclobemide; Finberg, 2016) or by blocking the reuptake of 5-HT (selective serotonin reuptake inhibitors, SSRI, e.g., citalopram, escitalopram, fluoxetine, sertraline) or 5-HT and other monoamines (e.g., selective serotonin and norepinephrine reuptake inhibitors, SNRI, such as duloxetine, venlafaxine) have slow antidepressive effects (Cipriani et al., 2018), indicating that these effects may be due to adaptive changes associated with the monoaminergic system (Heiskanen, Huttunen, Kampman, & Tuulari, 2017). The findings related to 5-HT-receptor activity have been inconsistent in functional neuroimaging studies, some of them presenting decreased 5-HT1A-receptor density in patients affected with depression (Heiskanen et al., 2017; Wise, Cleare, Herane, Young, & Arnone, 2014). In the tryptophan and tyrosine depletion studies, the tryptophan depletion, causing a lack of serotonin, or the tyrosine depletion, causing the lack of noradrenalin, induced depression in some subjects, but not all, indicating that the dysfunction of the monoaminergic system cannot solely cause depression for everyone, but more likely to subjects vulnerable to depression due to genetic liability (Heiskanen et al., 2017).

Stress induces glutamate, histamine and norepinephrine secretion, which reduces the production of monoamines (Jesulola, 2018). The Brain Derived Neurotrophic Factor (BDNF) functions in the stress response and has protective effects against the changes due to stress in the brain (Hacimusalar & Eşel, 2018). The decrease in BDNF has been found to associate with decreased 5-HT- and increased cortisol-levels, and recently, lower maternal serum BDNF levels in early pregnancy have been associated with antenatal depression (Serati et al., 2016).

Reproductive hormones are also found to take part in the regulation of monoamine signaling in certain brain regions (M. Kammerer et al., 2006), and significant associations between monoamine signaling and depression have been documented in pregnant women (Serati, 2016), although the monoamine system has not been found to be solely explanatory for the development of antenatal depression (Serati 2016).
The hypothalamic-pituitary-adrenal-axis

In depression, as well as in chronic stress, the baseline levels of cortisone are elevated due to increased CRH and/or arginine vasopressin -expression (Gelman 2015). A similar dysfunction of the HPA-axis as physiologic in pregnancy, with elevated CRH, ATCH and cortisol levels, dysfunctional glucocorticoid feedback mechanisms and blunted suppression of cortisol secretion by exogenous glucocorticoids, has been shown in subjects with non-puerperal major depression (Bloch, 2003; Jesulola, 2018). The induced cortisol signaling increases glutamate activation, which has been found to be neurotoxic especially in the hippocampus, potentially leading to hippocampal volume reduction (Heiskanen et al., 2017). In genetic and epigenetic studies, glucocorticoid receptor sensitivity, potentially regulated by the reproductive hormones, has been suggested to be associated with a risk of perinatal depression (Serati et al., 2016).

Besides the HPA-axis, CRH seems to have independent associations with depression given that it functions as a neurotransmitter that co-ordinates behavioral, autonomic, endocrine and immune responses to stress (Jesulola, 2018).

Inflammation

Pregnancy is regarded as an inflammatory state, with a carefully regulated homeostasis between pro- and anti-inflammatory agents (Shelton, Schminkey, & Groer, 2015). The inflammatory system is overactivated during the third trimester of pregnancy, and increased levels of certain cytokines have been measured in antenatally depressed mothers (Karlsson et al., 2017; Serati et al., 2016). The immune system may be associated in the pathogenesis of depression in certain subjects (Hacimusalar & Eşel, 2018). Depression and stress are shown to activate the immune system, resulting in elevated levels of cytokines, and antidepressants are shown to reduce the cytokine concentrations (Jesulola, 2018). Anti-inflammatory medication has reduced symptoms of depression in some patients (Heiskanen et al., 2017). The imbalance of inflammatory agents may associate with depression by reducing brain neuroplasticity via decreased BDNF activity, by inhibiting the monoaminergic activation, and by increasing the HPA-axis activity (Hacimusalar & Eşel, 2018; Jesulola, 2018). Inflammatory activation is also associated with energy saving sickness behavior, which includes reduction in activity and social interaction, decreased sexual activity, increased responsiveness...
to pain, loss of appetite, and depressed mood, much like with symptoms of depression (Segerstrom, 2004).

**Brain structural and functional changes**

Usually depression cannot be identified from brain imaging, but some brain morphological abnormalities have been reported in subjects affected with major depression, including reduction in the hippocampal volume; hyperintensity in the basal ganglia, anterior cingulate cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex, potentially associated with ischemia; decreased cortical thickness; decrease in gray matter volume, and white matter integrity deterioration (Hacimusalar & Eşel, 2018; Heiskanen et al., 2017), which are thought to be part of the wider neural network related to emotion processing and mood regulation (Hacimusalar & Eşel, 2018). It is under discussion, whether these changes are permanent, due to genetic predisposition, or if they are situational, associated with depressive episodes (Hacimusalar & Eşel, 2018).

In functional neuroimaging studies, functional changes in the limbic system, associated particularly with emotional function; in the prefrontal cortex, associated particularly with cognitive function; and in the communication between different brain regions, have been found in subjects with depression (Heiskanen et al., 2017). These functional abnormalities may appear e.g. as hypoactive responses to emotional stimuli in the frontal regions, and hyperactive responses in the limbic regions, possibly indicating selective attention to negative stimuli rather than positive emotional and reward related stimuli (Hacimusalar & Eşel, 2018). Subjects affected with depression have also often difficulties in learning and memory, which may be associated with hippocampal changes (Heiskanen et al., 2017).

A dysfunction of the biological circadian rhythm is also associated with depression. In sleep-electroencephalogram (EEG) studies, typical findings in depression patients are decreased slow-wave activity and increased rapid eye movement (REM) activity and short REM-latency (Heiskanen et al., 2017).

**Genetic factors**

First-degree relatives of patients with major depressive disorder have a two- to three-fold increase in likelihood of developing depression (Lohoff, 2010), with greater heritability in women than men (Jesulola, 2018). The genetic background of depression seems to include multiple genes with small independent effects,
which interplay with environmental factors. Although no universal genetic risk factor for depression has been found, many candidate genes related to synthesis, transportation and the signalling of monoamines as well as, the HPA-system, and hippocampal neurogenesis are associated with depression (Jesulola, 2018; Lohoff, 2010). The heritability of antenatal depression is approximately 37% (Viktorin, 2016).

**Environmental stress**

Although pregnancy has been previously thought to be protective of mental illness, it is now well known that pregnant mothers are more likely to be vulnerable to mental distress. Pregnancy, preparing for childbirth and the role transfer in becoming a mother, may be very stressful, especially if the subject has, e.g., social or economic problems. Depression often occurs after major psychosocial stress or life events (Jesulola, 2018). Stress can induce the activation of the HPA-axis and inflammation, reduce monoaminergic activation and result in structural changes in the prefrontal cortex, amygdala, hippocampus and nucleus accumbens, which are all associated with the pathogenesis of depression (Jesulola, 2018). Early environmental stress may also lead to epigenetic changes resulting in increased vulnerability for depression (Hacimusalar & Eşel, 2018). Environment, which causes an affect alongside genetic, endocrinological and immunological factors, has an important role in the development of depression.

**Risk factors for antenatal depression**

The strongest predictor of perinatal mental disorder is a history of previous psychiatric illness, particularly affective illness (Leight, Fitelson, Wston, & Wisner, 2010; Patton et al., 2015; Räisänen et al., 2014). Mothers with a history of personal, familial or spousal mental illness are vulnerable to depression during pregnancy (Coates et al., 2018). A discontinuation of medication induces a risk of relapse for depression and bipolar disorder during pregnancy (Leight et al., 2010).

Maternal risk factors for antenatal depression include low self-esteem, negative cognitive style (Lancaster et al., 2010; Leigh & Milgrom, 2008), extremes of age, obesity, and chronic illness (Kumpulainen et al., 2018; Melville, 2010). There are inconsistent findings on whether maternal race, parity, and alcohol or substance use affect the likelihood of antenatal depression. Other known risk factors related to maternal personal history include a history of premenstrual dysphoric disorder,
bereavement and other life stress, a history of miscarriage and pregnancy termination, and childhood sexual abuse (Biaggi, Conroy, Pawlby, & Pariante, 2016; Lancaster et al., 2010; Leigh & Milgrom, 2008; Underwood, Waldie, D’Souza, et al., 2017; Verreault et al., 2014). In a recent study, the association between childhood abuse and antenatal depression was found to be potentially mediated by depression prior to pregnancy and adverse experiences in adulthood (Lydsdottir et al., 2019).

Risk factors related to the current pregnancy include fear of childbirth, anemia, gestational diabetes (Räisänen et al., 2014), hyperemesis gravidarum (Kjeldgaard, Eberhard-Gran, Benth, & Vikanes, 2017), anxiety, single status, and unplanned pregnancy (Biaggi et al., 2016; Getinet et al., 2018; Lancaster et al., 2010). Maternal smoking during pregnancy is associated with antenatal depression (Lancaster, 2010), but no direct association between maternal depression and smoking during pregnancy was shown in a large study by Munafo and colleagues (Munafo, Heron, & Araya, 2008), although smoking cessation was found to be associated with reduction in depression scores.

Psychosocial factors, such as lack of social support, especially from one’s own partner, poor relationship quality, and domestic violence are found to increase the risk of antenatal depression (Lancaster et al., 2010; Melville, 2010). There are also findings of associations between socioeconomical factors, such as low income, unemployment, lower educational attainment, and increased risk of depression during pregnancy (Lancaster et al., 2010; Leight et al., 2010).

In contrast, younger age, good partner relationship, preparedness for delivery, active coping, and social support were found to be protective of antenatal depression in a Chinese study (Zeng, Cui, & Li, 2015).

### 2.2.2 Screening of antenatal depression

#### Development of screening methods

In the 1980s, John Cox and colleagues (J. L. Cox et al. 1982) found that postnatally depressed mothers did not get properly diagnosed and treated. The screening scales used on childbearing women at that time included the Beck Depression Inventory (BDI, Beck, 1961), Zung Depression Scale (ZSDS, Zung, 1965), the General Health Questionnaire (GHQ, Goldberg, 1970), and the Anxiety and Depression Scale (Bedford, Foulds, & Sheffield, 1976), which were all found to lack validity when used on childbearing women (J. L. Cox, 1983; Gotlib, 1989). Because of these
findings, the need to develop a screening questionnaire to detect postnatal depression was recognized (John L Cox, 1983; Kumar, 1984). Cox and his co-workers developed the Edinburgh Postnatal Depression Scale (EPDS) (J L Cox, Holden, & Sagovsky, 1987) to give primary care workers practical help in identifying postnatal depression. The scale consists of ten self-report questions, which were tested to ensure a high rate of acceptability among child-bearing mothers and health workers, as well as good likelihood of detecting depression. The scale was validated (Cox 1987), and a satisfactory validity, split-half reliability and sensitivity to changes in the severity of depression over time was found. The sensitivity and specificity of the scale may be increased if it is completed when other family members are not present. A threshold of 9/30 is appropriate in routine use for primary care workers, and women scoring above the threshold should be further assessed for clinical depression. Women scoring above 12/30 in the EPDS are likely to have clinical depression (J. L. Cox, Holden, & Sagovsky, 1987).

Later, the EPDS have been also validated for antenatal use in many cultures (Kozinszky & Dudas, 2015), and the scale is in routine use in antenatal clinics in many countries. It has also been evaluated to be the most accurate screening tool in low-resource settings (Chorwe-Sungani & Chipps, 2017).

After the EPDS, many other scales have been validated for screening depressed mood during pregnancy. The screening scales validated in pregnant women against a structured diagnostic interview by a healthcare professional are represented in Table 1. Of those, Center for Epidemiological Studies Depression scale (CES-D) is probably the second most often used (after the EPDS) for screening perinatal depressed mood in recent epidemiological studies (Table 2). The Patient Health Questionnaire (PHQ-9) is routinely used in the USA (E. O’Connor, Rossom, Henninger, Groom, & Burda, 2016). In a comparative study of the EPDS and PHQ-9, both scales were found to be valid and reliable in the detection of antenatal depression, but the EPDS performed better in detecting depressive and anxious symptoms and PHQ-9 somatic symptoms, which is why the scales were suggested to be administered simultaneously (Zhong, 2014). Also the short two-question scales (The Whooley questions and PHQ-2) were found to be useful in screening, but further evaluation is needed for screen positives (Louise Michele Howard et al., 2018; Vlenterie, 2017). Only one scale, The Pregnancy Depression Scale (PDS) (Altshuler et al., 2008) is developed specifically for screening depression during pregnancy.
Table 1. Depression rating scales validated as suitable for screening of antenatal depression

<table>
<thead>
<tr>
<th>Scale (reference)</th>
<th>Validation for antenatal depression</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Recommended cut-off score</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMQ (Matthey, Valenti, Souter, &amp; Ross-Hamid, 2013)</td>
<td>Matthey &amp; Della Vedova, 2018</td>
<td>81%</td>
<td>74%</td>
<td>Bothered 'A little' or more.</td>
<td>Self-reported</td>
</tr>
<tr>
<td>PDS (Altshuler et al., 2008)</td>
<td>Altshuler et al., 2008</td>
<td>82%</td>
<td>77%</td>
<td>≥5</td>
<td>Clinician-rated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65%</td>
<td>92%</td>
<td>≥8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40%</td>
<td>98%</td>
<td>≥11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>16%</td>
<td>100%</td>
<td>≥ 15</td>
<td></td>
</tr>
<tr>
<td>PRQ (M. P. Austin, Hadzi-Pavlovic, Saint, &amp; Parker, 2005)</td>
<td>M. P. Austin et al., 2005</td>
<td>44%</td>
<td>92%</td>
<td>&gt;46</td>
<td>Self-reported</td>
</tr>
<tr>
<td>PHQ-2 (Kroenke Kurt, 2003)</td>
<td>Vlerentie, 2017</td>
<td>69–84%</td>
<td>79–84%</td>
<td>Positive response to either question</td>
<td>Self-reported</td>
</tr>
<tr>
<td>PHQ-9 (Kroenke, Spitzer, &amp; Williams, 2001)</td>
<td>Sidebottom, Harrison, Godecker, &amp; Kim, 2012</td>
<td>85%</td>
<td>84%</td>
<td>≥ 10 for depression</td>
<td>Self-reported</td>
</tr>
<tr>
<td>PDSS (C. T. Beck &amp; Gable, 2000)</td>
<td>Pereira et al., 2011; Zhao et al., 2015</td>
<td>83-86%</td>
<td>78-100%</td>
<td>≥ 60 risk for major or minor depression. ≥ 80 positive screen for major depression</td>
<td>Self-reported</td>
</tr>
<tr>
<td>Scale (reference)</td>
<td>Validation for antenatal depression</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Recommended cut-off score</td>
<td>Reporting</td>
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</tr>
<tr>
<td>The Whooley questions (Whooley, Avins, Miranda, &amp; Browner, 1997)</td>
<td>Howard et al., 2018</td>
<td>41%</td>
<td>95%</td>
<td>Positive response in either question</td>
<td>Self-reported</td>
</tr>
<tr>
<td>BDI-II (A. Beck &amp; Steer, 1996)</td>
<td>Pereira et al., 2011</td>
<td>79%</td>
<td>86%</td>
<td>≥12 for Depressive disorder</td>
<td>Self-reported</td>
</tr>
<tr>
<td>K10 (R. Kessler &amp; Mroczek, 1996)</td>
<td>Spies et al., 2009</td>
<td>73%</td>
<td>54%</td>
<td>≥20</td>
<td>Self-reported</td>
</tr>
<tr>
<td>SRQ (Beusenberg, Orley, &amp; World Health Organization. Division of Mental Health, 1994)</td>
<td>Stewart, Umar, Tomenson, &amp; Creed, 2013</td>
<td>76%</td>
<td>75%</td>
<td>&gt;17</td>
<td>Self-reported</td>
</tr>
<tr>
<td>EPDS (J L Cox et al., 1987)</td>
<td>Kozinszky &amp; Dudas, 2015; Matthey Henshaw, C., Elliott, S., &amp; Barnett, B., 2006</td>
<td>70—100%. 74—97%</td>
<td>≥ 15 for major depression</td>
<td>Self-reported</td>
<td></td>
</tr>
<tr>
<td>CES-D (Radloff, 1977)</td>
<td>Mosack &amp; Shore, 2006; Natamba et al., 2014</td>
<td>72%</td>
<td>79%</td>
<td>≥20</td>
<td>Self-reported</td>
</tr>
<tr>
<td>GHQ (Goldberg, 1970)</td>
<td>Kitamura, Shima, Sugawara, &amp; Toda, 1994 T1 83% T1 71% T3 39% T3 82%</td>
<td>T1 83% T1 71% T3 39% T3 82%</td>
<td>7/8</td>
<td>Self-reported</td>
<td></td>
</tr>
<tr>
<td>ZSDS (Zung, 1965)</td>
<td>Kitamura et al., 1994 T1 91% T1 70% T3 70% T3 76%</td>
<td>T1 91% T1 70% T3 70% T3 76%</td>
<td>22/23</td>
<td>Self-reported</td>
<td></td>
</tr>
<tr>
<td>Scale (reference)</td>
<td>Validation for antenatal depression</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Recommended cut-off score</td>
<td>Reporting</td>
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<tr>
<td><strong>BDI</strong> (A. T. Beck, 1961)</td>
<td>Castro E Couto et al., 2015; C. de S. R. Martins et al., 2015</td>
<td>81—87%</td>
<td>74—85%</td>
<td>≥15</td>
<td>Self-reported</td>
</tr>
<tr>
<td></td>
<td>Ji et al., 2011</td>
<td>T1 88%</td>
<td>T1 81%</td>
<td>≥15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2 90%</td>
<td>T2 78%</td>
<td>≥13</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3 83%</td>
<td>T3 75%</td>
<td>≥12</td>
<td></td>
</tr>
<tr>
<td><strong>HAM-D</strong> (Hamilton, 1960)</td>
<td>Castro E Couto et al., 2015</td>
<td>88%</td>
<td>75%</td>
<td>≥9</td>
<td>Clinician-rated</td>
</tr>
<tr>
<td><strong>HRSD17</strong></td>
<td>Ji et al., 2011</td>
<td>T1 82%</td>
<td>T1 78%</td>
<td>≥14</td>
<td>Clinician-rated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2 78%</td>
<td>T2 85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3 74%</td>
<td>T3 84%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HRSD21</strong></td>
<td>Ji et al., 2011</td>
<td>T1 80%</td>
<td>T1 79%</td>
<td>≥15-16</td>
<td>Clinician-rated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2 82%</td>
<td>T2 80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3 74%</td>
<td>T3 84%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory, 2nd edition; CES-D = Center for Epidemiologic Studies Depression Scale; EPDS = The Edinburgh Postnatal Depression scale; GHQ = General Health Questionnaire; HAM-D = Hamilton Rating Scale for Depression; HRSD17 = Hamilton Rating Scale for Depression (17 items); HRSD21 = Hamilton Rating Scale for Depression (21 items); K10 = Kessler Psychological Distress Scale; MGMQ = Matthey Generic Mood Questionnaire; PDS = The Pregnancy Depression Scale; PDSS = Postpartum Depression Screening Scale; PHQ-2 = Patient Health Questionnaire-2, PHQ-9 = Patient Health Questionnaire-9; PRQ = Pregnancy Risk Questionnaire; SRQ = Self-Reporting Questionnaire; ZSDS = Zung Depression Scale
Novel strategies in screening antenatal depression, such as mobile applications for tablet computers (Marcano-Belisario et al., 2017; Marcano Belisario et al., 2017) and smart phones, are found to be feasible and promising in order to provide the healthcare workers more time for diagnostics and interventions for depression, rather than screening.

**Guidelines for screening of perinatal depression**

Generally, screening for depression during pregnancy has been recommended internationally by medical and public health organizations (Highet & Purcell, 2012; NICE, 2014; E. O’Connor et al., 2016). Mothers are recommended to be screened for depression at least once during pregnancy and postpartum with a standardized, validated tool. The aim of screening is to identify women and families, who may need further assessment and follow-up (Accottt & Wong, 2017). Every screen positive should be clinically evaluated.

In the Finnish standard by the National Institute of Health and Welfare (Klemetti & Hakulinen-Viitanen, 2013a), mothers’ and fathers’ depressive signs and symptoms are recommended to be discussed in every maternity clinic visit during pregnancy, and the EPDS can be used in addition, especially if the parent has a history of depression or any depressive symptoms are present at the time of evaluation. A further evaluation by a physician is recommended if the EPDS score is over 13, and a re-evaluation by the EPDS is recommended after two to four weeks if the EPDS score is 10-12. At 5-8 weeks postpartum, the EPDS is recommended to be administered to all mothers by the midwives/nurses. The mother-baby attachment and interaction are to be evaluated by an interview (VaVu) both during pregnancy and after childbirth, as well as the parents’ everyday resources (Klemetti & Hakulinen-Viitanen, 2013b). The Finnish Current Care Guidelines does not recommend screening for antenatal depression, but only for postpartum depression.

The UK NICE guidelines (NICE, 2014) suggest use of the following three ‘Whooley’ questions (Whooley et al., 1997) to identify pregnant women with possible depression: During the past month, have you often been bothered by feeling down, depressed or hopeless? During the past month, have you often been bothered by having little interest or pleasure in doing things? A third question should be considered if the woman answers ‘yes’ to either of the previous questions: Is this something you feel you need or want help with? The Whooley questions have recently been compared with the EPDS and validated against the Structured Clinical Interview DSM-IV-TR (SCID) in screening depression in pregnant women (Louise Michele Howard et al., 2018).
EPDS was found to be better than Whooley questions in identifying depression (likelihood ratios 9.8 for EPDS and 8.2 for Whooley), but the diagnostic accuracy in identifying any disorder (likelihood ratios 5.8 and 6) was similar within the two scales.

The U.S. Preventive Task Force recommend screening for perinatal depression at least once during pregnancy, and note that further evaluation of mental health is necessary in screen positives (E. O’Connor et al., 2016). The Task Force did not name any specific screening method but found the EPDS to have good sensitivity and specificity.

It should be noted that recognition of depression in both pregnant and non-pregnant women in primary care is low: less than half of the depressed patients are recognized by their physicians, and less than 10% get adequate treatment (E. Q. Cox et al., 2016; Ko, Farr, Dietz, & Robbins, 2012; Sundström, Bixo, Björn, & Åström, 2001). It is stated, that without standardized screening, 80% of antenatally depressed mothers remain undetected, and without early treatment, 50% to 70% of them will experience persistent symptoms throughout their children’s early years (Kingston et al., 2014). Screening for antenatal depression is cost-effective, and it decreases the risk of postpartum and later persistent depression and may also benefit the children’s mental health (Muzik & Borovska, 2010; E. O’Connor et al., 2016).

### 2.2.3 Diagnosis of antenatal depression

When a pregnant woman scores above screen positive on one of the aforementioned scales (Table 1), or symptoms of depression are identified clinically, a consultation with a physician or a psychiatrist is required for further evaluation. Structured interviews, such as The Structured Clinical Interview for DSM-III-R (SCID-I) (Spitzer, Williams, Gibbon, & First, 1992) or the The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) can be used in diagnostic assessment, but not much weight should be given to somatic symptoms in pregnant or postpartum women (Martin Kammerer et al., 2009; Matthey & Ross-Hamid, 2011). Major depression can be diagnosed with the DSM-5 or the International Classification of Diseases and Related Health Problems -10 (ICD-10) criteria (see chapter 1.2.3). No specific diagnostic codes for antenatal depression yet exist, but a DSM-V “With peripartum onset” specifier can be used in addition to Major depressive disorder (296.20-296.24), if the onset of mood symptoms is during pregnancy or in the four weeks following delivery, or ICD-codes for puerperal mild and severe mental disorders (F53.0, F53.1, F53.8, F53.9) can be used to describe non-
specific mental disorders with postpartum onset (World Health Organization, 1993). The upcoming ICD-11 is also planned to include codes 6E20 for Mental or behavioral disorders associated with pregnancy, childbirth and the puerperium without psychotic symptoms; and 6E21 for a similar disorder with psychotic features (World Health Organization, 2018).

Depressed mood may also be a symptom of another clinical condition apart from depression, such as bipolar disorder or psychosis, or a somatic condition, such as hypothyroidism or anaemia, or a sign of reaction to an adverse event, e.g., bereavement or intimate violence. The presence of mania, psychosis, or suicidal thoughts or attempts are crucial to identify. Suicidal ideation is common among depressed women, and it may be more prevalent during pregnancy than postnatally (Mauri, Oppo, Borri, & Banti, 2012), although suicide attempts and completed suicides are more common postnatally (Lindahl, Pearson, & Colpe, 2005).

2.2.4 The prevalence of antenatal depression

Antenatal depression is common. The prevalence of perinatal depression depends on the evaluation method: using symptom scales, the prevalence is higher compared to studies where diagnostic instruments have been used (odds ratio, OR, 1.6; 95% Confidence Interval, CI, 1.3-2.0) (Woody et al., 2017). The most recent global estimate on the prevalence of perinatal depression, based on a systematic review and meta-regression, is 11.9% (Wood et al., 2017). In developed countries the prevalence of antenatal depression is 10-17% of mothers (Evans et al., 2001; Gavin et al., 2005; Louise M Howard et al., 2014; Underwood, Waldie, D’Souza, et al., 2017), and the pregnant women in low and middle income countries (LAMIC) are at even higher risk (OR 1.8, 95% CI 1.4-2.2) (Woody et al., 2017), with a prevalence of 21-39% (Getinet et al., 2018; Golbasi, Kelleci, Kisacik, & Cetin, 2010; Hartley et al., 2011; Luke et al., 2009; Manikkam & Burns, 2012; Silva et al., 2010). Still, the lifetime prevalence of major depression in general population is higher in developed countries than in the LAMIC (14.6% vs. 11.1%) (Bromet et al., 2011). The point-prevalence of clinician diagnosed major depression during pregnancy is estimated to be 3.1 - 4.9%, and 8.5-11.0% for minor depression (Gaynes et al., 2005), although in a large Finnish register-based study, FinESSI (Malm, 2012b), the prevalence of a physician-diagnosed depressive disorder between one year before conception and until delivery was only 1.9% (Table 2). In low- and middle-income countries the prevalence of maternal antenatal depression is 21-39% (Getinet et al., 2018; Golbasi et al., 2010; Hartley et al., 2011; Luke et
The prevalence of depression in the general population is higher in developed countries (14.6% vs. 11.1%; (Bromet et al., 2011). The prevalence of depression increases towards the end of pregnancy (Leung & Kaplan, 2009). Depression is one of the most common pregnancy complications (Accott & Wong, 2017; Gaynes et al., 2005) and psychiatric morbidity is the leading cause of maternal perinatal mortality in the United Kingdom (Knight et al., 2017) and Australia (M.-P. Austin et al., 2007).

There have been mixed findings whether the perinatal period poses women at risk of depression. Many studies have found depression to be more common during pregnancy and postnatally than in the non-perinatal period (C. Dean & Kendell, 1981; Kendell, 1987; Leight et al., 2010; Rees, 1971), but there are also opposite findings (Cooper, 1988; Gotlib, 1989; Leach, Christensen, & Mackinnon, 2014; O’Hara, 1990; Troutman, 1990). In a register-based study of 4,398 women with at least one pregnancy (Dietz et al., 2007), 8.7% of the women had been diagnosed with depression during 39 weeks preconception, 6.9% antenatally, and 10.4% up to 39 weeks postnatally. Of the women with preconception depression, 56.4% had antenatal depression, and of the women with postpartum depression, 54.2% had preconception or antenatal depression (Dietz et al., 2007). In another population-based study of 10,000 women screened with EPDS, the prevalence of screen-positives (EPDS ≥10) was 26.5% before pregnancy, 33.4% during pregnancy, and 40.1% postpartum (Wisner et al., 2013). O’Hara and colleagues found no difference in clinically diagnosed depression between childbearing (second and third trimester and three weeks postpartum) and nonchildbearing subjects. Nevertheless, the childbearing women had significantly more depressive symptomatology and poorer social adjustment, compared to non-childbearing subjects, and these symptoms declined nearly to control level by nine weeks after delivery (O’Hara, 1990). Indeed, antenatal depressive symptoms, are much more common than clinically diagnosed depression during pregnancy (Andersson, Sundström-Poromaa, Wulff, Åström, & Bixo, 2006; Cutrona, 1983; Najman, Andersen, Bor, O’Callaghan, & Williams, 2000; O’Hara, 1984; Troutman, 1990).

It has also been debated, whether depression peaks postnatally, or is the prevalence more elevated during pregnancy. In longitudinal studies, the prevalence of depression seems to be higher antenatally than postnatally (e.g. Andersson et al., 2006; Deave, 2008; Najman et al., 2000; Underwood L. D’Souza S., Peterson ER., Morton S., 2016; Ververault et al., 2014, Table 2), but the incidence and prevalence of severe, inpatient treated depression (Andersson et al., 2006) and other mental disorders significantly increases after childbirth (Munk-Olsen et al., 2016).
Recently, maternal antenatal mood has been screened in many study sets (Table 2). To the authors’ knowledge, the Northern Finland 1966 Birth Cohort (NFBC 1966), with 12,058 subjects, was the first general population-based cohort study to describe maternal depressed mood during pregnancy with a long follow-up of the children. In the NFBC 1966, the prevalence of depressed mood was 13.9%.
<table>
<thead>
<tr>
<th>Cohort name (reference)</th>
<th>City, Country, Year of recruitment.</th>
<th>N</th>
<th>Design, follow-up</th>
<th>Tools, cut-point</th>
<th>Prevalence of depression antenatally</th>
<th>postnatally</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFBC 1966 (P Rantakallio, 1969)</td>
<td>Northern Finland, January - December 1966</td>
<td>12,058</td>
<td>An ongoing prospective longitudinal general population-based birth cohort study. Follow-up: 49 years so far.</td>
<td>One item</td>
<td>13.9%</td>
<td>N/A</td>
</tr>
<tr>
<td>MUSP (Najman et al., 2000)</td>
<td>Australia 1981-1984</td>
<td>7,775</td>
<td>A prospective longitudinal cohort study of pregnant women and their children. Follow-up: 21 years.</td>
<td>DSSI ≥ 2</td>
<td>20.5%</td>
<td>15.4%</td>
</tr>
<tr>
<td>ALSPAC (Evans et al., 2001)</td>
<td>UK April 1991 - 31 December 1992</td>
<td>14,521</td>
<td>An ongoing longitudinal, prospective, population-based birth cohort study. Follow-up: 22 years.</td>
<td>EPDS ≥ 13</td>
<td>13.5%</td>
<td>9.1%</td>
</tr>
<tr>
<td>FinESSI (Malm, 2012a)</td>
<td>Finland 1996-2010</td>
<td>845,345</td>
<td>A population-based prospective cohort study based on national registers. Follow-up: 14 years.</td>
<td>SSRI-exposure 30 days before/ during pregnancy, Depression 1 year before/ in pregnancy</td>
<td>1.9%</td>
<td>N/A</td>
</tr>
<tr>
<td>Cohort name</td>
<td>City, Country, Year of recruitment</td>
<td>N</td>
<td>Design, follow-up</td>
<td>Tools, cut-point</td>
<td>Prevalence of depression antenatally</td>
<td>postnatally</td>
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<tr>
<td>MoBa</td>
<td>Norway 1998-2008</td>
<td>92,814</td>
<td>An ongoing prospective longitudinal population-based study. Follow-up: 20 years so far</td>
<td>SCL-5 and SCL-8</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td>Project Viva</td>
<td>Massachusetts, USA 1999 - 2002</td>
<td>2,128</td>
<td>A prospective observational cohort study of women attending their initial prenatal visit at 8 urban and suburban obstetrical offices in eastern Massachusetts. Follow-up: 15 years.</td>
<td>EPDS ≥ 13</td>
<td>9.2% 6 months:</td>
<td></td>
</tr>
<tr>
<td>Generation-R</td>
<td>The Netherlands April 2002 until January 2006</td>
<td>4,865</td>
<td>A population-based, prospective cohort study investigating fetal and early-life determinants of growth, development, and health. Follow-up 13 years.</td>
<td>BSI &gt;0.75</td>
<td>9.6% 8.25%</td>
<td></td>
</tr>
<tr>
<td>Maternal Health Study</td>
<td>Australia April 2003 - December 2005</td>
<td>1,507</td>
<td>A population-based birth cohort of nulliparous mothers recruited at early pregnancy from public maternity hospitals. Follow-up 10 years.</td>
<td>EPDS &gt; 12</td>
<td>9.1% 6.9% 3 months:</td>
<td></td>
</tr>
<tr>
<td>EDEN Mother-Child Cohort Study</td>
<td>France September 2003 - January 2006</td>
<td>1,719</td>
<td>Women recruited from their first visit at the prenatal clinic at two University Hospital districts. Follow-up 8 years.</td>
<td>CES-D ≥ 16</td>
<td>13.2% 12.8%</td>
<td></td>
</tr>
<tr>
<td>Cohort name (reference)</td>
<td>City, Country, Year of recruitment.</td>
<td>N</td>
<td>Design, follow-up</td>
<td>Tools, cut-point</td>
<td>Prevalence of depression</td>
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<tr>
<td>2004 Pelotas Birth Cohort (Santos, Matijasevic, Barros, &amp; Barros, 2014)</td>
<td>Brazil January 2004 – December 2004</td>
<td>4,231</td>
<td>Prospective, general population-based birth cohort. Follow-up 6 years.</td>
<td>Antenatally one question. Postnatally SRQ-20</td>
<td>24.6% 22.5%</td>
<td></td>
</tr>
<tr>
<td>PREDO (Girchenko et al., 2016; Pesonen, 2016; Wolford et al., 2017)</td>
<td>Helsinki, Finland September 2005 - February 2010</td>
<td>4,777</td>
<td>An ongoing cohort study of primiparous women recruited at their first pregnancy ultrasound from 10 hospital maternity clinics. Follow-up 3.5 years so far.</td>
<td>Antenatally CES-D ≥ 16 Postnatally BDI ≥ 14</td>
<td>21.3% 21.1%</td>
<td></td>
</tr>
<tr>
<td>Wirral Child Health and Development Study (Braithwaite et al., 2017)</td>
<td>England February 2007 – October 2008.</td>
<td>1,233</td>
<td>A general population-based prospective epidemiological longitudinal study of prenatal and infancy origins of conduct disorders. Follow-up 7 years.</td>
<td>EPDS (mean) W32: 7.9 5 weeks: 5.7</td>
<td>4% 4.7%</td>
<td></td>
</tr>
<tr>
<td>The STEPS Study (Ahlqvist-Björkroth et al., 2016; Lagstrom et al., 2013)</td>
<td>Tukku, Finland September 2007 - April 2010</td>
<td>1,797 mothers 1,093 partners 1,827 children</td>
<td>General population-based birth cohort from the Hospital District of Southwest Finland. Families recruited during their first visit to the maternity healthcare clinics during pregnancy (W10–15). Follow-up 3 years.</td>
<td>EPDS, antenatally (W20) ≥ 15, postnatally ≥ 13</td>
<td>6.4% 4.7%</td>
<td></td>
</tr>
<tr>
<td>All Our Families (Kingston et al., 2014; Tough et al., 2017)</td>
<td>Canada May 2008 - May 2011</td>
<td>1,934</td>
<td>An ongoing population-based pregnancy cohort of mother-child dyads in Alberta, Canada. Follow-up 3 years so far.</td>
<td>EPDS &gt; 12 &lt; W25: W34-38:</td>
<td>6.3% 6.1%</td>
<td></td>
</tr>
<tr>
<td>Cohort name (reference)</td>
<td>City, Country, Year of recruitment.</td>
<td>N</td>
<td>Design, follow-up</td>
<td>Tools, cut-point</td>
<td>Prevalence of depression antenatally</td>
<td>postnatally</td>
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<tr>
<td>ABC: Akershus Birth Cohort (Junge, 2017)</td>
<td>Norway November 2008–April 2011</td>
<td>1,235</td>
<td>A prospective longitudinal cohort of pregnant women scheduled to give birth at Akershus University Hospital, Norway. Follow-up 3 years.</td>
<td>EPDS ≥ 10</td>
<td>W32: 12.1%</td>
<td>12.5%</td>
</tr>
<tr>
<td>An Iranian cohort of pregnant women (Abdollahi, Abhari, &amp; Zarghami, 2017; Abdollahi, Zarghami, Azhar, Sazlina, &amp; Lye, 2014)</td>
<td>Iran January – June 2009</td>
<td>2,279</td>
<td>Pregnant women attending to prenatal care at urban and rural primary health centers of Mazandaran University of Medical Sciences. Follow-up 4 years.</td>
<td>EPDS &gt;12</td>
<td>21%</td>
<td>14% (of those not depressed at T3)</td>
</tr>
<tr>
<td>Growing up in New Zealand (Underwood, Waldie, D’Souza, et al., 2017)</td>
<td>New-Zealand April 2009 - March 2010</td>
<td>6,167</td>
<td>An ongoing prospective longitudinal cohort study of pregnant women residing in the North Island, and their children. Follow-up 2 years so far.</td>
<td>EPDS &gt; 12</td>
<td>11.5%</td>
<td>8%</td>
</tr>
<tr>
<td>FinnBrain (Karlsson et al., 2018; Eeva-Leena Kataja, Karlsson, Kemppainen, &amp; Karlsson, 2017)</td>
<td>Turku, Finland 2010-2012</td>
<td>1,522</td>
<td>An ongoing birth-cohort study of families from Turku-area recruited from maternity clinics at their first ultrasound visit related to pregnancy. Follow-up 3 years so far.</td>
<td>EPDS &gt; 11</td>
<td>8%</td>
<td>not yet reported</td>
</tr>
<tr>
<td>CHILD-SLEEP (Paavonen et al., 2017; Pietikäinen et al., 2018)</td>
<td>Tampere, Finland April 2011 - December 2012</td>
<td>1,673</td>
<td>Longitudinal birth cohort. Follow-up 5 years.</td>
<td>CES-D ≥ 10</td>
<td>11.2%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Cohort name (reference)</td>
<td>City, Country, Year of recruitment.</td>
<td>N</td>
<td>Design, follow-up</td>
<td>Tools, cut-point</td>
<td>Prevalence of depression antenatally postnatally</td>
<td></td>
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<tr>
<td>KuBiCo (Ruohomäki et al., 2018)</td>
<td>Kuopio, Finland 2012-</td>
<td>1,917</td>
<td>Prospective, longitudinal birth cohort, with a target of collecting data from 10,000 mother–child pairs.</td>
<td>EPDS &gt; 10</td>
<td>10.3% 9.1%</td>
<td></td>
</tr>
</tbody>
</table>

ALSPAC = Avon Longitudinal Study of Parents and Children; BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; CIS = Clinical Interview Schedule; DSSI = Delusions-Symptoms-States Inventory; EPDS = Edinburgh postnatal depression scale; FinESSI = Finnish Register-Based Study; KuBiCo = Kuopio Birth Cohort; NFBC 1966 = The Northern Finland 1966 Birth Cohort; MoBa = The Norwegian Mother and Child Cohort Study; MUSP = A birth cohort for the Mater Misericordiae Mothers’ Hospital-University of Queensland Study of Pregnancy; PREDO = The Prediction and Prevention of Preeclampsia Study; SCL = Hopkins Symptom Checklist; SRQ = Self Report Questionnaire, The STEPS study = Steps to the Healthy Development and Well-being of Children; T = gestation trimester; W = gestational week.
2.3 Offspring of antenatally depressed mothers

Maternal antenatal depressed mood is a complex and multifactorial stage, which can affect both the mother’s, father’s and their children’s behavior and mental health, both genetically, and environmentally (Capron et al., 2015; Meltzer-Brody & Stuebe, 2014; Stein et al., 2014). The effects of mothers’ prenatal pharmacological treatment are beyond the scope of this literature review.

Antenatally depressed mothers have been found to attend less actively to prenatal care, gain less or more weight, use more often unhealthy substances, feel more stressed, and show more cognitive deficits, than mothers without depression during pregnancy (E-L Kataja et al., 2017; Ruohomäki et al., 2018; Sohr-Preston & Scaramella, 2006). Pregnancy complications (Bitew, Hanlon, Kebede, Honikman, & Fekadu, 2017; Räisänen et al., 2014), such as preeclampsia (Kurki, Hiilesmaa, Raitasalo, Mattila, & Ylikorkala, 2000; Qiu, Williams, Calderon-Margalit, Cripe, & Sorensen, 2009), gestational diabetes (Räisänen et al., 2014; Ruohomäki et al., 2018), hyperemesis gravidarum, prolonged sick leave, planned caesarean section (S Gentile, 2017), and intrauterine growth restriction (Davalos, Yadon, & Tregellas, 2012; S Gentile, 2017) are found to be more common in depressed than in nondepressed women in some studies, although these associations were not confirmed in two meta-analyses (Stein et al., 2014). The risk of preterm birth is 1.5 fold in depressed women, compared to nondepressed women (Jarde et al., 2016; Stein et al., 2014). In a large Finnish National Register-based study, an elevated risk of Cesarean section, emergency or urgent Cesarean section and for bleeding during or after delivery (Malm et al., 2015) was found among antenatally depressed mothers, which have been also documented in other studies (S Gentile, 2017). The risk for postpartum depression is elevated among antenatally depressed mothers, and the course of postnatal depression is more severe in this group of mothers (Kettunen, 2019; Underwood, Waldie, D’Souza, et al., 2017).

Fetuses of untreated depressed mothers have higher resting-state heart rate, weaker reactions to external stimuli and slower recovery, compared to the fetuses of nondepressed mothers (Davalos et al., 2012; S Gentile, 2017). Fetal activity is increased among antenatally depressed mothers (S Gentile, 2017).
2.3.1 Neonatal outcomes

Depressed mothers may have an elevated risk of complications in labor and at the postpartum period (Bitew et al., 2017). The newborns of unmedicated antenatally depressed mothers are shown to have low birth weight (LWB) (OR 1.96; 95% CI 1.24-1.94) (Jarde et al., 2016), prematurity, higher cortisol levels, and lower dopamine and serotonin levels (Field, 2011c; S Gentile, 2017), compared to newborns of nondepressed mothers. On the other hand, one study found a greater ACTH, but not cortisol concentration in umbilical cord blood sample in the newborns of depressed mothers, than of nondepressed mothers (Marcus et al., 2011). On the Brazelton Scale, infants of antenatally depressed mothers had less optimal habituation, orientation, motor, range of state, autonomic stability, and higher depressed symptoms scores, than controls (Davalos et al., 2012; S Gentile, 2017). Compared to controls, a greater relative right frontal EEG and lower vagal tone in depressed mothers and their newborns have been documented (Davalos et al., 2012; S Gentile, 2017), but in another study, no differences in vagal tones were found between the infants of depressed and nondepressed mothers at 29 weeks postnatally (Sharp et al., 2012). Neonates born to antenatally depressed mothers are found to be less awake and alert and spend more time fussing and crying than infants born to nondepressed mothers (Armitage et al., 2009; Davalos et al., 2012).

Amygdala is considered a brain regimen associated with vulnerability for depression (Manji et al., 2001; van Eijndhoven et al., 2009). In a sub-study (N = 189) of the Growing Up in Singapore Towards Healthy Outcomes (GUSTO)-cohort (N = 1,152), different amygdala microstructure was found in the neonates of mothers with a high EPDS score, compared to neonates of mothers with a low-to-normal (<13) EPDS score (Rifkin-Graboi et al., 2013). Further, a study of about 6-week-old infants (N = 64) (Posner et al., 2016) revealed an association between maternal antenatal depressed mood and altered amygdala-prefrontal cortex connectivity, which may be associated with an increase in fetal heart rate reactivity to in utero perturbation. Finally, at 6 months, a greater functional connectivity of the amygdala with the left temporal cortex, insula, the bilateral anterior cingulate, medial orbitofrontal and ventromedial prefrontal cortices was found in the infants of antenatally depressed mothers (N = 42) in the GUSTO-cohort (Wen et al., 2017). Those findings resemble similar connectivity observed in adolescents and adults with major depressive disorder (Zeng et al., 2012). In a recent study (Dean et al., 2018), the lower right frontal white matter microstructure in infants at 1 month of
age was associated with higher prenatal maternal symptoms of depression and anxiety.

### 2.3.2 Neurologic and psychiatric offspring outcomes

#### Childhood outcomes

Some of the early alterations in the central nervous system (CNS) in the infants of antenatally depressed mothers may still be detectable later in childhood. Similar alterations in the right frontal EEG asymmetry, and in vagal tone, as in the neonates of depressed mothers, have also been found in infants at ages 3 to 6 months (S Gentile, 2017), but maternal antenatal depression was not associated with infant autonomic function at age 14 months (Dierckx Bram, 2009). The brain structure and function has been increasingly studied in the offspring of antenatally depressed mothers. Child brain cortical thinness in right inferior frontal and middle temporal regions at 2-5-years of age (Lebel et al., 2016) and at 6-9 years of age, a thinner superior frontal cortex in the left hemisphere and a larger caudal middle frontal area in the left hemisphere (El Marroun et al., 2016), increased amygdala responses to negative emotional faces (van der Knaap et al., 2018), and cortical thinning in the whole cortex and in the frontal lobe have been documented in the children of antenatally depressed mothers (Sandman, Buss, Head, & Davis, 2015).

Maternal antenatal depression has been found to affect infant sleep from birth until 3.5 years of age (Netsi et al., 2015; Nevarez et al., 2010; T. G. O’Connor et al., 2007; Petzoldt, Wittchen, Einsle, & Martini, 2016; Toffol et al., 2018; Wolford et al., 2017). Of the behavioral outcomes in the offspring, maternal antenatal depressed mood has been associated with child internalizing symptoms at ages 1, 2, 3 and 5 years, but not at 8 years of age (Lahti et al., 2017; Soe et al., 2016; Stein et al., 2014); externalizing symptoms at ages 1, 2, 8 and 9 years (Barker, Jaffee, Uher, & Maughan, 2011; Luoma, 2001; Soe et al., 2016; Stein et al., 2014), negative affectivity between 3 and 36 months and at 5 years (Green et al., 2017; Lahtti et al., 2017; Stein et al., 2014; Zhang et al., 2018); behavioral problems at 2, 4 and 9 years (Luoma et al., 2004; Raskin, Easterbrooks, Lamoreau, Kotake, & Goldberg, 2016; Woolhouse, Gartland, Mensah, Giallo, & Brown, 2016); social problems at ages 2, 4, 10 and 10-11 years, (Junge, 2017; Koutra et al., 2017; Leis, Heron, Stuart, & Mendelson, 2014; Stein et al., 2014), and dysregulation and age 4 and 7 years (Pina-Camacho, Jensen, Gaysina, & Barker, 2015). No associations between maternal
antenatal depressed mood and child physical aggression or crying behavior at age 3 years (Bekkhus, Rutter, Barker, & Borge, 2011), or negative affectivity at age 4 years (T. G. O’Connor, Heron, Glover, & Team, 2002) were found. According to a recent meta-analysis (a total of 33,211 mother–child dyads), maternal antenatal depression was associated with offspring’s socioemotional development up to age 18, with an effect size of OR = 1.76 (CI = 1.60–1.94) (Madigan et al., 2018).

In a recent Finnish study, the 8-month-old infants of antenatally depressed mothers showed elevated fear bias, indicating that these children may be more prone to disengage from happy/neutral faces, than of fearful faces, compared to children of nondepressed mothers (Eeva-Leena Kataja et al., 2018). Other findings of temperament in the offspring of antenatally depressed mothers include anxiety and problems in regulation of states neonatally (Gerardin et al., 2011), elevated distress to limitations 29 weeks postnatally (Sharp et al., 2012), anxiety at one year (Gerardin et al., 2011), reactivity at 1.5 years (Netsi et al., 2015), difficult temperament at 2 years (Stroustrup et al., 2016), and dysregulation at 3-7 years (Babineau et al., 2015; Pina-Camacho et al., 2015).

Maternal antenatal depressed mood may be associated with increased risk of psychiatric disorders in the offspring. A persistent antenatal depression was found to be associated with child elevated ADHD symptoms at 3-6 years of age (OR 2.80, 95% CI 2.20-3.57, p < 0.001) in the Finnish study Prediction and Prevention of Preeclampsia (PREDO) (Wolfford et al., 2017). In the Generation-R study, childhood pervasive developmental and affective problems were found more frequently in the children of unmedicated antenatally depressed mothers, whereas medicated antenatally depressed mothers had children with autistic traits more frequently than of unmedicated (El Marroun et al., 2014). The potential association with maternal antenatal depression and child autism spectrum disorders was also found in a recent Japanese register study (Yamamoto-Sasaki et al., 2019). The Avon Longitudinal Study of Parents and Children (ALSPAC)-studies have found lower cognitive function (Barker, 2013), increased risk of hyperactivity, emotional symptoms, conduct problems, peer problems, and total difficulties (Leis et al., 2014), and for symptoms of borderline personality disorder (Winsper, Wolke, & Lereya, 2015) in the offspring of antenatally depressed mothers. Two large cohort studies, the ALSPAC (Lereya & Wolke, 2013) and the 2004 Pelotas cohort (Azeredo, Santos, Barros, Barros, & Matijasevich, 2017) have found an elevated risk of being bullied and victimized by peers among those subjects whose mothers have been antenatally depressed. The 2004 Pelotas Cohort also found an increased
risk of disruptive mood regulation syndrome in the children of antenatally depressed mothers at age 11 (Munhoz et al., 2017).

Maternal antenatal depressed mood may have differential effects on male and female offspring. Male newborns of antenatally depressed mothers may have more problems with motor skills and regulation of states, and more anxiety at one year of age, than females (Gerardin et al., 2011). De Bruijn and colleagues found, that maternal antenatal emotional complaints in pregnancy may be associated with internalizing problems in boys, and both internalizing and externalizing problems in girls between 14 and 54 months of age (de Bruijn, van Bakel, & van Baar, 2009). Differential effects of maternal antenatal mood was also found in a magnetic resonance imaging (MRI) study, where larger right amygdala volume was found in girls but not in boys with maternal prenatal depressive symptoms (Wen et al., 2017).

These findings, considering the previous literature on the psychiatric outcomes in the children of antenatally depressed mothers from general population studies with more than 100 subjects, are presented in Figures 1-2.
Fig. 1. Childhood (0-3y) psychiatric outcomes in non-clinical follow-up studies (N > 100) in the offspring of antenatally depressed mothers, compared to offspring without maternal depressed mood during pregnancy. W = weeks of age; m = months of age; y = years of age.
Fig. 2. Childhood (4-10y) psychiatric outcomes in non-clinical follow-up studies (N > 100) in the offspring of antenatally depressed mothers, compared to offspring without maternal depressed mood during pregnancy. Y = years of age; ADHD = attention deficit / hyperactivity disorder; IQ = Intelligence Quotient; SDQ = Strengths and Difficulties Questionnaire; CBCL = Child Behavior Checklist.
**Adolescent outcomes**

Long follow-up studies of the offspring of antenatally depressed mothers until adolescence and adulthood are still rare, but the results of the studies are quite consistent (Figure 3). In the ALSPAC, there were associations between maternal antenatal depression and internalizing and externalizing symptoms (Dominic T Plant, Jones, Pariante, & Pawlby, 2017), difficulties in attention, emotion, and conduct behavior (O’Donnell, Glover, Barker, & O’Connor, 2014), and with ticks and Tourette’s syndrome (Ben-Shlomo, Scharf, Miller, & Mathews, 2016) in children up to 13 years of age. The Australian birth cohort for the Mater Misericordiae Mothers’ Hospital-University of Queensland Study of Pregnancy (MUSP) reported an increased risk of internalizing problems in 14-year-old youths of mothers with high levels of depressive, anxious, and stress symptoms during pregnancy (Betts, Williams, Najman, & Alati, 2014). In a community-based longitudinal South London Child Development Study (SLDCS) of 151 mother-child dyads, maternal antenatal depression was associated with youth intelligence quotient (IQ), depression and antisocial outcomes. In a Finnish prospective longitudinal study of 192 mother-child-pairs, low social competence and externalizing problems were reported in the adolescent offspring of antenatally depressed mothers (Korhonen, Luoma, Salmelin, & Tamminen, 2012). In the large Finnish register-based studies, maternal antenatal unmedicated depression was associated with increased risk of speech and language disorders (Brown et al., 2016), autism spectrum disorders, and ADHD (Malm et al., 2016) in the 14-year-old offspring, and SSRI-treated antenatal depression was associated with increased risk of depression in adolescent offspring (Malm et al., 2016).

**Young adulthood outcomes**

The emotional problems in the offspring of antenatally depressed mothers seem to persist until adulthood. The 18-year-old children (Rebecca M Pearson et al., 2013), especially daughters (Quarini et al., 2016) of antenatally depressed mothers had an increased risk of depression in the ALSPAC study, and up to 25 years of age in the SLDCS, where an association between maternal antenatal depression and offspring inflammation was also documented, but this finding was not the mediating factor between maternal antenatal depression and offspring depression (DT Plant, Pawlby, Sharp, Zunszain, & Pariante, 2016; Dominic T Plant et al., 2015) (Table 3).
Maternal antenatal depression was also associated with offspring depression and behavior problems up to 25 years of age in the MUSP-study (Betts et al., 2014; Raposa, Hammen, Brennan, & Najman, 2014), where poor childhood physical health was found to have a mediating effect (Figure 2 and Table 3).
Fig. 3. Adolescent and young adulthood outcomes in non-clinical follow-up studies (N > 100) in the offspring of antenatally depressed mothers, compared to offspring without maternal depressed mood during pregnancy. Y = years of age; ADHD = Attention deficit/hyperactivity disorder; IQ = Intelligence Quotient.
Adulthood outcomes

Studies where the offspring of antenatally depressed mothers have been followed for over 30 years have been published only based on the NFBC 1966 (Table 3). In a study on the association of schizophrenia in the offspring and undesirability of a pregnancy (Myhrman, Rantakallio, Isohanni, Jones, & Partanen, 1996), mothers’ frame of mind during pregnancy was also detected. Of the unwanted pregnancies, 49.6% of the mothers had a depressed mood during pregnancy in comparison with the wanted or mistimed but wanted pregnancies, 9.2% of the mothers felt their mood as depressed during pregnancy. An association with unwanted pregnancy and elevated risk of schizophrenia in the offspring was detected (OR 2.5; 95% CI 1.5-4.2).

The association of schizophrenia in the offspring and mothers’ mood during pregnancy was further studied by Jones et al. (Jones, Rantakallio, Hartikainen, Isohanni, & Sipila, 1998), who found that mothers of schizophrenic probands were more likely to report their mood as depressed during pregnancy (OR 1.8, 95% CI 1.1-3.1). The association of schizophrenia in the offspring and mothers’ mood during pregnancy was further studied by Jones and colleagues (P.B. Jones et al., 1998), who found that mothers of schizophrenic probands were more likely to report their mood as depressed during pregnancy (OR 1.8, 95% CI 1.1-3.1).

Mäki et al. studied schizophrenia in the 31-year-old offspring (Mäki, Veijola, Rantakallio, & Jokelainen, 2004) and criminality in the 33-year-old offspring (Mäki, Veijola, et al., 2003) of antenatally depressed mothers in her dissertation (Mäki, 2003). The main finding was that the relationship of maternal antenatal depression and schizophrenia in the offspring could be explained by correlation between maternal antenatal depressed mood and familial risk for psychosis (RR 2.24, 95% CI 1.12-4.51), and no evidence was found for an independent association between maternal antenatal depression and elevated risk for schizophrenia in the offspring (Mäki et al., 2004). An association between maternal antenatal depression and non-violent offenders (OR 1.4; 95% CI 1.1-2.4), violent offenders (OR 1.6; 95% CI 1.1-2.4), and violent recidivists (OR 1.7; 95% CI 1.0-3.9) in the male, but not in female, offspring was found (Mäki, Veijola, et al., 2003) (Table 3).

Herva and colleagues studied the influence of birthweight on the risk of depression measured by the Hopkins Symptom Checklist -25 (SCL) (Herva et al., 2008) in the NFBC 1966. They considered maternal antenatal depression a potential confounding factor and found the depression risk to be increased in the
offspring of depressed mothers, when compared to the offspring of non-depressed mothers (prevalence 17.3% vs. 13.9%, p = 0.003).

In a study of interactions between parental psychosis and early risk factors for schizophrenia, among many other findings, an interaction between maternal antenatal depression and parental psychosis was found to increase the risk of schizophrenia (HR 2.7; 95% CI 1.0-7.0) in the offspring in a 43-year follow-up (Keskinen et al., 2013). The elevated prevalence of maternal antenatal depressed mood in cohort members diagnosed for psychosis, compared to cohort members without psychosis (18.4% vs. 13.8 %, p. 0.012) was replicated in a recent 45-year follow-up study (Rautio et al., 2017), where maternal antenatal depression was also associated with slightly elevated mortality in non-psychotic offspring (OR 1.33, 95% CI 1.0-1.8; Table 3, Fig 4).

In other reports from the NFBC 1966, maternal depressed mood during pregnancy was not associated with suicidality (Alaräisänen et al., 2012), educational attainment (Juho Härkönen, Hande Kaymakçalan, Pirjo Mäki, & Anja Taanila, 2012), or with pain related symptoms in temporomandibular pain disorder (Pelkonen et al., 2013) in offspring (Table 3, Fig. 4).
Table 3. Prospective longitudinal studies on the offspring of antenatally depressed mothers until adulthood (18 years onwards).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>N</th>
<th>Cohort</th>
<th>Offspring outcome / measure</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Mäki, Veijola, et al., 2003)</td>
<td>Finland</td>
<td>10,705</td>
<td>NFBC 1966</td>
<td>Criminality / Criminal record</td>
<td>22 years</td>
</tr>
<tr>
<td>(Härkönen et al., 2012)</td>
<td>Finland</td>
<td>4,095</td>
<td>NFBC 1966</td>
<td>Educational attainment</td>
<td>31 years</td>
</tr>
<tr>
<td>(Pelkonen et al., 2013)</td>
<td>Finland</td>
<td>5,541</td>
<td>NFBC 1966</td>
<td>Temporomandibular Disorder symptoms.</td>
<td>31 years</td>
</tr>
<tr>
<td>(Alaräisänen et al., 2012)</td>
<td>Finland</td>
<td>10,742</td>
<td>NFBC 1966</td>
<td>Suicidality / FHDR</td>
<td>39 years</td>
</tr>
<tr>
<td>(Keskinen et al., 2013)</td>
<td>Finland</td>
<td>10,526</td>
<td>NFBC 1966</td>
<td>Psychoses / FHDR</td>
<td>44 years</td>
</tr>
<tr>
<td>(Rautio et al., 2017)</td>
<td>Finland</td>
<td>10,933</td>
<td>NFBC 1966</td>
<td>Mortality / Cause of Death Register, CRCH</td>
<td>45 years</td>
</tr>
<tr>
<td>(Capron et al., 2015; Rebecca M Pearson et al., 2013; Quarini et al., 2016)</td>
<td>UK</td>
<td>8,937</td>
<td>ALSPAC</td>
<td>Depression / CIS-R</td>
<td>18 years</td>
</tr>
<tr>
<td>(Betts et al., 2014)</td>
<td>Australia</td>
<td>3,099</td>
<td>MUSP</td>
<td>Behavioral and emotional problems / YASR, CES-D</td>
<td>21 years</td>
</tr>
<tr>
<td>(Raposa et al., 2014)</td>
<td>Australia</td>
<td>815</td>
<td>MUSP</td>
<td>Depression / BDI.</td>
<td>25 years</td>
</tr>
<tr>
<td>(D T Plant et al., 2016; Dominic T Plant et al., 2015)</td>
<td>UK</td>
<td>103</td>
<td>SLDCS</td>
<td>Depression / SCID-I</td>
<td>25 years</td>
</tr>
</tbody>
</table>

ALSPAC = Avon Longitudinal Study of Parents and Children; BDI = Beck Depression Inventory; CIS-R = The Clinical Interview Schedule Revised; CRHC = Care Register for Healthcare (former FHDR); FHDR = Finnish Hospital Discharge Register; MUSP = A birth cohort for the Mater Misericordiae Mothers’ Hospital-University of Queensland Study of Pregnancy; NFBC 1966 = Northern Finland 1966 Birth Cohort; SCID-I = Structured Clinical Interview for DSM-III-R-1; SLDCS = South London Child Development Study; YASR = Achenbach Young Adult Self-Report
2.3.3 Somatic outcomes

Although the offspring of antenatally depressed mothers have been mainly studied for neurologic, and psychiatric outcomes, some somatic studies have also been conducted (Figure 4). During their first year of life, increased airway track wheezing (T. S. Cheng et al., 2015), poor growth and diarrhoea (Rahman, Iqbal, Bunn, Lovel, & Harrington, 2004), and gastrointestinal complaints (Krause, Einsle, Petzoldt, Wittchen, & Martini, 2017) have been found in the offspring of antenatally depressed mothers. No association between maternal antenatal depressed mood and offspring motor development was found at 3 years of age (Handal et al., 2016), but the language competence was found to be weaker in the children of antenatally depressed mothers, as compared to children without maternal antenatal depressed mood (Skurtveit, 2014). In the MUSP-study, the children of antenatally depressed mothers had worse physical health, than control subjects (Raposa et al., 2014).

In studies considering atopy later in childhood, no associations between maternal antenatal depressed mood, and allergy and atopy at 3 years (Ramratnam et al., 2017), and 5 years of age (Zhou, 2017) was found, but at 10 years of age, the risk for allergy was increased in the offspring of antenatally depressed mothers.
(Elbert et al., 2017). The offspring of antenatally depressed mothers have been found to have more unhealthy diet at 8 years of age (Barker, Kirkham, Ng, & Jensen, 2013), but no association between BMI at 7 years of age and maternal antenatal depressed mood was found (Ertel et al., 2010).

The author is not aware of studies on somatic outcomes in the adolescent offspring of antenatally depressed mothers, but at 31 years of age, temporomandibular disorder (TMD) was studied in the NFBC 1966, and no association between TMD and maternal antenatal depressed mood was found (Pelkonen et al., 2013, Figure 4).
Fig. 5. Childhood somatic and developmental outcomes in non-clinical follow-up studies (N > 100) in the offspring of antenatally depressed mothers, compared to offspring without maternal depressed mood during pregnancy. W = weeks of age; m = months of age; y = years of age; ACTH = Adrenocorticotropic hormone; EEG = Electroencephalogram; BMI = Body mass index.
2.3.4 The offspring of antenatally depressed mothers with parental severe mental disorder

There are several studies exploring the association between parental severe mental illness and offspring mental health (see chapter 2.1). No previous studies considering the impact of maternal antenatal depression in association with parental severe mental disorders on offspring’s mental health have come to the authors’ knowledge.

2.4 The potential mediating factors between maternal antenatal depression and mental disorders in the offspring

The effects of maternal antenatal depression on offspring outcomes are a result of interactions between the genes, the intrauterine environment, the postpartum environment, and nurture. For examples, in the offspring of antenatally depressed mothers, the vulnerability to negative affectivity, and internalizing and externalizing symptoms may be mediated through certain genotypes (Green et al., 2017; Hannigan et al., 2018). The association between antenatal maternal depression and child externalizing behavior is also found to be mediated by brain structural changes (Sandman et al., 2015). Poor postnatal nutrition was found to be the mediating factor between maternal antenatal depression and offspring dysregulation (Pina-Camacho et al., 2015).

Mothers suffering from antenatal depression are at increased risk of postpartum depression (Underwood L. D’Souza S., Peterson ER., Morton S., 2016) and depression later in life (Cents et al., 2013; Meltzer-Brody & Stuebe, 2014). Maternal antenatal depression is also associated with marital distress and paternal depression (Ahlqvist - Björkroth et al., 2016; Meltzer-Brody & Stuebe, 2014; Paulson & Bazemore, 2010). All of these factors related to maternal depression, and many others, such as mothers’ medication, somatic health, mothers’ education, employment and economy, as well as her social environment, can also affect the mental health in the children. The accumulation of multiple risk factors usually results in poorer outcomes in the offspring (Apter et al., 2017). The protective factors, such as maternal education and social support can attenuate the negative effects of antenatal depression to the offspring (Stein et al., 2014).
2.4.1 Psychosocial factors

Mother-child attachment during pregnancy

Maternal antenatal depression may interrupt the early mother-baby attachment (Meuti, 2015; Rubertsson, Pallant, Sydşjö, Haines, & Hildingsson, 2015) and affect the maternal representations of the unborn baby (Ahlqvist-Björkroth et al., 2016; Lee & Hans, 2015; Rusanen, Lahikainen, Pölkki, Saarenpää-Heikkilä, & Paavonen, 2018), which may subsequently impair the interaction between the mother and the child (Lee & Hans, 2015; C. Martins & Gaffan, 2000; Perry, Ettinger, Mendelson, & Le, 2011). Depressive symptoms in early pregnancy also complicate the interpretation of infant emotions and signals modifying the relationship between the mother and the child. This may lead to insecure attachment (Apter et al., 2017; Hayes, Goodman, & Carlson, 2013) that may predispose the child to subsequent psychiatric disorders (Sroufe, 2005; Zeanah, Keyes, & Settles, 2003). Nevertheless, no association between prenatal maternal depression and infant insecure or disorganized attachment at 14 months was found in the Generation-R study (Tharner et al., 2012).

Breastfeeding

There are findings of prolonged initiation and shorter duration of breastfeeding among prenatally depressed women (Ahlqvist - Björkroth et al., 2016; Dias & Figueiredo, 2015; Grigoriadis et al., 2013; Meltzer-Brody & Stuebe, 2014). The association between shorter lactation duration and maternal depression may be mediated via maternal postnatal depression (Ahlqvist - Björkroth et al., 2016), or the lactation problems may cause depressive symptoms (Meltzer-Brody & Stuebe, 2014). Breastfeeding has been associated with positive outcome in the children, but not only the physiological effects, but rather psychosocial and socio-economic factors may explain these associations (Colen & Ramey, 2014).

Parenting

Depressed mood during pregnancy may affect maternal sensitivity to the child and parenting. There are findings, that antenatally depressed mothers may be avoidant for infant distress (R M Pearson, Cooper, Penton-Voak, Lightman, & Evans, 2010). Maternal sensitivity to the child seems to partially mediate the effects of antenatal
depression to child behavioral problems, especially in boys (Edwards, 2016). In the ALSPAC, antenatal depression has been associated with suboptimal parenting and parent conflict (Winsper et al., 2015), but marital conflict during pregnancy was not found to be a significant mediating factor between antenatal depression and child emotional and conduct difficulties at 42 months (Hanington, Heron, Stein, & Ramchandani, 2012).

**Maltreatment of the child**

In the SLDCS, antenatal depression was found to increase the risk of subsequent maltreatment of the child about four-fold (Pawlby, Hay, Sharp, Waters, & Pariante, 2011), and these mothers were likely to have experienced childhood maltreatment themselves (D T Plant, Barker, Waters, Pawlby, & Pariante, 2013). Offspring experience of child maltreatment was found to mediate the association between exposure to maternal depression in pregnancy and psychopathology in childhood and adolescence (Goodman, 2012; Pawlby et al., 2011), and depression of the offspring in early adulthood (Plant et al., 2015). In the Generation R study, parental hostility was found to potentially mediate the association between parental prenatal symptoms of depression and increased risk of child internalizing and externalizing problems (Velders et al., 2011).

**Spousal mental health**

Paternal antenatal depressed mood is found to be associated with maternal antenatal depressed mood (Nath et al., 2016; Paulson & Bazemore, 2010; Underwood, Waldie, Peterson, et al., 2017), and on the other hand, the trajectories of low, but not high, depressive symptoms during pregnancy associated between mothers and fathers in the FinnBrain-study (Korja et al., 2018). Paternal antenatal depression is less studied than maternal antenatal depression, but according to previous findings, it also seems to have effects on many offspring outcomes (Salvatore Gentile & Fusco, 2017). The association between parental severe mental disorders and offspring mental health problems are reviewed in chapter 2.1.

**Mothers’ postnatal and later depression**

Maternal antenatal depression increases the risk of postnatal depression (Underwood L. D'Souza S., Peterson ER., Morton S., 2016), which is connected to
adverse cognitive and emotional infant outcomes (Granat, Gadassi, Gilboa-Schechtman, & Feldman, 2017; Murray & Cooper, 1997). There are mixed findings, whether the effects of maternal antenatal depression are mediated through postnatal depression: taking postnatal and later depression into account as a potential confounding factor has not significantly attenuated the associations between antenatal depression and offspring long-term outcomes in many studies (e.g. Betts et al., 2015; Pearson et al., 2013; Quarini et al., 2016), but many have also found postnatal or later depression to mediate this association (Leech, Larkby, Day, & Day, 2006; Maselko et al., 2015; Park et al., 2018; Wolford et al., 2017). In some studies, not only antenatal or postnatal, but rather more persistent maternal depressive symptoms are found to be associated with offspring adversity (Maselko et al., 2016; Park et al., 2018; Pawlby, Hay, Sharp, Waters, & O’Keane, 2009; van der Waerden et al., 2017), and to be associated with more severe outcomes in the offspring (Lahti et al., 2017).

2.4.2 Genetic factors

The genetic factors play an important role as a risk factor for depression. The heritability of depression has been estimated to be 37% (Sullivan, Neale, & Kendler, 2000), and the heritability of antenatal depression is in the same range (Viktorin, 2016). Serotonin transporter genes are shown to be associated with genetic risk of depression (Talati et al., 2015), and to interact in the association between antenatal depression and child negative emotionality (Green et al., 2017), and early adversity and children’s neurodevelopmental outcomes (Silveira et al., 2017). Shared genetic factors are also found to explain about 40% of the variance of externalizing and internalizing problems in the 5-year-old offspring of antenatally depressed mothers (Hannigan et al., 2018).

Antenatal depression also seems to induce epigenetic alterations in the developing fetus, which can have lifelong effects (Nemoda & Szyf, 2017). Child internalizing problems have been associated with epigenetic alterations induced by maternal antenatal depression (Suarez et al., 2018).

2.4.3 Biological factors – foetal programming

Fetal programming refers to a phenomenon that a certain change to the in utero environment occurs during a sensitive period in fetal development, which can change fetal development increasing the risk of disease later in life (Barker, 2013;
Kim, Bale, & Epperson, 2015). This change can be an adaptive endocrinological or inflammatory response to an environmental stimulus (Vivette Glover & Hill, 2012).

**Maternal stress and hypothalamic-pituitary-adrenal axis dysfunction**

As described in the chapter 2.1.1, depression is associated with overactivity of the hypothalamic-pituitary-adrenal (HPA) axis and consequent secretion of glucocorticoids that resembles the neuroendocrine response to stress (Pariante, 2003). Over-secretion of glucocorticoids during pregnancy has been shown to elevate the glucocorticoid levels in the foetus (Gitau, Cameron, Fisk, & Glover, 1998; Pariante, 2003), but the fetal levels are usually much lower from maternal cortisol levels (Gitau et al., 1998) because of the 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) -enzyme barrier, which converts active glucocorticoids (cortisol and corticosterone) to less potent cortisone and 11-dehydrocorticosterone (K. Chapman, Holmes, & Seckl, 2013). The 11β-HSD-2 is regulated by proinflammatory cytokines, and maternal nutrition and stress (K. Chapman et al., 2013), and maternal antenatal anxiety and depression are also shown to be associated with down-regulation of this enzyme, resulting in elevated fetal corticosteroid levels (O’Donnell et al., 2012).

The increased fetal corticosteroid concentration may alter the function of the HPA axis in the fetus and disturbs brain development (Maccari et al., 2003; Wyrwoll & Holmes, 2012). In animal studies, long-term exposure to corticosterone has been found to induce anxiety, depression, fear, neurochemical changes, and brain morphological changes in adult animals (Leight et al., 2010; Wyrwoll & Holmes, 2012). Further, a stress-induced maternal increase of glucocorticoids is associated with a dysfunction of the fetal HPA-axis and adverse effects on fetal brain development, especially in males (Leight et al., 2010; Maccari et al., 2003; Wyrwoll & Holmes, 2012). Short-term prenatal exposure to glucocorticoids seems to result in elevated glucocorticoid-levels and induced stress-responsivity, whereas repeated or chronic exposure may result in hypocortisolism and blunted stress-associated cortisol responses (Wyrwoll & Holmes, 2012). A deletion of the parental 11β-HSD2 has been shown to be associated with reduced fetal cerebellum size, increased anxiety, fearfulness, and depression-like behavior in adulthood but with no changes in HPA-axis activity. The HPA-axis and early life stress also has effects on dopaminergic and serotonergic systems, and catecholamines, potentially resulting in mental changes (Wyrwoll & Holmes, 2012). The male and female fetuses may respond differently to the elevated cortisol levels: the prenatally
stressed female rodents are shown to be more stress responsive, anxious and depressive, while prenatally stressed males have more cognitive deficits (Weinstock, 2007).

In humans, the children of antenatally depressed mothers have had elevated cortisol levels (S Gentile, 2017), and the dysfunction of the HPA axis is shown to be associated with short- and long-term adversities such as reduced birth weight, increased infant morbidity, locomotion and cognition retardation, increased anxiety, and sleep disturbances (Field et al., 2004; Maccari et al., 2003). Prenatal exposure to increased cortisol has widespread effects on gene expression in fetal brain cells (Leight et al., 2010). Long-term disturbances in HPA-axis function in association with prenatal stress have been described in pre-adolescent children (T. G. O’Connor et al., 2005). Excess exposure to cortisone in early life is associated with child brain development and sensitivity, which may result in later psychopathology (O’Donnell & Meaney, 2017). Maternal SSRI-treatment during pregnancy may attenuate the increase in neonatal cortisol levels (Brennan et al., 2008).

Prenatal exposure to maternal stress may also directly affect the fetus by vasoconstriction-causing fetal hypoxia (V Glover, 1997). The overactivation of HPA-axis, as well as antenatal depression are both connected to preterm birth, low birthweight (LBW), placental hypofusion, fetal hypoxia, and a disturbed function of the fetal immune system (Field, 2011c; Grote et al., 2010).

On the other hand, there are also many findings of negative associations between maternal antenatal depression and maternal and infant cortisol levels (O’Donnell & Meaney, 2017), which may be associated partly with methodological factors in different studies, but also with the fact that transient mood fluctuation is usually associated with elevated cortisol levels, but more chronic depression and stress with blunted cortisol response and thus hypocortisolemia (Seth, Lewis, & Galbally, 2016). It is also possible, that a certain group of depressed mothers, such as women with more severe illness, resemble with elevated glucocorticoid concertation (O’Donnell & Meaney, 2017). Although antenatal depression and stress seem to be associated with altered cortisol levels in at least some mothers and fetuses, according to a review, maternal prenatal cortisol levels cannot be supposed to be the only, or even the main mediator between maternal antenatal depression and child outcomes (Zijlmans, Riksen-Walraven, & de Weerth, 2015).
**Oxytocin**

Oxytocin plays an important role in parturition, lactation, and attachment, but it is also involved in stress physiology, inflammation, and vascular reactivity (Meltzer-Brody & Stuebe, 2014). Perinatal depression may be associated with decreased levels of oxytocin in women (Lonstein, Maguire, Meinlschmidt, & Neumann, 2014; Moura, Canavarro, & Figueiredo-Braga, 2016). It has been discussed whether the low levels of oxytocin in depressed women could be associated with lactation problems (Meltzer-Brody & Stuebe, 2014), postnatal care (Lonstein et al., 2014) and in the intergenerational transmission of early-life stress (Toepfer et al., 2017).

**Serotonin**

The potential roles of serotonin and other monoamines in the etiology of depression are described in chapter 2.2.1. Maternal antenatal depression may affect fetal serotonin-regulation in at least two ways: depressed mothers often use SSRI-medication (Ford, Lee, Shakespeare, & Ayers, 2017), and on the other hand, antenatal depression has been associated with down-regulation of placental MAO-A-expression (Blakeley, Capron, Jensen, O’Donnell, & Glover, 2013), both of which can result in elevated fetal serotonin-levels. No studies on child monoamine metabolism in relation to maternal antenatal depression have come to authors’ knowledge, without taking pharmacological studies into account.

**Inflammation**

Current evidence suggests that pregnancy is a carefully regulated inflammatory state, and disruptions in this homeostasis may result in adverse outcomes in the fetus (Shelton et al., 2015). Maternal antenatal depression, as well as elevated cortisol-levels, are found to be associated with alterations in cytokine-levels (Karlsson et al., 2017; Shelton et al., 2015). An increase in certain cytokine-levels, associated with antenatal depression was found to potentially associate with infant growth (Nazzari et al., 2019), and it could also potentially mediate the effect between antenatal depression and offspring atopy (Karlsson et al., 2017). In a study based on the SLDCS, maternal antenatal depression was found to be associated both with depression and with elevated inflammation (measured by hs-CRP) in the adult offspring, but offspring
depression was not associated with elevated inflammation (D T Plant et al., 2016; Dominic T Plant et al., 2015).

Mothers’ medication

The effects of antidepressive medication to the fetus and child is beyond the scope of this review. Although antidepressive medication may have effects on the developing fetus (Brown et al., 2016; Malm et al., 2016, 2015; Oberlander et al., 2006; Prady et al., 2017; Skurtveit, 2014), many studies have also found that outcomes in the offspring may associate more likely with antenatal depression than the pharmacological treatment (El Marroun et al., 2014; Grzeskowiak et al., 2016; Malm et al., 2016; Yamamoto-Sasaki et al., 2019).

Mothers’ substance use and nutritional factors

Antenatal depression is also associated with elevated risk of maternal smoking (Lancaster et al., 2010), and the use of other substances during pregnancy (Pajulo, Savonlahti, Sourander, Helenius, & Piha, 2001), and with unhealthy diet, including frequent consumption of processed food (i.e. fried food, meat pies or pasties, chips, crisps) and junk food (i.e. chocolate bars, cakes or buns, biscuits) and infrequent consumption of healthy nutrients, such as fish, non-meat proteins and vegetables. (Barker, 2013; Pina-Camacho et al., 2015). Smoking and substance use are associated with a variety of adverse outcomes in the offspring (Cook et al., 2017; Polańska, Jurewicz, & Hanke, 2015). Prenatal unhealthy diet has been associated with obstetric complications (Leung & Kaplan, 2009), child dysregulation (Pina-Camacho et al., 2015), and reduced cognitive function at age 8 years (Barker, 2013).

Obstetric complications

Women with depression during pregnancy have an increased risk of preterm birth and low birth weight (Field, 2011a; Grote et al., 2010). Preterm birth can, on its own, cause cognitive difficulties and psychiatric problems in the offspring (Bhutta, Cleves, Casey, Cradock, & Anand, 2002), and low birth weight is recognized as a risk factor for mental disorders, such as ADHD, schizophrenia, substance use disorders and mood disorders (O’Donnell & Meaney, 2017). Obstetric complications are associated with later psychosis in the offspring (Cannon, Van Erp, & Glahn, 2002; V Glover, 1997; P.B. Jones et al., 1998; Verdoux & Sutter, 2002),
possibly trough dopaminergic hypersensitization (Di Forti, Lappin, & Murray, 2007).

Maternal mental health and obstetric complications may be linked through three stress-related systems: the neuroendocrine, immune/inflammatory and cardiovascular systems (Federenko & Wadhwa, 2004). The overactivation of HPA-axis and increased concentrations of catecholamines can cause placental hypofusion and fetal hypoxia trough vasoconstriction (Grote et al., 2010; Waters, Hay, Simmonds, & van Goozen, 2014), which may also be in connection with preterm birth (McLean et al., 1995). The imbalanced immune system functioning (Serati et al., 2016) may be associated with preterm birth and fetal development (Boyle, Rinaldi, Norman, & Stock, 2017).

In recent studies of high risk sub-sample of the PREDO cohort, a new biomarker potentially acting between antenatal depression and fetal development factor, called the epigenetic clock or epigenetic gestational age, has been introduced (Suarez et al., 2018). Low epigenetic age may indicate fetal prematurity, although the infant has born term, and it has been found to associate both with maternal antenatal depression and the infant outcome (Suarez et al., 2018; Wolford et al., 2017). It should be noted, that because these findings are based on a high-risk study, they may not be generalizable to general population.

**Placental function and morphology**

The programming effects of maternal depression may also affect placenta, which may mediate the effects to the fetus. In recent findings in the Finnish PREDO study, maternal antenatal depression was found to be associated with placental villous barrier thickness, which in turn was associated with toddler psychiatric problems (Lahti-Pulkkinen et al., 2018). In the same cohort, antenatal depression was also associated with placental glucocorticoid sensitivity (Reynolds et al., 2015). Antenatal depression may also result in altered placental function via nerve growth factor signaling, which is associated with obstetric complications (Kaihola, Olivier, Poromaa, & Åkerud, 2015).

### 2.5 Summary of the literature review

Parental severe mental disorders and maternal antenatal depression are both relatively common and are found to have adverse effects on the mental health of the offspring. Of all the outcomes in the offspring of antenatally depressed mothers,
an increased risk of both internalizing and externalizing behavior have been quite consistently documented, and the elevated risk of depression and behavioral problems is shown to continue until young adulthood. The mediating factors between maternal depression and offspring outcomes are under active research, but early attachment, maternal health behavior during, endocrinological or immunological imbalance, the genetic and epigenetic factors may all be associated in this process. Pharmacological treatment of antenatal depression may also have adverse effects on the developing fetus, although the effects of severe depression and medication is difficult to assess separately.

In studies where both parents have been affected with mental disorder, the risk of adverse outcome in the offspring is greater than in those with only one parent affected. The author is not aware of previous studies examining the combined effect of maternal antenatal depression and parental severe mental disorder on the offspring’s outcomes.
3 Aims of the study

The aim of this thesis was to study mental health problems in the offspring of antenatally depressed mothers, also taking into account parental hospital-treated mental disorders

1. *Schizophrenia in the offspring of antenatally depressed mothers in the Northern Finland 1966 Birth Cohort – relationship to family history of psychosis (I).* The aim was to study, whether maternal antenatal depressed mood increased the risk of schizophrenia and other psychoses in the offspring with and without genetic risk of psychosis due parental psychosis. Maternal antenatal depressed mood was hypothesized to be associated with elevated risk of schizophrenia and other psychosis in both groups, and the association would be stronger among offspring in genetic risk of psychosis.

2. *Mood Disorders and Schizophrenia in the Offspring of Antenatally Depressed Mothers in the Northern Finland 1966 Birth Cohort: Relationship to Family History of Severe Mental Disorder (II).* The aim of the study was to determine whether maternal antenatal depressed mood increased the risk of hospital-treated depression, bipolar disorder and schizophrenia in the offspring, with and without parental severe mental disorder. The hypothesis was that the risk of depression would be higher than the risk of schizophrenia or bipolar disorder in the offspring of antenatally depressed mothers, especially among offspring with parental severe mental disorder.

3. *Antisocial and borderline personality disorders in the offspring of antenatally depressed mothers in the Northern Finland 1966 Birth Cohort (III).* The aim was to study whether the offspring of antenatally depressed mothers have an elevated risk of antisocial personality disorder (ASPD) or borderline personality disorder (BPD), also taking parental severe mental disorder into account. The hypothesis was that maternal antenatal depression is associated with an increased risk of ASPD and BPD in the offspring.

4. *Schizotypal and affective traits in the offspring of antenatally depressed mothers – Relationship to family history of psychosis in the Northern Finland 1966 Birth Cohort (IV).* The objective was to study schizotypal and affective traits in the offspring of antenatally depressed mothers with and without a parental history of psychosis. The hypothesis was that the scores on the schizotypal and affective scales in the offspring of antenatally depressed
mothers and with parental history of psychosis differ from the scores of cohort members without one or both of the risk factors.
4 Subjects and study design

4.1 The Northern Finland 1966 Birth Cohort

The data is based on the Northern Finland 1966 Birth Cohort (NFBC 1966), which is an unselected, population-based sample of 12,058 children born alive (Rantakallio 1969). The data was collected from pregnancy until the year 2015, but the follow-up time varies between the sub-studies (Figures 6 and 7). Permission to gather data was obtained from the Ministry of Social Affairs and Health. The Ethical Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland has approved the study and keeps it under review. An informed consent was obtained from all subjects included in the study.

4.2 Maternal antenatal depression

Data concerning the mother and offspring were gathered antenatally and at birth in 1965-1966. The mothers were asked at the antenatal clinic during mid-gestation whether they felt their mood as far during pregnancy had been as normal, depressed or very depressed. The information regarding the mothers’ antenatal mood is available for 10,658 (96.7%) of offspring living in Finland at the age of 16 years. Of the mothers, 86.1% (9,173) felt themselves as normal, and 13.9% (1,485) considered themselves depressed (11.8% depressed and 2.1% very depressed).
Fig. 6. Data collection of the Northern Finland Birth Cohort 1966 during 1965-2015 and the main variables used in the present thesis. CRHC = Care Register for Healthcare; FHDR = Finnish Hospital Discharge Register; LBW = Low birthweight; NERS = The National Educational Registry of Statistics, Finland; N = Number of cohort members
Fig. 7. Flow-chart with the drop-outs in the NFBC 1966 and the total number of subjects included in the original studies I-IV in the present thesis. * Data available on at least one of the scales and < 3 endorsing answers on the infrequency scale. **More data available due different confounding factors.
4.3 Parental history of psychosis and other severe mental disorders

Parental severe mental disorders were identified from the national Finnish Care Register for Health Care (CRHC, former Finnish Hospital Discharge Register, FHDR), which covers all hospital discharge diagnoses from mental and general hospitals, beds in local health centers and military, prison and private hospitals nationwide. The CHRH-data was available beginning from the year 1972, when the cohort members were 5-6 years old. The cohort members were linked with parental CRHC-data by their Personal Identity Code. The CRHC outpatient data from specialized care is available starting from year 1998, but it has not been used for detecting parental diagnoses in this study. The FHDR diagnoses are found to be relatively reliable (Moilanen et al., 2003; Perälä et al., 2007; Poikolainen, 1983).

In study I, all the cohort members’ mothers and fathers appearing on the Finnish Hospital Discharge Register between 1972–1997 for any psychosis (i.e., ICD-8 and ICD-9 codes 295–299 and ICD-10 codes F20-33, except nonpsychotic mood disorders) were identified. Of the NFBC 1966 cohort members, 4.2% (N = 448) of parents had been diagnosed with psychosis from 1972-1997. Also, data on maternal hospital-treated depression (i.e., ICD-8 codes 2960, 2968, 3004; ICD-9 codes 2961, 2968, 3004; and ICD-10 codes F32-F34), between 1972-1997, was gathered.

In studies II and III, all parents with severe non-organic mental disorders (ICD-8 codes 295-309 and ICD-9 codes 295-311) were identified from 1972 until 1984, when the offspring were 6-18 years old. The prevalence of parental severe mental disorders was 9.7% (N = 1,019). Parental mental disorders were considered severe because they were hospital inpatient ward-treated.

In study IV, mothers and fathers of cohort members appearing on the FHDR between 1972 and 2005 with any diagnosis of psychosis (i.e., ICD-8 290–299, ICD-9 diagnoses 295, 2961E, 2962E, 2963E, 2964E, 2965E and 297–299, and ICD-10 F 20, F22-29) were identified. Of the parents, 211 had been diagnosed with psychosis.
4.4 Offspring outcomes

4.4.1 Schizophrenia (I)

In study I, all cohort members over 16 years of age who appeared on the CRHC between the years 1982 and 1997 for any mental disorder were identified. All case records were scrutinized, and diagnoses were validated against the DSM-III-R criteria, after which the diagnoses were re-reviewed by a professional panel (Isohanni, 1997; Moilanen, 2003). There were 160 subjects with a psychotic episode prior to the age of 31 years, of whom 146 were living in Finland in 1999. Those 146 subjects were asked to participate in a field study during the years 1999-2001, and 91 subjects agreed to participate. The Structured Clinical Interview (SCID-I) for DSM-III-R and all available anamnestic information of the subjects with hospital case records were used for diagnostic assessment. Through these methods, a total of 111 cases of DSM-III-R schizophrenia and 45 cases of other psychosis were identified.

Schizophrenia in the offspring was also studied in study II in addition to mood disorders, with a follow-up of 43 years. See further description in the next chapter.

4.4.2 Mood disorders (II)

In study II, all the NFBC 1966 members appearing on the FHDR for mood disorders – depression (ICD-8 2960, 2980, 3004, 709; ICD-9 2961, 2968, 3004, 2969; ICD-10 F32-F33) or bipolar disorder (ICD-8 2961-2969; ICD-9 2962-2967; ICD-10 F30-F31) between the years 1982-2009 were identified. All case records from 1982-1997 were scrutinized, and diagnoses were validated against DSM-III-R criteria, after which they were re-reviewed by a professional panel. Diagnoses during 1998-2009 were based on clinical hospital discharge diagnoses as defined by the physicians responsible for the treatment.

4.4.3 Antisocial and Borderline personality disorder (III)

Cluster B, i.e., erratic personality disorders, including antisocial personality disorder (ASPD) and borderline personality disorder (BPD), are found to be the most common hospital-treated personality disorders (Liisa Kantojärvi et al., 2004), although they are quite rare in the general population (Huang et al., 2009). Both of
these disorders have high psychiatric comorbidity (Huang et al., 2009; Liisa Kantojärvi et al., 2006), functional impairment and mortality, due to substance abuse and suicidality.

**Antisocial personality disorder (ASPD)**

The prevalence of ASPD is 2-3% in the general population, but in prison studies, the prevalence of ASPD is up to 47% in men and 21% in women (Glenn, 2013). ASPD is thought to be perhaps the most severe personality disorder, because of the criminal behavior and violence, and poor adherence to treatment (Tyrer & Mulder, 2006).

In the original article *III*, with a 49-year follow-up, the cohort members appearing in the CRHC for ASPD (ICD-8 301.70 / ICD-9 3017 / ICD-10 F60.2) treated as inpatients between 1982 and 2015, or as specialized health care outpatients between the years 1998 and 2015, were detected.

**Borderline personality disorder (BPD)**

The prevalence of BPD is 1-6% in the general population (Leichsenring, 2011). It is the most common personality disorder in clinical samples, with a prevalence of 10% of all psychiatric outpatients and 15-25% of all inpatients.

In the original article *III*, with a 49-year follow-up, the cohort members appearing in the CRHC for BPD (ICD-8 301.30 / ICD-9 3018D / ICD-10 F60.3) treated as inpatients between 1982 and 2015, or as specialized health care outpatients between the years 1998 and 2015, were detected.

**4.4.4 Schizotypal and affective traits (IV)**

Schizotypy can be regarded as a continuum from slightly deviant beliefs and experiences to psychotic experiences (Chapman; LJ, Chapman, & Raulin, 1976; Meehl, 1962). Rather than a psychiatric disorder, it is a permanent personality trait, and subjects with schizotypy have a genetic vulnerability to schizophrenia (Grant, 2015; Lenzenweger, 2006; Meehl, 1962). Schizotypy increases the risk of transition into psychosis in high-risk patients (Mason et al., 2004; Salokangas, R.K.R. Dingemans et al., 2013). Affective traits or symptoms are distinct from schizotypy, but they are also associated with psychosis proneness, as they often manifest among prodromal symptoms of psychosis (Yung et al., 1996).
In the 31-year field study (IV) in the NFBC 1966, four psychometric instruments were selected to function as proxies for schizotypal traits, including the Perceptual Aberration Scale (PER; L. J. Chapman, Chapman, & Raulin, 1978), Revised Social Anhedonia Scale (SAS), Revised Physical Anhedonia Scale (PAS; Chapman; LJ et al., 1976), and Schizoidia Scale (SCHD) by Golden and Meehl (Golden & Meehl, 1979). PER measures distorted perceptions of one’s own body and other objects. High-scorers in PAS indicate a reduced ability to experience physical and sensory pleasures. High-scorers in SAS indicate a schizoid lack of interest in social interaction.

The three scales related to affective disorders were the Bipolarity II Scale (BIP2; Akiskal et al., 1995), the Hypomanic Personality Scale (HPS; Eckblad & Chapman, 1986) and the Hopkins Symptom Checklist -25 (SCL; Derogatis, Lipman, & Covi, 1973). The BIP2 was developed to identify those depressed subjects who have a risk of bipolar disorders and the HPS to measure hypomanic personality. The SCL includes questions about anxiety and depression. Although the HPS and BIP2 were originally developed to measure symptoms of bipolar disorder, they have also been found to measure psychosis proneness (Miettunen et al., 2011), and thus these scales are included as both schizotypal and affective scales.

At the 31-year follow-up study, the participants were given a questionnaire called the ‘Survey of Opinions and Experiences’, which consisted of true/false questions (scored 0 or 1) collected from the psychological scales (PER, SAS, PAS, SCHD, BIP2 and HPS), and the Infrequency Scale, which were all randomly rearranged into a 354-item format. The 12-item version of the Infrequency Scale (Chapman LJ, Chapman JP. Infrequency Scale. Unpublished test, 1983) was used to assess careless responding. The cohort members had received the SCL-questionnaire with an invitation to the 31-year field study. The SCL scores were only included for those subjects who also participated in the latter part of the study.

If more than 10% of the items on a psychopathology scale were left unanswered, the scale in question was excluded. Participants who endorsed three or more items indicating a random response style in the infrequency scale were excluded from the analyses (n = 105). On average, only 0.5% of the questionnaire replies were excluded.
4.5 Confounding variables

4.5.1 Sex of the offspring (I, IV)

The risk of schizophrenia has been found to be higher in men than in women (Aleman, Kahn, & Selten, 2003). Schizotypal and affective scales are also found to be gender dependent; in the NFBC 1966, men scored higher (had more psychopathological symptoms) in PAS, SAS and BIP2, and women had higher scores in SCHD, HPS and PER (Miettunen, 2010), and in a meta-analysis men were found to score higher in negative schizotypy (anhedonia scales), whereas in the scales of positive schizotypy (magical ideation scale and perceptual aberration scale) there were no sex differences (Miettunen & Jääskeläinen, 2010). Sex as a covariate in the analyses in the original papers I and IV. In study II, sex was not found to be associated with mood disorders in the offspring. In study III, female and male offspring were studied separately. Of the total offspring, 5,636 (51.2%) were boys and 5,381 (48.8%) girls, and of the offspring participating in the 31-year field study (Figure 2), 2,203 (44.7%) were men and 2,725 (55.3%) women.

4.5.2 Maternal smoking during pregnancy (I-III)

Maternal smoking was considered as a confounding factor in studies I-III. Mothers with severe mental disorders tend to smoke during pregnancy more often than mentally healthy mothers (Goodwin et al., 2017). Smoking during pregnancy elevates risks for antenatal depression (Lancaster et al., 2010) and for obstetric complications (Ellman, Huttunen, Lönnqvist, & Cannon, 2007). It may also increase the risk of subsequent mental disorders in the offspring (Wakschlag, 2002). The classification of maternal smoking was dichotomized: 1 = none or the mother stopped before pregnancy (N = 8,804, 85.0%), 2 = smoked daily more than one cigarette during the entire duration of pregnancy (N = 1,551, 15%).

4.5.3 Perinatal complications (I-III)

Women with a mood disorder or schizophrenia are at higher risk of obstetric complications (Jablensky, Morgan, Zubrick, Bower, & Yellachich, 2005). Antenatally depressed mothers also have a greater risk of preterm birth and low birth weight (Field, 2011b; Jablensky et al., 2005). As perinatal complications have
also been linked to increased risk of mood disorders and schizophrenia in the offspring (Peter B Jones, Rantakallio, Hartikainen, Isohanni, & Sipila, 1998; Schmitt et al., 2014), they were considered as confounding factors in original articles I and II. The classification of perinatal complications was dichotomized: 1 = no complications (N = 9,870, 92.6%), 2 = LBW (<2500g) or short gestational age (<37 weeks), or perinatal brain damage (Paula Rantakallio, 1987) (N = 788, 7.4%).

In the original article III, perinatal brain damage was not included in perinatal complications, which is why perinatal complications were considered as LBW or short gestational age in that study (N = 900, 8.2%).

4.5.4 Father's socioeconomic status at birth (I.I-III)

Low social class is a risk factor for maternal antenatal depression and for later depression in the offspring (Lancaster et al., 2010; Lorant et al., 2003). The father’s occupation at birth was used as a marker of parental socioeconomic status (SES) and was dichotomized into unskilled workers (N = 2,443, 22.9%) versus other social classes (N = 8,208, 77.1%). Paternal SES at birth was used as a confounding variable in studies II and III.

4.5.5 Family type at birth (II-III)

Maternal single status is a risk factor for both antenatal depression (Lancaster et al., 2010) and later depression in the offspring (Fendrich, Warner, & Weissman, 1990). Family type during the year the offspring were born (1966) was dichotomized into single-parent family and two-parent family (L Kantojärvi et al., 2008; Mäki, Veijola, et al., 2003). Of the offspring, 3.1% (N = 358) was born in single-parent families and 96.9 % (N = 11,200) in a two-parent family. Family type at birth was used as a confounding variable in studies II and III.

4.5.6 Grand multiparity (II)

In a previous study of the NFBC 1966, grand multiparity was found to be associated with elevated risk of depression in the offspring (Kemppainen et al., 2000), and in the analysis included in the present study, it was also found to be associated with maternal antenatal depressed mood (p < 0.001). Grand multiparity was defined as
≥ 6 previous live-births (N = 1,240, 11.8%), and used as a confounding factor in the adjustments in original article II.

4.5.7 Educational level of the offspring (IV)

A lower level of education was found to be associated with higher schizotypy (Miettunen et al. 2010), and thus educational level was considered as a confounder in original article IV. Information on the length of the subjects’ education had been collected in 1997 from the National Educational Registry of Statistics, Finland. The length of education was divided into three categories: primary level (less than 10 years), secondary level (10–12 years) and tertiary level (more than 12 years). Of the cohort members participating in the 31-year field study (Fig. 7), 26.8% (N = 1,320) had tertiary level, 64.3% (N = 3,170) secondary level and 8.5% (N = 421) basic-level education.

4.6 Statistical analyses

Cross-tabulations and chi-square tests (Pearson two-sided and Wald) were used to assess the relationships between maternal depressed mood during pregnancy, parental psychosis and parental severe mental disorders, and cumulative incidence of schizophrenia, other psychoses, mood disorders and ASPD and BPD in the offspring. Logistic regression analyses were conducted to examine the association between maternal antenatal mood, parental psychosis/severe mental disorder, and the offspring’s outcome, which were adjusted for sex (I,IV), maternal smoking during pregnancy (I-III), perinatal complications (I-III), grand multiparity (II), father’s socioeconomic status at birth (II,III), family type at birth (II,III), and offspring education (IV). Crude and adjusted odds ratios with 95% confidence intervals (95% CI) were calculated for the different groups of offspring (I-III). Since there was little difference between crude and adjusted odds ratio and confidence interval data, adjusted results of the original studies I and II are presented.

In the original articles I-II, additional analyses were conducted in subgroups with parental psychosis/severe mental disorder, where offspring with parental psychosis/severe mental disorder, but no maternal antenatal depression were the reference group.
In the original article III, the regression analyses were conducted in three different models, where Model 1 was unadjusted; Model 2 adjusted for maternal smoking during pregnancy, and LBW or short gestational age; and Model 3 was Model 2 with additional adjustments for father’s social class in 1966, and marital status ad 1966. Only crude OR:s are presented here, because there were no significant differences between the three models. Parental severe mental disorder could not be included in statistical tests due to low number of subjects.

In study IV, means and standard deviations for continuous test score variables are presented. Cohen’s d values were used as a measure of effect sizes (ES) for differences between diagnostic groups. Cohen describes d values as follows: 0.2 indicates small, 0.5 medium and 0.8 large effects (Cohen, 1992). A two-way analysis of covariance (F test) was used to test differences in mean values between diagnostic categories, with scores on the scales included in the analyses as dependent variables and diagnostic group, adjusting for education and sex.

Dichotomized variables were also used for the psychopathology scales, the cut-off values for the PER, SAS, PAS, SCHD, BIP2 and HPS scores being based on their distribution, with at least the highest 10% by gender considered to have a risk of future illness based on the previous studies (Meehl, 1962; Meyer & Hautzinger, 2003; Veijola, 2003). Because of many outcome measures in many risk categories being included, the multiple comparison test of Bonferroni adjustment was performed.

All of the tests were two-tailed, with 0.05 as the limit for statistical significance (I-IV).

4.7 Drop out

All cohort members alive and living in Finland at the age of 16 years (N = 11,017) were included in studies I-III. Data on maternal mood during pregnancy were available for 10,658 (96.7%) offspring. Data on parental psychosis were available for 10,658 offspring, and on parental severe mental disorders for 10,521 offspring. Of the mothers, 90 denied the use of their pregnancy and delivery data. Twins (N = 115) were excluded because they were missing their fathers’ CRHC-data. The offspring (cohort members) data on psychiatric disorders is register-based and thus the drop out in the original studies I-III was only due to death and emigration (Figure 7).
In the 31-year field study (IV) (Haapea et al., 2008), all 8,463 cohort members living in Northern Finland or in the Helsinki area on 1 January 1997 and who had returned a previous postal questionnaire (containing one of the psychopathology scales) were invited to a clinical examination. Based on the analysis of non-participation in the 31-year field study, of the invited, 5,960 (71%) participated in the clinical examination and received the ‘Survey of Opinions and Experiences’, containing the rest of the schizotypal and affective scales (see chapter 4.4.4; Figure 7). Of the cohort members participating in the field study, 5,084 returned the questionnaire (81% of males and 90% of females; Haapea et al., 2008) resulting in a 61% participation rate. Highly educated subjects participated more actively than subjects with lower education, and subjects with psychiatric disorder participated less actively than subjects without FHDR psychiatric diagnoses (males 54% vs. 35%, females 69% vs 57%; Haapea et al., 2008). Altogether 4,928 participants (59% of those invited; 45% males) with proper answers on at least one of the scales and a maximum of two endorsing answers on the infrequency scale were included in the study IV.

4.8 Ethical considerations

The Ethics Committee of the Northern Ostrobothnia Hospital District has accepted the study design of the NFBC 1966 and keeps it under review. Permission to gather data for the NFBC 1966 was obtained from the Ministry of Social Welfare and Health Affairs in 1994. The research plan for the NFBC 1966 31-year follow-up study was accepted by the Ethics Committee of Oulu University, Faculty of Medicine on 17 June 1996, and the 43-year follow-up on 18 February 2008. Data protection has been scrutinized by the Privacy Protection Agency, as well as by the principles of the Ministry of Health and Social Affairs. Written informed consent has been obtained from all participants. Cohort members have been assigned an ID-number, and their identities have not been revealed. All cohort subjects have had the right to deny the usage of information concerning themselves at any time. The study design of this doctoral thesis was approved by the Postgraduate Research Committee of the Faculty of Medicine at the University of Oulu on the 27th of October 2009.
5 Results

5.1 Schizophrenia and other psychosis in the NFBC 1966 cohort members (I,II)

The cumulative incidence of schizophrenia in the NFBC 1966 cohort members until the age of 31 years was 1.0% (N = 107) (I) and 1.3% (N = 139) until the age of 43 years (II).

5.1.1 The offspring of antenatally depressed mothers (I,II)

In the original article I, the cumulative incidence of schizophrenia was somewhat higher, 1.3% in the offspring of antenatally depressed mothers, compared to 0.9% in the offspring of mothers without antenatal depressed mood, but the difference was not statistically significant (Table 1, original article I). The risk of schizophrenia among offspring with antenatally depressed mothers and without parental psychosis was not elevated, compared to the offspring with neither of the risk factors (adjusted OR 1.0; 95% CI = 0.6–1.8). The prevalence of other psychoses was the same (0.4%) in the offspring of antenatally depressed mothers as in the offspring without maternal antenatal depressed mood (Table 1, original article I).

In the original article II, the cumulative incidence of schizophrenia was 1.6% in the offspring of antenatally depressed mothers, in comparison to 1.3% in the offspring of nondepressed mothers. Maternal antenatal depressed mood was not associated with an elevated risk of schizophrenia in the offspring in study II, either (Table 1, original article II).

5.1.2 The offspring with parental psychosis (I)

Of the offspring with parental psychosis, 3.3% had schizophrenia, compared with 0.9% of those without a history of parental psychosis (adjusted OR = 3.9, 95% CI = 2.2 – 6.8). Of the 107 schizophrenia patients, 15 (14.0%) had a history of psychosis in one or both parents, 10 (9.3%) had a history of maternal psychosis and six (5.6%) had a history of paternal psychosis (one had a history of psychosis in both parents; Table 1, original article I).
Of the other psychosis patients (N = 44), seven (15.9%) had a history of parental psychosis. Five of them (11.3%) had a history of maternal psychosis, and three (6.8%) had a history of paternal psychosis (one had a history of psychosis in both parents). There were 92 (86.0%) cohort members diagnosed with schizophrenia and 37 (84.1%) with other psychosis without a known psychotic episode in their parents (Table 1, original article I). The risk of schizophrenia (adjusted OR 3.9; 95% CI 2.2-6.8) and other psychoses (4.5; 2.0-10.1) was elevated in the offspring with a history of parental psychosis in comparison to those subjects without parental psychosis (Table 2, original article I).

5.1.3 The offspring with parental severe mental disorder (II)

Of the offspring with parental severe mental disorder and without maternal antenatal depressed mood (N = 838), 2.9% (N = 24) had been diagnosed with schizophrenia until age 43, compared to 1.8% (N = 146) of the offspring without parental severe mental disorder or maternal antenatal depressed mood. The offspring with a history of parental severe mental disorder and without maternal antenatal depressed mood did not have an elevated risk of schizophrenia (adjusted OR 1.5; 95% CI 0.96-2.4) compared to the offspring without either risk factor (Table 4, original article II).

When all offspring were included in the analysis (without excluding offspring with maternal antenatal depressed mood), of the offspring with one parent affected with severe mental disorder, 2.6% (N = 27) had been diagnosed with schizophrenia, compared to 1.2% (N = 117) of offspring without parental severe mental disorder. None of the offspring with schizophrenia had both parents affected with severe mental disorder.

5.1.4 The offspring of antenataly depressed mothers and with parental psychosis (I) or parental severe mental disorder (II)

The offspring of antenataly depressed mothers who also had a history of parental psychosis had a markedly elevated risk of schizophrenia (adjusted OR 9.4; 95% CI 4.2-20.9) and other psychoses (6.2; 1.5-26.3), when compared to those offspring without both of these risk factors. The risk of schizophrenia in the offspring with both of the risk factors remained elevated even when the offspring with a history
of parental psychosis and without maternal antenatal depressed mood were used as a reference group (3.6; 1.3–10.2; Chi²=5.7, p=0.017) (Table 1, original article I).

Of all the risk factors studied in the present thesis, the combination of maternal antenatal depression and a history of paternal psychosis resulted in the highest risk of schizophrenia (adjusted OR 14.2; 95% CI 4.9–41.2). The respective adjusted odds ratio was 8.0 (2.8–22.8) among the offspring of mothers with both antenatal depressed mood and psychosis. In additional analyses, maternal subsequent hospital-treated depression was checked as a potential confounder, but it was not found to explain the association between antenatal depression and elevated risk of schizophrenia in offspring with parental risk of psychosis (Table 1, original article I).

In the original article II, the offspring of antenatally depressed mothers who also had parental severe mental disorder had an elevated risk of schizophrenia (adjusted OR 3.9; 95% CI 2.0-7.5) compared to the offspring without maternal antenatal depressed mood and without parental severe mental disorder (Figure 8). The offspring with father’s severe mental disorder had a 5-fold risk of schizophrenia (5.4; 1.7-17.4), if their mothers had depressed mood during pregnancy compared to offspring with only paternal severe mental disorder. The combination of maternal antenatal depressed mood and a later maternal psychosis did not result in elevated risk of schizophrenia in the offspring (1.1; 0.3-4.4; Table 4, original article II).
Fig. 8. Cumulative Incidences of Schizophrenia in the Offspring with and without Antenatally Depressed Mothers and with and without Parental Severe Mental disorder during 1972-1984 in the NFBC 1966. Data includes all subjects alive and living in Finland at 16 years of age. Individual follow-up time was calculated up to the date of first admission due to depression or to the date of censoring (death, emigration, or the end of the follow-up), whichever came first.

5.2 Severe mood disorders in the NFBC 1966 cohort members (II)

5.2.1 Severe bipolar disorder

The cumulative incidence of hospital-treated bipolar disorder in the NFBC 1966 cohort members was 0.5% (N = 53) until 43 years of age.

The offspring of antenatally depressed mothers

The risk of bipolar disorder was not statistically significantly higher in the offspring of antenatally depressed mothers (1.7; 0.9-3.5) than in the offspring of nondepressed mothers (Table 3, original article II).
The offspring with parental severe mental disorder

The offspring with parental severe mental disorder and without maternal antenatal depression had an elevated risk of severe bipolar disorder (adjusted OR 2.9; 95% CI 1.4-6.2), compared to offspring without both of the risk factors (Table 3, original article II). The offspring of whom both parents had been affected with severe mental disorder were at increased risk of bipolar disorder (p = 0.02) compared to offspring with one parent affected.

The offspring of antenatally depressed mothers and with parental severe mental disorder

The risk of bipolar disorder was not statistically significantly elevated in the offspring with both maternal antenatal depressed mood and parental severe mental disorder (adjusted OR 2.4; 95% CI 0.6-10.2;), although the prevalence of bipolar disorder was somewhat higher in this risk group (Figure 9 and Table 3, original article II).

Fig. 9. Cumulative incidences of bipolar disorder in the offspring with and without antenatally depressed mothers and with and without parental severe mental disorder during 1972-1984 in the NFBC 1966. Data includes all subjects alive and living in Finland at 16 years of age. Individual follow-up time was calculated up to the date of first admission due to bipolar disorder or to the date of censoring (death, emigration, or the end of the follow-up), whichever came first.
5.2.2 Severe depression

The total cumulative incidence of severe, hospital-treated depression in the NFBC 1966 cohort members was 2.0% (N = 212) until 43 years of age (II).

The offspring of antenatally depressed mothers

The offspring of antenatally depressed mothers had an elevated risk of depression (adjusted OR 1.5; 95% CI 1.03-2.2), compared to offspring without maternal antenatal depressed mood (Table 2, original article II).

The offspring with parental severe mental disorder

The offspring of nondepressed mothers who had a parent hospital-treated for a severe mental disorder during 1972-1984 did not have a statistically significantly elevated risk of depression (adjusted OR 1.5; 95% CI 0.96-2.4, compared to offspring without maternal antenatal depressed mood or parental severe mental disorder (Table 1, original article II).

When considering all offspring with parental severe mental disorder (without considering maternal antenatal mood), the offspring with two parents affected with severe mental disorder did not have an elevated risk of depression, when compared to offspring with one parent affected (4.2% vs. 3.5%; p = 0.69).

The offspring of antenatally depressed mothers who also had parental severe mental disorder

The offspring of antenatally depressed mothers with also parental severe mental disorder had a higher risk of severe depression (adjusted OR 3.3; 95% CI 1.8-6.2), than the offspring with only maternal antenatal depressed mood (1.2; 0.8-1.9) or parental severe mental disorder (1.5; 0.96-2.4) when the reference group was the offspring without both risk factors (Figure 10 and Table 2, original article II).

Maternal antenatal depressed mood in addition to subsequent maternal severe mental disorder was also associated with elevated risk of depression in the offspring (adjusted OR 3.6; 95% CI 1.1-12.0). Among offspring with father’s severe mental disorder, a history of maternal depressed mood during pregnancy was not
associated with elevated risk of non-psychotic depression in the offspring (1.8; 0.7-4.6) (Table 2, original article II).

Fig. 10. Cumulative Incidences of depression in the offspring with and without antenatally depressed mothers and with and without parental severe mental disorder during 1972-1984 in the NFBC 1966. Data includes all subjects alive and living in Finland at age 16. Individual follow-up time was calculated up to the date of first admission due to depression or to the date of censoring (death, emigration, or the end of the follow-up), whichever came first.

5.3 Antisocial and borderline personality disorder in the NFBC 1966 cohort members (III)

The number of hospital discharge diagnoses of personality disorders was low in the NFBC 1966. Due to the low numbers, analyses of the association of maternal antenatal depressed mood and parental severe mental disorder could not be performed. Thus, we only studied the association of maternal antenatal depressed mood with personality disorders in the offspring.

5.3.1 Antisocial personality disorder in the offspring of antenatally depressed mothers

Of the NFBC 1966 cohort members, 0.2% (N = 22; 82% males) had been diagnosed with ASPD until the age of 49 years, and of those, 21 (95.5%) were treated as hospital inpatients and one (4.5%) as a specialized health care outpatient. One
The occurrence of ASPD was 1.0% (N = 8) in the male offspring of antenatally depressed mothers (N = 792), and 0.2% (N = 10) in the male offspring without maternal antenatal depressed mood (N = 4,869). The risk of ASPD (crude OR 5.0; 95% CI 2.0-12.6) was elevated in the male offspring of antenatally depressed mothers. After logistic regression analyses with adjustments for perinatal biological risk factors and psychosocial risk factors, the results remained statistically significant (Table 2, original article III).

Of the female offspring, 0.07% (N = 4) had been diagnosed with ASPD during the 49-year follow-up, of whom one was born to an antenatally depressed mother. The statistical power was too low to make reliable estimates of the risk of ASPD in daughters of antenatally depressed mothers compared to female offspring without maternal antenatal depressed mood (Table 2, original article III).

5.3.2 Borderline personality disorder in the offspring of antenatally depressed mothers

Of the cohort members, 0.8% (N = 86; 38% males) were diagnosed with BPD until 49 years of age, of whom 67 (77.9%) had been treated as hospital inpatients, 36 (41.9%) as specialized health care outpatients, and 17 (20.0%) as both inpatients and outpatients. The mean age of first BPD-diagnosis was age 32.4 years (range 16-48 years of age).

The occurrence of BPD in the male offspring of antenatally depressed mothers was 0.6% (N = 5), and 0.6% (N = 28) in the male offspring without maternal antenatal depressed mood. The risk of BPD was not elevated in the sons of antenatally depressed mothers in the 49-year follow-up (crude OR 1.1; 95% CI 0.4-2.9) (Table 3, original article III).

The occurrence of BPD in the female offspring was 1.0% (N = 53), of whom 11 (21%) were born to antenatally depressed mothers. The risk of BPD was not elevated in the daughters of antenatally depressed mothers (Table 3, original article III).
5.4 Schizotypal and affective traits in the offspring of antenatally depressed mothers (IV)

5.4.1 Offspring of antenatally depressed mothers without parental psychosis

The mean scores and the prevalence of high scores were not statistically significantly different in the offspring of antenatally depressed mothers in comparison to the scores of the cohort members without maternal antenatal depression on most of the schizotypal or affective scales. The prevalence of a high PAS score was lower among the offspring of antenatally depressed mothers than in the children without maternal antenatal depression (9.2% vs. 11.5%, p = 0.030), which indicates lower schizotypy in this risk group (Table 1, original article IV).

5.4.2 Offspring with parental psychosis

The mean scores and the prevalence of high scores on most of the psychopathology scales did not differ statistically significantly between the subjects with or without a parental history of psychosis. A larger group of subjects with parental (15.2%, p = 0.036) or maternal (16.0%, p = 0.041) psychosis had HPS scores in the highest 10% amongst subjects without parental or maternal psychosis (10.8%; Table 2). When the multiple comparison test of Bonferroni adjustment was performed, the differences with regard to the HPS were no longer statistically significant. The mean scores on the PAS, SCHD and BIP2 scales were statistically significantly lower among the subjects with paternal psychosis than in those without (PAS 13.3 vs. 15.0, p = 0.046; SCHD 2.3 vs. 2.6, p = 0.017; and BIP2 9.6 vs. 10.6, p = 0.006). The adjusted p-values were calculated from the analysis of covariance with sex and education as covariates (Table 2, original article IV).

5.4.3 Offspring of antenatally depressed mothers who also had parental psychosis

The mean scores and the prevalence of high scores of schizotypal or affective scales were not statistically significantly different in the subjects with both maternal depressed mood during pregnancy and parental psychosis on any of the schizotypal
and affective scales, compared to subjects without one or both of these risk factors (Table 3, original article IV).

### 5.5 Parental severe mental disorders in families with a history of maternal antenatal depression (II)

An additional analysis was performed to study severe mental disorders in parents of families with maternal antenatal depressed mood. Mothers who had antenatal depressed mood were hospital-treated for depression during the years 1972-1984 (when the offspring were aged 5-18 years) more than twice as often as mothers without antenatally depressed mood (p < 0.001). The cumulative incidence of schizophrenia was also higher in mothers with a history of antenatal depressed mood (p = 0.003).

Fathers, whose spouses had been antenatally depressed, had been more often hospital-treated for mood disorders (p = 0.041), schizophrenia (p = 0.033) and especially for substance use disorder (p < 0.001) during the years 1972-1984, than fathers whose spouses had not had antenatal depressed mood.
6 Discussion

6.1 Main findings

In the present study, the offspring of antenatally depressed mothers had an elevated risk for depression (II), and the male offspring for antisocial personality disorder (III), as compared to NFBC 1966 subjects without maternal antenatal depressed mood. The risk of schizophrenia (I,II), bipolar disorder (II), borderline personality disorder (III), or schizotypal and affective traits (IV) was not statistically significantly elevated in the adult offspring of antenatally depressed mothers when compared to offspring of mothers without depressed mood during pregnancy. Parental psychosis was associated with an increased risk of schizophrenia (I) and other psychoses (I), but not with schizotypal or affective traits in the offspring (IV). The offspring with parental severe mental disorder had an elevated risk of bipolar disorder, especially if both parents had been affected (II), and the male offspring had an increased risk of BPD (III). The risk of schizophrenia (II) was not elevated among subjects with parental severe mental disorder, if their mothers did not have depressed mood during pregnancy.

In those offspring of antenatally depressed mothers who also had parental psychosis, the risk of schizophrenia and other psychoses was significantly higher, as compared to those with only maternal antenatal depressed mood or parental psychosis, or to those without both of these risk factors (I). The combination of maternal antenatal depressed mood and paternal psychosis resulted in especially high risk of schizophrenia in the offspring (I). The subjects with both maternal antenatal depressed mood and parental psychosis did not differ in schizotypal or affective traits when compared to subjects without one or both of the risk factors.

The offspring with both maternal antenatal depressed mood and parental severe mental disorder had a markedly elevated risk of depression and schizophrenia, when compared to NFBC 1966 cohort members without one or both of the risk factors (II).

In the mothers (of the NFBC 1966 cohort members) with a history of antenatal depressed mood, the risk for subsequent hospital inpatient treatment for schizophrenia and depression was elevated, when compared to those mothers who did not report depressed mood during pregnancy (II). The fathers of the cohort members, whose spouses had antenatal depressed mood, had an elevated risk for subsequent hospital-treated schizophrenia, mood disorders and substance use.
disorder (II). However, because of the observational nature of the study, cause-effect relationships cannot be conclusively stated.

6.2 Comparison of the findings with previous research

6.2.1 The prevalence of parental severe mental disorders and maternal antenatal depressed mood in the NFBC 1966

In the present study, the prevalence of severe mental disorders in the parents of the NFBC 1966 cohort members during their childhood (between ages 5-18 years) was 10.2% (4.4% maternal; 7.0% paternal, 0.5% both parents) (II). The prevalence of parental mental disorders is reported to be up to 20% (K. Dean et al., 2010; Reupert et al., 2013), but only hospital-treated, severe mental disorders were included in the present study. The prevalence of parental psychosis was 4.2% (2.5% maternal psychosis, 1.8% paternal psychosis) (I). As previously reported (Mäki, Veijola, et al., 2003), the prevalence of maternal antenatal depressed mood was 13.9% in the NFBC 1966, which is in line with other population-based cohort studies (Table 2).

6.2.2 Cumulative incidence of mental disorders in the NFBC 1966

The cumulative incidence of schizophrenia (I,II) in this study was 1.4%, which is relatively high when compared to the estimated global lifetime prevalence of 0.4% (10%-90% quantile: 0.2–1.2%; Saha, Chant, Welham, & McGrath, 2005). It is still in line with earlier findings of schizophrenia in Finland, such as a prevalence of 1.3% in adult population (Lehtinen et al., 1990), and a lifetime prevalence of 0.9% in the Finnish Health-2000 study (Perälä et al., 2007).

The cumulative incidence of bipolar disorder (II) in the NFBC 1966 was 0.5% (N = 53), which is somewhat higher when compared to the Health 2000 study, where the life-time prevalence of bipolar I disorder was 0.24% (Perälä et al., 2007). The Global Burden of Disease (GBD) -research found a 0.3% prevalence of bipolar disorder in Eastern European males (Russia) and a prevalence of 0.5% in males and 0.8% in females in the Western Europe (Ferrari, Baxter, & Whiteford, 2011), and a global 12-month prevalence of 0.6% in the GBD 2016 update (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017).

The cumulative incidence of hospital-treated depression (II) in the 43-year follow-up of the NFBC 1966 was 2.1% (N=217), which is in line with the global 100
12-month prevalence of 2.4% of Major Depressive Disorder (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017), although in the Finnish Health 2000-2011 follow-up, the weighted 12-month prevalence of depression was higher, 5.4% (Markkula et al., 2015). On the other hand, only a small proportion of patients with depression are hospital-treated, and only hospital inpatient-treated depression was included in the present study.

During the 49-year follow-up, 0.2% (N = 22; 82% males) of the cohort members had been diagnosed with ASPD, and 0.8% (N = 86; 38% males) with BPD (III). Compared to previous studies, the prevalence of both ASPD and BPD were lower than previously reported (ASPD 2-3%, BPD 1-6%) (Glenn, 2013; Leichsenring, 2011). The low prevalence of ASDP and BPD are further discussed in chapters 6.3 and 6.5.2.

6.2.3 The offspring of antenatally depressed mothers

In an earlier study of the NFBC 1966, Mäki and colleagues (Mäki et al., 2004) found that the association between maternal antenatal depressed mood and elevated risk of schizophrenia in the offspring was explained by parental psychosis. The pregnant mothers were found to report themselves as depressed more frequently if their spouse or themselves had a subsequent psychotic disorder, compared to those without, and parental psychosis was found to be the original risk factor for schizophrenia in the offspring (Mäki et al., 2004). Because of these findings, in the present study, the psychiatric outcomes in the offspring of antenatally depressed mothers were studied in relation to parental psychosis and other severe mental disorders, being able to look at the offspring with and without maternal antenatal depression and with and without parental psychosis/severe mental disorder.

When the offspring of antenatally depressed mothers were studied excluding those with parental psychosis, the risk of schizophrenia and other psychosis (I), or the prevalence of schizotypal or affective traits (IV) was not elevated. In those offspring with maternal antenatal depressed mood and without parental severe mental disorder, the risk of severe depression (II) was elevated, as well as the risk of ASPD in the male, but not in female offspring. The risk of schizophrenia, bipolar disorder (II), or BPD (III) was not elevated in this risk group. The author is not aware of other studies considering psychiatric outcomes in the offspring of antenatally depressed mothers, where subjects with other parental severe mental disorders would have been excluded.
The findings in the present study are in line with previous studies, where an elevated risk of affective problems in childhood (El Marroun et al., 2014) and depression in adolescence (Quarini et al., 2016) and young adulthood (Betts et al., 2015; Herva et al., 2008; Rebecca M Pearson et al., 2013; Dominic T Plant et al., 2015; Raposa et al., 2014), and for antisocial and criminal behavior (Hay, Pawlby, Waters, Perra, & Sharp, 2010; Mäki, Veijola, et al., 2003) in the offspring of antenatally depressed mothers have been documented. On the contrary, affective traits, measured by the SCL-25, HPS and BIP2, were not found to be elevated in the offspring of antenatally depressed in the present study. In previous literature, there are studies where no association between maternal antenatal depressed mood and offspring emotional problems were found. In the ALSPAC, antenatal anxiety, but not depression, was associated with offspring emotional problems at age 4 years (T. G. O’Connor et al., 2002), and in the SLDCS, no association between antenatal depression and offspring emotional disorders at age 16 years were found (Hay, Pawlby, Waters, & Sharp, 2008). In a previous study of the NFBC 1966, Herva and colleagues (Herva et al., 2008) found the SCL-score to be elevated in the offspring of antenatally depressed mothers. In that study, the number of included 31-year-old subjects was 8,339, and in the original study IV of the present thesis, the N was 4,894, so almost half of the population included in the study by Herva et al. 2008 was missed in the present study because the inclusion criteria were different.

Maternal depressed mood has been associated with a variety of other negative outcomes in the offspring as presented in chapter 2.3. Of those studies, many have been able to study postnatal depression and later depression as a confounding or mediating factor, and most of those studies have concluded that antenatal depression affects the fetus, resulting in subsequent adverse outcomes, and this effect is not entirely explained by postnatal or later maternal depression (Betts et al., 2015; Rebecca M Pearson et al., 2013; Quarini et al., 2016). Still, both postnatal and especially persistent maternal depression are also associated with adverse outcomes in the offspring (Leech et al., 2006; Maselko et al., 2015; Park et al., 2018; Pawlby et al., 2009; van der Waerden et al., 2017; Wolford et al., 2017), and some studies have not found associations between offspring outcome and maternal antenatal depression at all (Alaräisänen et al., 2012; Bekkhus et al., 2011; Dierckx Bram, 2009; Ibanez, 2015; Ingstrup et al., 2012; Wen et al., 2017; Zhou, 2017). Persistent maternal mental illness (antenatal depressed mood and subsequent severe mental disorder) was associated with higher risk of depression, than offspring with only maternal antenatal depressed mood also in the present study.
In additional analysis related to the original publication I, the association between maternal antenatal depressed mood, mother’s later hospital-treated depression and offspring schizophrenia was studied. Of mothers with antenatal depressed mood, 5.2% later had hospital-treated depression, compared to 2.8% of mothers without depressed mood during pregnancy (OR 1.9, 95% CI=1.4–2.4). Of the offspring with schizophrenia, 12 had mothers with hospital-treated depression, two with both antenatal depressed mood and later severe depression. Thus, the markedly increased risk of schizophrenia in the offspring of antenatally depressed mothers who also had parental psychosis was not explained by mother’s later severe depression.

6.2.4 The offspring with parental psychosis

In the present study, the subjects of whom one or both parents had been in hospital treated for psychosis during 1972–1997 (offspring age 5-31 years, original article I) were found to have an increased risk of schizophrenia (adjusted OR 3.9; 95% CI 2.2-6.8) and other psychoses (4.5; 2.0-10.1). When only those offspring with parental psychosis and without maternal antenatal depressed mood were included in the analysis, the risk of schizophrenia (adjusted OR 2.6; 95% CI 1.2-5.4) and other psychoses (3.9; 1.5-10.1) was somewhat lower (I). The risk of schizophrenia in the offspring of parents with psychosis was lower than in the meta-analysis by Rasic and colleagues (RR 7.54) (Rasic et al., 2014), and in the recent Taiwanese high-risk study (RR 4.76) (C.-M. Cheng et al., 2018). The prevalence of parental psychosis in the NFBC 1966 (4.2%) (I) was lower than in previous reports (Gottesman, 1991). Some parents’ psychotic disorders may have been missed, since the FHDR was founded in 1972, when the offspring were 5-6 years old, and no data on parental mental disorders was available before that. Further, only hospital-treated mental disorders in the offspring were included, which has probably resulted in lower prevalence of mental disorder than in the general population. Parental history of psychosis was present in 14% of the offspring with schizophrenia and in 16% of the offspring with other psychosis, as compared to 4% in those offspring without psychotic illness (I), which is in line with previous studies (Rasic et al., 2014).

The prevalence of schizotypal or affective traits was not elevated among subjects with parental psychosis (IV). In fact, the mean scores on the PAS, SCHD and BIP2 scales were statistically significantly lower among the subjects with
paternal psychosis than in those without. Because of this surprising finding, the data analyses of the original article IV were re-checked and were found to be correct. According to the previous literature, the first-degree relatives of patients with psychosis are found to have elevated levels of schizotypal traits, measured by the Wisconsin Schizotypy Scales (Docherty & Sponheim, 2008; Keshavan et al., 2008; Laurent et al., 2000) and the Schizotypal Personality Questionnaire (SPQ) (Mechri et al., 2010; Yaralain et al., 2000), however there are also opposite findings (Bollini et al., 2007; Catts, Fox, Ward, & Mcconaghy, 2000; Katsanis, Iacono, & Beiser, 1990). A study by Soler and colleagues (Soler et al., 2017) could provide one explanation of why schizotypy was not elevated in the high-risk offspring in the present study. According to their findings, disorganization in the psychotic proband could correlate with low schizotypy in the first-degree relatives, and low schizotypy could be more hereditable, than high. There are also findings that physical anhedonia is decreased in the relatives of schizophrenia patients (Catts et al., 2000) and in subjects at risk of psychosis (Miettunen et al., 2011), but there are also opposing reports (Fanous et al., 2007; Grove et al., 1991; Kendler, Thacker, & Walsh, 1996). In the present study, the PAS score was lower in the subjects with a paternal history of psychosis (IV).

### 6.2.5 The offspring with parental severe mental disorder

During the 43-year follow-up, the cumulative incidence of depression in the offspring with one parent affected with severe mental disorder was 3.5%, 1.0% of bipolar disorder, and 2.6% of schizophrenia (II), These numbers are much lower as compared with the meta-analysis by Rasic and colleagues, where the rates of 21% for depression, 7% for bipolar disorder and 8% for schizophrenia in adult offspring of parents with severe mental illness were reported, although those offspring were not all hospital-treated for their mental disorders as in the present study. In the present study, in offspring with two parents affected, the cumulative incidence of depression was 4.2%, and 6.3% of bipolar disorder; no schizophrenia-cases were found in this risk group. The prevalence of parental severe mental disorder was 10.2%, which is in line with previous reports (Reupert et al., 2013; Stambaugh et al., 2017).

Parental mental disorders are found to increase the risk of offspring mental disorders (K. Dean et al., 2010; Rasic et al., 2014; Reupert et al., 2013), and personality disorders (Coid, 1999; K. Dean et al., 2010). In the present study, the
risk of bipolar disorder was statistically significantly elevated in the offspring with one or two parents affected with severe mental disorder, and the risk of BPD was elevated in male, but not in female offspring of parents with a severe mental disorder (III). The risk of schizophrenia, depression (II), or ASPD was not elevated in this risk group (III), which was unexpected.

6.2.6 The offspring with both maternal antenatal depressed mood and parental psychosis or severe mental disorder

In the NFBC 1966, 0.9% (N = 94) of the offspring had both maternal antenatal depressed mood and parental psychosis until the year 1997. Parental severe mental disorder during 1972-1984 (i.e., in the offspring’s childhood) in addition to maternal antenatal depressed mood was found in a total of 2% (N=212) of the offspring. The author is not aware of previous studies other than the NFBC 1966, where parental psychosis or severe mental disorder would have been studied in association with maternal antenatal depressed mood as a risk factor for offspring mental health problems. According to the findings in the present study, maternal antenatal depressed mood seems to have a significant additive or even multiplicative effect on the risk of mental disorders in offspring at risk of mental disorders due to parental severe mental disorder or parental psychosis.

The offspring of antenatally depressed mothers with also a parental history of psychotic illness had a markedly elevated risk of schizophrenia (adjusted OR 9.4; 95%CI 4.2-20.9) and other psychoses (6.2; 1.5-26.3), compared to offspring without one or both of the risk factors (I). The combination of maternal antenatal depressed mood and paternal psychosis resulted in a 14-fold risk of schizophrenia and other psychoses in the offspring. Despite these findings, the prevalence of high scores or mean scores of the schizotypal or affective scales did not differ between subjects with maternal antenatal depressed mood and paternal psychosis and subjects without these risk factors (IV). These surprising findings have been discussed in chapter 6.3.

The offspring of antenatally depressed mothers with parental severe mental disorder had an elevated risk of schizophrenia and depression (II). This risk was larger than the risk associated with antenatal depression or parental severe mental disorder per se added or even multiplied together, indicating a multiplicative effect. In the original article III, the relationship of maternal antenatal depressed mood and parental severe mental disorder to the risk of ASPD and BPD was planned to be
studied, but the number of the affected offspring with both of these risk factors was too low to make statistically reliable analyses.

Spousal similarity for mental disorders has been documented in previous studies (Galbaud du Fort et al., 1998, 2002; Marmorstein et al., 2004). In additional analyses of the present study (II), the parents in families which had been affected with mother’s antenatal depression were more likely to be affected by subsequent severe mental disorders than those parents in families without maternal antenatal depression. This association may be explained by the mothers’ possible underlying severe mental disorder, and not only with antenatal depression. Some shared factors, such as assortative mating or shared environmental factors may explain why the risk of paternal severe mental disorders was elevated in families with maternal antenatal depression (Galbaud du Fort et al., 1998; Maes et al., 1998). Also, the fathers’ severe mental disorders may have originated prior to or during the pregnancy in 1966, which may have affected the mothers’ mood.

6.3 Methodological discussion

The NFBC 1966 provides a unique opportunity to follow the offspring of antenatally depressed mothers beginning from pregnancy until adulthood, up to 49 years of age, so far. The long follow-up is a great strength of the study, but some difficulties are also included. The pregnant women of whom calculated term fell between 1st January – 31th December 1966 were asked at the mid pregnancy, mainly between gestational weeks 24-28, if the mothers’ mood during this pregnancy been ordinary, depressed or very depressed (Mäki, 2003). At that time, Finland was recovering from the World War II. The war and its consequences may have traumatized some of the mothers, which may have affected their mood. On the other hand, mental disorders were still a taboo at that time, which may have inhibited some from reporting of their mental problems (depressed mood). The mood-question was asked only once during pregnancy, and some mothers may have forgotten if they were depressed in early pregnancy, and some may have become depressed later.

Depressed mood is the main symptom of depression, but it may also be a symptom of another mental disorder, such as anxiety disorder, bipolar disorder, schizophrenia or post-traumatic stress disorder (World Health Organization, 2012), and based on the one question asked in the NFBC 1966, it cannot be determined, which condition the mother had been affected by. It is also unclear, whether it is the
antenatal depression, or another factor behind it, such as an environmental factor, genetic or epigenetic factor, anxiety, or stress, which is directly associated with the outcome in the offspring (Vivette Glover, 2014; O’Donnell & Meaney, 2017).

Many studies reviewed in the chapter 2.3 suffer the potential reporting bias, where the mother reports the infant outcomes. This may lead to over- or underestimation of the infant symptoms. In the present study, the offspring outcomes (I-III) are obtained from the CRHC, based on physician’s clinical evaluation. The CRHC-data for psychiatric inpatient-diagnoses was available beginning from 1972 and for psychiatric outpatients from 1998, and the drop out from the CRHC is very small. The CRHC-diagnoses have been found to be relative reliable (M Isohanni et al., 1997; Moilanen et al., 2003; Perälä et al., 2007). Still, the diagnostic criteria of mental disorders have changed in time, and it is possible that patients with a certain mental disorder at the 1970’s could have a different diagnosis at 2010’s, for example severe mania may have been treated as psychosis at that time. Also, the definition of BPD has changed over time. The availability of mental health services has also changed, and it is possible that more severe cases have appeared in the CRHC decades ago than recently.

Register-based studies of personality disorders should also be interpreted with caution. In the present study, the diagnoses of ASPD and BPD were drawn from the CRHC (III). Subjects with ASPD tend not to seek healthcare and not commit to treatments (Sher et al., 2015). On the contrary, subjects with BPD tend to seek treatment more often than the general population (Leichsenring, 2011), and they may be overrepresented in clinical registries, but probably with variating diagnoses, as BPD often overlap with other internalizing conditions (Baryshnikov et al., 2016). Personality disorders are highly comorbid with axis I psychiatric disorders (Huang et al., 2009; Liisa Kantojärvi et al., 2006), and sometimes only the main (axis-I) diagnosis is coded, and the underlying personality disorder often remain undiagnosed (Bender et al., 2001).

In the original article IV, schizotypal and affective traits were studied by several psychopathology scales. In the 31-year follow-up field study, the cohort members filled the Survey of Opinions and Experiences containing the psychopathology scales, excluding the SCL-25, which they had received earlier. The drop out in study IV was quite remarkable, only 59% of the interviewed subjects had proper answers in the psychopathology scales. The Survey of Opinions and Experiences -question form contained over 300 questions, and it was only one part of the whole 31-year field-study. It is possible, that those with more schizotypal or affective traits,
i.e. those in probably worse mental condition, compared to those without mental health problems, may have failed to answer all the questions, and were thus excluded from the study. The NFBC 1966 cohort members with mental disorders have been found to attend less actively to the study, compared to those without (Haapea et al., 2008). This phenomenon may have biased the findings, as the scoring in the psychopathology scales may have been skewed towards lower scores.

It could be also speculated whether the offspring of parents with psychosis could be more suspicious and defensive in answering questions considering mental disorders. In the present study, the possible effect of defensive answering was studied by comparing if anhedonia scales associate more weakly to PER in those with parental psychosis than among others, but no significant differences between these two groups were found (IV).

6.4 Interpretation of the findings in the present study

The results of this study can be interpreted in more than one way, and direct cause-effect relationships should not be directly drawn, because of the observational nature of the present study. The complexity of the study design, where both genetic risk factors, the fetal environment, and childhood environment all may have individual and combined effects to the offspring, leads to several possibilities in interpretation of the findings.

In the present study, the offspring of antenatally depressed mothers with parental severe mental disorder had a high risk of schizophrenia and depression. The risk of schizophrenia was the highest – about 14-fold – in offspring with both an antenatally depressed mother and a father with a history of psychosis. This finding may reflect a gene-environment interaction in the development of mental disorders. Genetic risk is the strongest individual risk factor for schizophrenia (Gottesman, 1991), bipolar disorder (Smoller & Finn, 2003) and depression (Sullivan et al., 2000). Emerging evidence has shown that the gene-environment-interaction often has synergistic or potentiating effects. Caspi and colleagues (Caspi et al., 2005) found that adolescent cannabis exposure is associated with increased risk of schizophreniform disorders among individuals with certain catechol-O-methyltransferase (COMT) genotypes. In that study, cannabis exposure was considered as an environmental risk factor and Val/Val or Val/Met COMT genotype was considered a genetic risk factor for schizophreniform disorder. In a more recent study, maternal antenatal depression was found to associate with negative
emotionality in offspring with a certain genetic profile (Green et al., 2017). A history of severe mental disorder (including psychosis) in one or both parents is indicative of a genetic risk of mental disorders in the offspring, and maternal antenatal depression could be an environmental exposure acting adversely on fetal neurodevelopment and rearing during early childhood. Under this interpretation, maternal depressed mood in pregnancy may act as an additive or potentiating risk factor for subjects with a pre-existing genetic vulnerability for mental disorders. However, parental severe mental disorder may not be only genetic and maternal depressed mood may not be an entirely environmental factor, but both may have genetic and environmental effects on children.

An alternative explanation could be a gene-gene interaction. In the present study, it was rather surprising that the offspring with only parental severe mental disorder did not have statistically significantly elevated risk of depression or schizophrenia (II). The risk of depression and schizophrenia was only elevated among offspring with both maternal antenatal depression and parental severe mental disorder, and offspring with both parents affected by severe mental disorder had higher risk of bipolar disorder than offspring with only one parent affected (II). Still, parental psychosis was associated with elevated risk of schizophrenia and other psychoses in the offspring (I). Familial schizophrenia seems to be more genetically inherited than associated with environmental factors, and the genetics of schizophrenia is highly polygenic (Bigdeli et al., 2016). The genetic aetiology of mental disorders is shown to be partially shared in genome-wide analyses, and a genetic correlation between schizophrenia and bipolar disorder, schizophrenia and major depressive disorder, and between bipolar disorder and major depressive disorder has been shown (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013). In this study, maternal depressed mood may have been a consequence of genetic vulnerability for or a symptom of severe mental disorder, such as depression, bipolar disorder or psychosis, and in association with other parental severe mental disorder, it may have resulted in cumulation of risk alleles for schizophrenia or depression in the offspring.

Apart from genetic factors, parental mental illness, both prenatally and in childhood is a significant environmental risk factor. Antenatal mental illness may affect the developing fetus in various ways (see chapter 2.4), and it may also disturb the mother-child attachment and interaction (Stein et al., 2014). Parents, affected with a severe mental disorder, may not be capable of nurture, and warm and secure interaction with the child, and the most extreme difficulties in the interaction may
lead to neglect or emotional separation of the child. Parental mental illness is also often associated with socioeconomical problems, which increases the offspring risk of mental disorders (Ranning, Munk Laursen, Thorup, Hjorthøj, & Nordentoft, 2016). As in this study, parental mental illness may result in hospital treatment, which causes separation from the child. On the other hand, children of parents with severe mental disorders are often placed outside of home (Ranning et al., 2016; Simoila et al., 2019). Early separation of a child from their parent is associated with elevated risk for mental disorders and criminality (Mäki, Hakko, et al., 2003).

In the present study, the sons of antenatally depressed mothers had an elevated risk of ASPD. This is in line with previous studies, where an elevated risk of conduct problems (Hanington et al., 2012; Koutra et al., 2017), antisocial symptoms in young adulthood (Hay et al., 2010), and criminality (Mäki, Veijola, et al., 2003) have been found in the sons of antenatally depressed mothers. In the present study, there was no opportunity to study paternal personality, but in previous studies, paternal ASPD has been associated with maternal depression (Marmorstein et al., 2004), which could elevate the risk of ASPD in the offspring. The behavioral outcomes in the offspring of antenatally stressed or depressed mothers may also be adaptive: as a response to maternal stress, the male offspring may be more aggressive and have more blunted stress reactions to be able to encounter the environmental dangers (resembling ASPD), whereas the female offspring are more likely to hide and protect their brood, and thus may be more vigilant and sensitive to stress (resembling depression or anxiety; Vivette Glover & Hill, 2012). Maternal antenatal depression is also associated with increased risk of maltreatment of the child (D T Plant et al., 2013), which may be associated with the risk of offspring internalizing and externalizing problems, depression and antisocial behavior may be mediated by maltreatment of the child (Dominic T Plant et al., 2017, 2015).

In the original article IV, the offspring of antenatally depressed mothers were not found to have an elevated risk for BPD, which was contradictory to the hypothesis of the study. The etiology of BPD is multifactorial and varying between subjects, and only a few factors, such as maltreatment and other childhood traumas (Bandelow et al., 2005; Zanarini et al., 1997), are found to individually increase the risk for BPD in the general population. In the present study, the risk of BPD was elevated in the male offspring with severe parental mental disorder. It is likely that maternal antenatal depressed mood per se does not increase the risk for adulthood BPD, but it
may be one factor among other adversities which are involved with the etiology of the disorder.

In this study, many of the potential mediating effects of maternal antenatal depressed mood on the offspring outcomes, such as postnatal depression, attachment, maltreatment of the child or hormonal factors, could not have been studied. Still, maternal smoking during pregnancy (I-III), perinatal complications (I-III), father’s SES (II-III), family type at birth (II-III), or grand multiparity (II) were not found to mediate the potential associations between antenatal depressed mood and offspring outcomes in the present study.

6.5 Strengths and limitations

6.5.1 Strengths

To the author’s knowledge, the NFBC 1966 is the first general population-based birth cohort study where the pregnant mothers’ mood has been evaluated as a possible risk factor for later infant adversities. The author is not aware of any other cohort study where the incidence of schizophrenia, severe mood disorders, ASPD, BPD, and schizotypal and affective traits in the offspring of antenatally depressed mothers have been followed for over 30 years. The subjects were representative, with all cohort members born in the same year and in a geographically defined area.

Data on parental history of severe mental disorders, as well as the offspring diagnoses of schizophrenia and other psychoses, mood disorders, and ASPD and BPD were based on the national register, the Finnish Care Register for Health Care, covering all mental and general hospitals, beds in local health centers and private hospitals nationwide. Because the diagnoses were retrieved from national registers, the attrition rate in studies I-III were small. All NFBC 1966 subjects (offspring) diagnosed with hospital-treated psychoses or mood disorders between 1982 and 1997 were scrutinized, and diagnoses were validated against DSM-III-R criteria, after which they were reevaluated by a professional panel (Moilanen et al., 2003), which increased the diagnostic reliability. Diagnoses during 1998–2009 were based on clinical specialized care discharge diagnoses as defined by the physicians responsible for the treatment. The register data on hospital-treated mental disorders have been found to be relatively reliable (Moilanen et al., 2003; Perälä et al., 2007; Poikolainen, 1983).
The topic of the study is novel; to the author’s knowledge, this is the first report on schizophrenia, bipolar disorder, depression, ASPD, BPD and schizotypal and affective traits in the adult offspring of antenatally depressed mothers, where familial vulnerability for severe mental disorders was taken into account in a population-based sample.

6.5.2 Limitations

There are many limitations in the study. It should be noted that maternal antenatal depressed mood did not necessarily signify a clinical condition, but it was screened by one structured question ‘During this pregnancy, has your mood been ordinary, depressed or very depressed?’, asked by an interviewing nurse during the 24th-28th gestation weeks. In another large general population-based birth cohort study, ALSPAC, with about 12,000 mothers having babies in 1991 and 1992 (Evans et al., 2001), maternal mood during pregnancy was similar (13.9%) as in the NFBC 1966, although it was identified with the Edinburg Postnatal Depression Scale (EPDS) (J L Cox et al., 1987), which does not result in clinical diagnosis, either. In the year 1965, specific screening tools for antenatal depression, such as the EPDS did not exist. The Beck Depression Inventory was developed in 1961, but it was not yet in clinical or scientific use in Finland in 1965-66 (A. T. Beck, 1961). It should also be noticed that one-item-questionnaires have been shown to be valid in screening major depression in the general population (Blozik, Scherer, Lacruz, Ladwig, & KORA study group, 2013).

Depressed mood is a core symptom of depression but may also be a symptom of another clinical condition, such as bipolar disorder or psychosis, which were not identified in the mothers during pregnancy in the present study. The study was also lacking information on parental severe mental disorders during pregnancy and in early childhood, as well as on maternal postnatal mental state. However, information on later hospital-treated maternal depression was available from the offspring’s age of 6 years onward.  

In the NFBC 1966, with over 12 000 live-born babies, the cumulative incidence of ASPD (0.2%) and BPD (0.8%) (III) was rather low compared to previous studies (Glenn, 2013; Leichsenring, 2011; Volkert, Gablonski, & Rabung, 2018). Because of low number subjects, type II statistical error is possible. Among female offspring, there was only four ASPD cases, for it was not possible to conduct statistical tests related to ASPD in daughters of antenatally depressed vs. non-depressed mothers.
The combined effect of maternal antenatal depressed mood and parental severe mental disorder on the risk for ASPD and BPD in the offspring could not be studied because low number of subjects.

In the original article IV, no associations between maternal antenatal depressed mood, parental psychosis and offspring schizotypal and affective traits were found. Of the 8463 cohort members invited, only 59% participated in the 31-year follow-up (Miettunen, 2010). Drop-out analysis showed that cohort members with psychosis participated less actively than those without (Haapea et al., 2008), and it is possible that the scoring in the schizotypal and affective scales was skewed towards lower scores, which may have affected the findings.

The data include only severe hospital-treated mental disorders; hence the author is unsure whether the results of the study may be generalized to milder, outpatient-treated mental disorders. However, subjects with non-hospitalized and hospitalized mental disorders can be supposed not to differ systematically, had they maternal antenatal depression or not.

In this study, launched in 1966, all potential mediating factors between maternal antenatal depression and offspring outcomes, such as mother-child attachment style, maltreatment of the child, marital disharmony, nutritional, substance use, and pharmacological factors, and parental genetics were not available.
7 Conclusions

According to the findings in the present study, maternal antenatal depressed mood is associated with elevated risk of depression in the offspring, and ASPD in male offspring. As documented in previous literature, parental psychosis is associated with elevated risk of psychoses in the offspring (Rasic et al., 2014). Parental severe mental disorder was associated with elevated risk of bipolar disorder in the offspring, especially if both parents were affected. Maternal antenatal depressed mood combined with later parental psychosis, especially paternal psychosis, was associated with highly elevated risk of schizophrenia in the offspring. Maternal antenatal depressed mood combined with parental severe mental disorder was associated with elevated risk of depression and schizophrenia in the offspring, where maternal antenatal depressed mood seems to have a potentiating effect on the genetic risk.

7.1 Clinical Implications

In the present study, the effects of prenatal screening for depression or of interventions on later maternal or offspring outcomes were not studied. The current Finnish Current Care Guidelines does not recommend screening for antenatal depression, but only for postpartum depression (Suomalaisen Lääkärieseuran Duodecimin ja Suomen Psykiatriyhdistys ry:n asettama Työryhmä, 2016). However, the findings in this study, as well as the previous research in this topic, raises the question of whether the efficient prevention and treatment of antenatal depression and parental severe mental disorders could attenuate the risk of mental disorders in the offspring. The frequent health care contacts at the perinatal period provide a good opportunity to identify parental mental disorders.

The prevention of antenatal depression requires efforts in identifying risk factors for antenatal depression in women before or during pregnancy. Psychosocial assessment, such as the Antenatal Psychosocial Health Assessment (ALPHA) or the psychosocial risk assessment model (PRAM) (Priest, Austin, Barnett, & Buist, 2008), could provide an opportunity to screen many of the crucial risk factors, which may also have direct effects on the postnatal outcome (Carroll et al., 2005).

The detection and treatment of antenatal depression is not efficient enough at present time in primary care or in obstetric care (Alder, Fink, Urech, Hösli, & Bitzer, 2011; Ko et al., 2012); only about 50% of women with antenatal depression
get diagnosed, and less than 10% get adequate treatment (E. Q. Cox et al., 2016). The diagnostics and management of antenatal depression is usually handled in the primary care (Muzik & Borovska, 2010), where the general practitioners often lack of education on perinatal psychiatry. Psychotropic medication is the most commonly used treatment option in antenatal depression, usually because psychosocial or psychosocial interventions are not sufficiently available (Ford et al., 2017; Ko et al., 2012). On the other hand, decision making on medication is found to be difficult both for the mothers and the physicians (Ford et al., 2017).

Early recognition of depressive symptoms in primary care by systematically screening depressive symptoms in pregnancy with a valid method, such as the EPDS, have been shown to reduce depressive symptoms from the antenatal to the postnatal period, with a reduction of 2.1-9.1% in depression prevalence (E. O’Connor et al., 2016). Screening of perinatal depression has not been found to cause harm to the women. Still, only the screening cannot be supposed to lead to recovery from depression, but after screening, structured diagnostic and treatment strategies are needed in efficient managing of antenatal or postnatal depression. (Kendig et al., 2017).

According to a recent systematic reviews and a meta-analysis on the interventions in antenatal depression (Nillni, Mehralizade, Mayer, & Milanovic, 2018; Ravesteyn, Lambregtse-van den Berg, Hoogendijk, & Kamperman, 2017; Sockol, 2015, 2018), Cognitive Behavioral Therapy (CBT) and Interpersonal Psychotherapy (ITP) are found to be effective interventions for the prevention in postnatal depression and for treatment of perinatal depression, and the Finnish Current Care Guidelines also prefer psychosocial and psychotherapeutic interventions in the management of antenatal depression (Suomalainen Lääkäriseuran Duodecimin ja Suomen Psykiatriyhdistys ry:n asettama Työryhmä, 2016). To make the psychological interventions more available, CBT-based internet-delivered interventions (Forsell et al., 2017; Loughnan et al., 2019), and text message-delivered support (Fletcher et al., 2018) have been designed with promising reports. The treatment of antenatal depression with CBT, IPT, or body-oriented intervention (massage) is shown to have beneficial effects for parenting and child development (Letourneau, Dennis, Cosic, & Linder, 2017). In a small sample of women (N = 24) treated with CBT or routine care for antenatal depression, the CBT showed a beneficial effect for the children’s development at the age of 2, but not at 5 years of age (Milgrom et al., 2018).
In the meta-analysis by Ravesteyn and colleagues (2017), body-oriented interventions also showed a significant medium effect in the reduction of depressive symptoms, and integrative collaborative care showed long-standing benefits, up to one year postpartum, but it was only studied in one trial (Ravesteyn et al., 2017). Acupuncture also had a significant medium effect, but it was only studied in two trials. Bright light therapy and food supplements were not found to be associated with a decrease of depressive symptoms in the meta-analysis (Ravesteyn et al., 2017). Mindfulness-based interventions may also have some positive short-term effects on the symptoms of perinatal depression, anxiety and stress, but according to the current knowledge, those cannot be recommended as a clinical treatment option for antenatal depression (Lever Taylor, Cavanagh, & Strauss, 2016).

Recently, antidepressants have also been prescribed increasingly during pregnancy, but in the middle of 1960s, when the mothers of the NFBC 1966 cohort members were pregnant, there were far less psychotropic drugs available, and selective serotonin reuptake inhibitors (SSRI) were developed later (Malm, 2012b). Pharmacological treatments in the antenatal period is controversial because of their positive effects on maternal depression and thus indirect potential protective effects for the fetus, but on the other hand, medication may have direct harmful effects to the fetus. Pharmacological treatment of antenatal depression is scarcely studied, and the reliability of the findings is hard to assess, because psychotropic medication is indicated only for pregnant women with moderate to severe depression, and both the medication and the depression may have adverse effects on the fetus. According to recent literature, the SSRI-medication is found to have good efficacy in the treatment of antenatal depression, but it does not outperform other effective treatment options, such as CBT and IPT (Nilni et al., 2018). Antidepressive medication must always be considered first-line drugs in pharmacological treatment of antenatal depression because of their efficacy for depression and low risk for the fetus (Muzik & Borovska, 2010). In the management of severe, drug-resistant depression, electroconvulsive therapy can also be considered (Muzik & Borovska, 2010).

In the management of antenatal depression and other parental mental disorders, the whole family must be taken into account and also the fathers’ mental health should be evaluated. Parents with mental illness should be discussed with about the wellbeing of their children. In Finland, the Let’s Talk About Children intervention is in routine use (Reupert, Maybery, & Kowalenko,
2012; Solantaus & Toikka, 2006), and it has been shown to be an effective intervention for parents with mental illness (Maybery et al., 2019). Multi-professional co-operation between primary and specialized health care, social services, and child protection services is often needed in managing parental mental health problems.

7.2 Implications for further study

Although the NFBC 1966 is a large birth cohort study with over 12,000 subjects, the number of subjects with specialized care diagnosed mental disorder is rather low and taking multiple confounding factors into account decreases these numbers even more. Large birth cohort studies, where maternal antenatal and postnatal mood is screened, and subjects who are systematically reviewed for potential mental disorders are needed to further assess the risk of mental disorders in the offspring of antenatally depressed mothers. Future research should also focus on the mediating and moderating factors between maternal antenatal depression and offspring psychopathology. More research is needed on the effects of screening and different treatments of antenatal depression and other parental severe mental disorders on the outcomes for the whole family. It is likely that the efficient treatment of parental mental disorders requires multi-professional intervention models where familial socioeconomic and other environmental factors are accounted for, in addition to the medical treatment.

The mediating effects of antenatal depression needs further research in many regards. Adoption studies could provide information on the effects of antenatal depression without the postnatal exposures. The biomarkers of maternal antenatal stress have provided promising, but somewhat inconsistent findings, and further research could help to clarify the mechanisms which function between mother and child.

Also, the effects of maternal antenatal depression on the mother’s later life, such as on education, employment, general health, etc., should be studied. These factors may have significant associations with offspring mental health, which could mediate some of the effects of antenatal depression to the child.

It would also be interesting to study maternal preconception factors, such as previous mental illness, stress vulnerability, HPA-axis function, and inflammatory markers, and their associations with antenatal depression and child mental health. The associations of all mental disorders, and not just depression or anxiety, during
pregnancy, both maternal and paternal, and the resulting offspring outcomes should also be studied to develop a wider picture on perinatal psychiatry.
References


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Original articles


Original publications are not included in the electronic version of this dissertation.
1495. Pääkkö, Tero (2018) Predictors of left ventricular hypertrophy, diastolic dysfunction and atrial fibrillation: the roles of adiponectin, ambulatory blood pressure and dietary sodium intake


1500. Leppänen, Joni (2019) The role of hypoxia, innate immunity receptors and stromal response in pancreatic cancer


1503. Varpuluoma, Outi (2019) Drugs, dermatitis herpetiformis and celiac disease as risk factors for bullous pemphigoid in Finland


1505. Lahtinen, Antti (2019) Rehabilitation after hip fracture: Comparison of physical, geriatric and conventional treatment

1506. Alakärppä, Antti (2019) Primary sinonasal surgery and health-related quality of life in adults


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MENTAL HEALTH PROBLEMS IN THE ADULT OFFSPRING OF ANTENATALLY DEPRESSED MOTHERS IN THE NORTHERN FINLAND 1966 BIRTH COHORT; RELATIONSHIP WITH PARENTAL SEVERE MENTAL DISORDER

Tiina Taka-Eilola