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MOOD DISORDERS *and* CONSEQUENCES *of* PHARMACOLOGICAL TREATMENT

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ABSTRACT

Mental health issues are medical problems getting increased attention throughout the world, and depression, only one among several types of mental illnesses, are currently reported as the second leading cause of disability world wide by the World Health Organization. Along this development, increased number of psychiatric diagnoses and increased utilization of medication can be observed. However, whether this increase is because of an actual increase in number of individuals suffering from these disorders, or due to improvements in diagnostics and understanding, or both, is not fully known. What is known, however, is that mental health related suffering is nothing new and can be traced back several thousands of years in human history. Throughout this history, our understanding and view of these disorders that affect our mood and behavior have changed substantially, from being assumed caused by gods or magic, to our modern view of combined environmental and genetic causes. But psychiatry is still a comparatively recent field of medicine and it was not long ago effective drugs targeting these disorders were first introduced. Our understanding of the underlying mechanisms of this suffering is still limited, but recent developments in psychiatric genetics have provided some of the first stable biological underpinnings to mental disorders. In light of these findings, a complicated picture is beginning to take form, in which the etiology appears caused by thousands of genetic factors, but also that a lot of the underlying genetics is shared among the disorders previously thought of as separate.

It is within this setting, where many of the current disorder definitions are starting being questioned and the appreciation of genetics behind these disorder is increasing, the studies within thesis have been conducted.

In **study I**, the potential side effect of manic switching due to antidepressant treatment was investigated in a population sample of 3,240 individuals with bipolar disorder. A within-individual design was used to adjust for otherwise unmeasured genetic confounding, and the results indicated that manic switching was confined to bipolar disorder patients treated with an antidepressant monotherapy, whereas patients treated with an antidepressant in combination with a mood stabilizer rather displayed a reduced risk.

Study II instead focused on depression around the time of pregnancy, perinatal depression, and to what extent genetics explain the variance in this disorder, and to what extent perinatal depression genetically overlap with depression at other time of life. This was studied with a twin design in a sample of twin mothers (N=3,427) that had answered the Edinburgh Postnatal Depression Scale, and with a sibling design in a sample of sisters

(N=580,006) using register data of healthcare contacts. The genetic contribution to, or heritability of, perinatal depression was estimated at 54 and 44% in the twin and sibling designs respectively. Using a bivariate model, a third of the genetic contribution to perinatal depression was found unique for the disorder and not shared with depression at other times of life.

Study III was also related to perinatal depression, but focused on potential side effects of antidepressants. In a sample of 392,029 pregnancies, associations between prenatal SSRI exposure and offspring birth size and gestational age was observed. This was followed by within-family analyses (N=1,007) that adjusted for genetic and familial environmental confounding, where the associations between SSRIs and offspring birth size was attenuated, indicating that these associations were likely due to familial confounding. An association between prenatal SSRI exposure and reduced gestational age was observed in both analyses, and could be either due to a causal effect of the medication, or due to confounding factors that the within-family design could not adjust for.

Perinatal depression was further explored in **study IV**, where patterns of healthcare utilization were studied among both mothers and fathers based on register data. This included 3.6 million parents and 3.5 million pregnancies, and the occurrence of diagnoses for depressive illness, anxiety disorders, and mental illness in general around the time of pregnancy was contrasted to the occurrence of these diagnoses at other times of life. Overall, a reduction in healthcare utilization for all studied disorder types were observed around this time of life, which may indicate barriers to getting a diagnosis during this time of life.

In conclusion, the studies within this thesis demonstrate that genetically informed designs are very useful in epidemiological research. And through the application of these designs with large-scale register data, the studies of this thesis provide enhanced understanding of mental illness in general, and bipolar disorder and perinatal depression in particular.

SAMMANFATTNING PÅ SVENSKA

Psykisk ohälsa är ett medicinskt problem som får allt mer utrymme i vårt samhälle och i världen. Depression, som bara är en utav många olika psykiska sjukdomar, anses i dag av Världshälsoorganisationen WHO vara den näst största orsaken till funktionsnedsättning i hela världen. Med denna utveckling syns en ökning i antal psykiatriska diagnoser och användning av läkemedel. Men huruvida denna ökning beror på en ökning i antal sjuka, eller om det är en ökning som kan härledas till ökad förståelse och bättre diagnostik, eller båda delar, är i dag inte känt. Däremot är det känt att psykiskt lidande inte är något nytt, utan något som kan följas flera tusen år tillbaka i den mänskliga historien. Genom denna historia har vår förståelse och syn på dessa sjukdomar som påverkar humör och beteende förändrats avsevärt, från tron på inverkan av gudar och magi, till dagens moderna uppfattning att psykisk ohälsa beror på miljö och arv i samspel. Men psykiatrin är fortfarande ett relativt ungt område inom medicinen, och det var inte länge sedan det inte fanns några specifika läkemedel mot psykiskt lidande. Vår förståelse kring de underliggande mekanismerna bakom psykiska sjukdomar är fortfarande mycket begränsade, men den senaste tidens utveckling inom den psykiatriska genetiken har försett forskare med de första solida kopplingarna mellan psykiskt lidande och biologi. I ljuset av dessa fynd har en komplicerad bild börjat ta form, där tusentals genetiska faktorer verkar ligga till grund för dessa sjukdomar, och där flertalet psykiska sjukdomar som tidigare ansetts vara skilda nu förefaller ha delad genetik.

Det är i denna kontext, där många av dagens definitioner av psykiska sjukdomar börjat ifrågasättas och där insikterna kring genetikens betydelse för dessa sjukdomar ökar, som studierna i denna avhandling har genomförts.

I **studie I** undersöktes den potentiella bieffekten "manisk switch" - d.v.s. en plötslig övergång från depression till mani eller hypomani - på grund utav antidepressiv medicinering i en grupp bestående utav 3240 individer som lider av bipolär sjukdom. En inom-individs-analys applicerades för att kunna kontrollera för effekter som beror på individens specifika genetik, och resultaten pekade på att manisk switch var begränsad till de individer med bipolär sjukdom som behandlats med antidepressiv medicinering enbart. Bland individer med bipolär sjukdom som även erhållit stämningsstabiliserande medicin observerades istället en minskad risk.

Studie II fokuserade istället på depression kring tiden för graviditet, också kallad perinatal depression, och i vilken utsträckning genetik förklarar orsaken till denna sjukdom, och i vilken utsträckning perinatal depression överlappar genetiskt med depression under annan tid i livet. Detta

studerades i en tvillingstudie bestående utav 3 427 tvillingmödrar genom svar som lämnats på formuläret Edinburgh Postnatal Depression Scale, samt i en syskonstudie bestående utav 580 006 systrar där registerdata på sjukhusbesök istället användes. Ärftligheten, det vill säga i vilken utsträckning genetik bidrar, av perinatal depression estimerades till 54 respektive 44% i tvilling- och syskonstudien var för sig. Dessutom uppskattades en tredjedel av genetiken bakom perinatal depression vara unik för denna sjukdom, och delades inte med depression under annan tid av livet.

Studie III var också relaterad till perinatal depression, men fokuserade på potentiella bieffekter av antidepressiv medicinering. I en studie av 392 029 graviditeter observerades först associationer mellan prenatal SSRI-medicinering och födelsestorlek samt gestationsålder. Detta följdes av en inom-familjs-analys (N=1 007) som kontrollerade för arv och miljö delat mellan två helsyskon. Denna analys fann inte några associationer mellan SSRI och födelsestorlek, vilket tyder på att denna koppling troligtvis berodde på underliggande arv eller miljö, och inte på medicineringen. Däremot observerades en association mellan prenatal SSRI-exponering och lägre gestationsålder i båda analyserna, vilket kan bero på en kausal effekt av SSRI-medicineringen, eller på grund utav andra underliggande faktorer som inom-familjsanalysen inte kunde kontrollera för.

Perinatal depression studerades vidare i **studie IV**, där mönster i sjukvårdsnyttjande studerades hos 3,6 miljoner föräldrar och 3,5 miljoner graviditeter. Förekomsten av depressions-, ångest-, samt generella psykiska diagnoser estimerades under tiden kring graviditet och jämfördes med kringliggande perioder. Överlag observerades en minskning av sjukvårdsanvändande för alla studerade sjukdomstyper, vilket kan innebära att det finns hinder för att få en psykiatrisk diagnos under denna tid i livet.

Sammanfattningsvis ger denna avhandling stöd för att studier som utnyttjar genetisk information är mycket användbara i epidemiologisk forskning. Genom applicering av dessa metoder tillsammans med storskalig registerdata ger studierna i denna avhandling ökad förståelse kring psykiska sjukdomar i allmänhet, och kring bipolär sjukdom och perinatal depression i synnerhet.

LIST OF SCIENTIFIC PAPERS

I. ALEXANDER VIKTORIN, Paul Lichtenstein, Michael E. Thase, Henrik Larsson, Cecilia Lundholm, Patrik K. Magnusson, Mikael Landén. *The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer*. Am J Psychiatry. 2014;171(10):1067-73

II. ALEXANDER VIKTORIN, Samantha Meltzer-Brody, Ralf Kuja-Halkola, Patrick F. Sullivan, Mikael Landén, Paul Lichtenstein, Patrik K. Magnusson. *Heritability of perinatal depression and genetic overlap with non-perinatal depression*. Am J Psychiatry. Epub ahead of print. doi:10.1176/appi.ajp.2015.15010085.

III. ALEXANDER VIKTORIN, Paul Lichtenstein, Cecilia Lundholm, Catarina Almqvist, Brian M. D'Onofrio, Henrik Larsson, Mikael Landén, Patrik K. Magnusson. *Selective serotonin re-uptake inhibitor use during pregnancy: association with offspring birth size and gestational age*. Int J Epidemiol. Submitted.

IV. ALEXANDER VIKTORIN, Samantha Meltzer-Brody, Cecilia Lundholm, Mikael Landén, Paul Lichtenstein, Patrik K. Magnusson. *Occurrence of depression diagnoses around the perinatal period: patterns from a nation-wide study*. Manuscript.

RELATED PUBLICATIONS

♦ Mikael Landén, ALEXANDER VIKTORIN. *Response to Ostacher et al.* Am J Psychiatry 2015;172:586-587.

CONTENTS

LIST OF ABBREVIATIONS

BC	Before Christ (time)
AD	Anno Domini (time)
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Statistical Classification of Diseases
SSRI	Selective serotonin reuptake inhibitor
SNRI	Serotonin–norepinephrine reuptake inhibitor
FDA	Food and Drug Administration
ATC	Anatomical Therapeutic Chemical Classification System
SALTY	Screening Across the Lifespan Twin Study: the Younger
EPDS	Edinburgh Postnatal Depression Scale
SAMS	Small Area Marketing Statistics (SAMS) Register
BMI	Body mass index
HR	Hazard ratio
CI	Confidence interval
TCA	Tri-cyclic antidepressant
LISA	The longitudinal integration database for health insurance and labor market studies

1. INTRODUCTION

1.1 BACKGROUND

Whereas the field of psychiatry is a relatively young medical specialty, its focus, mental illness, is nothing new and it is said that Hippocrates, born in 460 BC in ancient Greece, coined the term melancholia.[1-3] However, the ancient Greeks were not the only culture at the time to distinguish mood disorders and the distress and impairment it entails. Similar states of mood were described in India approximately a hundred years before Hippocrates,[4] and continued to be described throughout history; among isolated Egyptian monks circa 350 AD, in medieval Europe, and into modern times.[5] The cause of this suffering has been attributed to both magic and Gods,[6] and is today generally believed to be due to a combination of environmental and genetic factors. However, in contrast to many somatic disorders, discerning the causal mechanisms behind mental illnesses has proven difficult, and our understanding of the underlying processes is still limited.[7-9]

To better grasp these difficulties, it can be useful to contrast psychiatric disorders with somatic disorders. A somatic disorder such as leukemia - a cancer that affects the bone marrow or blood - can initially present with signs and symptoms including fatigue, fever, and bruises.[10] The illness can further be diagnosed by blood and bone marrow tests that allow blood cells to be counted and the morphology of the cells studied, information that is used to classify the type of leukemia.[10] Clinicians can additionally investigate how organs in the body are affected by the leukemia using an array of imaging techniques based on x-ray, magnetic resonance, computed tomography, or ultrasound.[10] The cancerous cells can also be genotyped, allowing identification of certain mutations that are associated with better or worse outcome,[11] or present targets for specific pharmacological treatment.[11-13]

In comparison, the definition and detection of non-organic psychiatric disorders do not involve any underlying biology, and are instead based on descriptive symptoms related to the mood or behavior of the affected individual.[14,15] This is, at least in part, because these disorders affect the brain, the most complicated and least understood component of the human body, which is protected from the rest of the circulation by a blood-brain barrier. This renders peripheral blood tests unsuitable for studying the blood composition inside the brain, and makes invasive tests potentially very dangerous. While there are numerous methods employed in psychiatric research, including brain imaging, biomarkers, and genetics, none of theses approaches have yet resulted in new ways to diagnose mental illnesses. Behavioral or mood symptomatology is still the golden standard in psychiatric diagnosis, which can prove problematic. This is because a psychiatric diagnosis is dependent on what information the patient provides, and what information a clinician is able to comprehend. And even if this

information exchange is perfect, the symptoms that can be identified are likely shared by many different underlying causes. A similar, although not perfect, example would be the somatic symptom of fever. Fever is useful to distinguish illness, and could even provide an indication of the type of illness. But by itself, this symptom is not very useful if we want to distinguish the exact underlying mechanism behind the illness. The fever could be due to a viral or bacterial infection, related to cancer, or an effect of an autoimmune disorder. In all of these disorders, a general anti-inflammatory treatment could decrease the fever symptoms, but to treat the underlying cause different approaches would need to be employed. In a similar way, an antidepressant medication may reduce the symptoms of depression, but the exact underlying mechanisms behind the depressive symptoms are not yet understood and there could be many different processes causing the mood symptoms defined as depression.

Much research is focused on finding biological underpinnings to mental illness,[7] and psychiatric genetics has so far been one of the most successful approaches.[8,9,16-24] Our genes are stable over life and can be assessed quantitatively by modeling familial structures, or direct by genotyping of DNA from peripheral cells. However, the extent of understanding of mental illness provided by genetic research is still limited and has not yet produced new means of clinical diagnosis. Nevertheless, the research into psychiatric genetics has provided new insights into the underlying structure of mental illness, indicating shared genetic determinants between many, if not all, mental disorders,[8,22,25] and potential heterogeneity in depressive illness.[9] This etiological heterogeneity and genetic overlap suggest that our current disorder definitions are not as distinct as previously thought,[26] and may partially explain the difficulties in finding a suitable medication for many patients. While there are general guidelines for the pharmacological treatment of specific psychiatric disorders with a first line of treatment,[27] the reality is often that the individual response can be very varied and include everything from a good response, to a low response requiring higher dosing, to non-response.[28,29] On top of that there are side effects that also vary between individuals, including for example extrapyramidal side effects, weight gain, and the potentially lethal side effect Stevens-Johnson Syndrome.[30-32]

1.2 DEPRESSION

Depressive illness is mainly diagnosed either based on the criteria presented in the Diagnostic and Statistical Manual of Mental Disorders (DSM),[14] provided by the American Psychiatric Association, or based on the criteria

presented in the International Statistical Classification of Diseases and Related Health Problems (ICD),[15] provided by the World Health Organization. The most recent version of the DSM is the DSM-5 that was introduced in 2013, whereas the most recent version if the ICD is the ICD-10 introduced in 1992, with the 11th version of the ICD planned for 2017.

Although the nomenclature differs between the DSM and ICD, with the DSM using *major depressive episode* to denote a single episode of depression, and *major depressive disorder* to denote a recurrent or chronic illness, and the ICD instead using *depressive episode* and *recurrent depressive disorder*, both systems defines depressive illness as distinct and persistent depressed mood accompanied with somatic and cognitive signs and symptoms, and the criteria used by the DSM and ICD display similar abilities to identify depression.[33,34] In Sweden, both somatic and psychiatric illness is diagnosed according to the ICD system,[35] and the 2015 version of the ICD-10 uses the code F32 for a depressive episode and provides the following definition:

"In typical mild, moderate, or severe depressive episodes, the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often present. The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as loss of interest and pleasurable feelings, waking in the morning several hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Depending upon the number and severity of the symptoms, a depressive episode may be specified as mild, moderate or severe."

Depression is a common illness with a one-year prevalence estimated at 5-7%,[36,37] and is a devastating disorder that is associated with substantial morbidity and mortality,[38-40] and can include suicide.[41] In 1996, using data from 1990, The World Health Organization reported depressive illness as the fourth leading cause of disability world wide,[42] while also projecting depressive illness to become the second leading cause of disability by 2020.[43,44] In 2004, using data from 2000, the World Health Organization reported that depressive illness was now the third leading cause of disability.[45] When the data from 2010 was reported in 2013, depressive illness had become the second leading cause of disability, ten years earlier the predictions made in 1996.[46] The extent of the disability caused by depressive illness further entails a large economic impact on the society. The cost of

depression in Europe, in 2005 alone, has been estimated at 120 billion euro,[47] or approximately 1,110 billion Swedish kronor. Studies of Swedish patients have estimated the cost of depression at 17,000 euro per patient and year.[48-50]

The criteria used to classify depression are broad,[14,15] and the specified symptoms are similar to symptoms displayed by an individual who experience "understandable" intense sadness. Heritability studies of depression have estimated the genetic contribution at around 37%,[51,52] which is considerably lower than for bipolar disorder or schizophrenia at around 70%.[22,53,54] This implies that, quantitatively, environmental factors play a dominant role in the development of depression. Further, whereas multi-national large-scale genome wide association studies of schizophrenia and bipolar disorder have successfully identified several risk loci,[16-19,55] similar efforts with major depressive disorder have so far failed to distinguish any robust findings.[9] The low estimated heritability and lack of findings from genome-wide association studies have been suggested to indicate that depression is a heterogeneous disorder,[9] and that the current definition may cover subtypes of depression that by themselves may have a higher heritability.[51,56,57]

1.2.1 DEPRESSION AROUND THE TIME OF PREGNANCY

The prevalence of depression during the perinatal period, that is either during pregnancy or within a 3 to 12 month postpartum period, has been estimated at around 10-15% among women.[58-61] This is a high figure considering the limited time the perinatal period(s) make up in most women's life and can, like depression in general, present with considerable morbidity, mortality, and costs both for the suffering individual and the society,[58,59,62-65] But whereas depression as a whole has been extensively studied, depressive illness specifically around the time of pregnancy and childbirth has been conspicuously understudied.[66,67] This is manifested by the numerous designations and definitions used in the literature to describe depressive illness during this specific time of life, and the lack of a good distinction. Both the DSM and ICD include *postpartum depression* as a separate category of depression,[14,15] which has made this term the most well recognized one. However, both the DSM-IV and ICD-10 classify postpartum depression as depressive illness with an onset during the puerperium, that is, within four to six weeks after delivery. This is potentially a quite narrow definition considering research have shown that the risk of a psychiatric hospital admission is elevated through 3 months following childbirth,[68,69] and through 5 months for depression in particular.[69] Research has further shown that depression with an antenatal onset, i.e. during pregnancy, is almost as common as postnatal onset depression.[70,71] With the release of the

fifth edition of the DSM, the definition of postpartum depression saw an expansion by including antenatal onset. However, while this modification is important as it acknowledge the pregnancy as a risk period for developing depression, it also risk generating further confusion by including the antenatal time period under a name that specifically implies the time period after childbirth. Another term with increasing use in the literature is *perinatal depression*.[58,64,72-79] The perinatal period includes both the pregnancy (antepartum, or the antenatal period) and a period after childbirth (postpartum, or the postnatal period). However, neither the DSM, nor the ICD, recognizes this term, and the length of the postpartum period included in the perinatal definition varies among studies.[58]

To complicate matters further, there are large discrepancies between prevalence estimates of perinatal depression depending on the identification method used, with estimates based on healthcare utilization generally only being a fraction (0.5-1.6%)[73,80,81] of the estimates based on self-report instruments like the Edinburgh Postnatal Depression Scale (10-15%).[58-60] This opens up for different potential explanations; either the self-report instruments overestimate the problem, or a lot of depression around the time of pregnancy is not being treated. Anxiety disorders, beside depressive illness, has been shown to constitute a substantial problem in the postpartum period.[82,83] Studies have further shown that the Edinburgh Postnatal Depression Scale is detecting, but not distinguishing, anxiety,[83-86] which could potentially explain the higher prevalence of perinatal depression estimated using the Edinburgh Postnatal Depression Scale. However, studies have also revealed a number of barriers to healthcare seeking among pregnant or new mothers, including insufficient understanding of pregnancy related mental issues, acceptance of exaggerated or false information, and concerns of stigma around mental illness.[87,88] It has been shown that few pregnant women fulfilling the criteria for major depressive disorder receive treatment,[89,90] and that treatment received is not adequate.[91] Moreover, studies show that some women oppose further healthcare interaction after an initial screening,[92] and there is an increased discontinuation in antidepressant use and depression care visits during pregnancy.[93] It is therefor likely that the figures based on hospital treatment underestimate the size of the problem.

Moreover, besides being a potentially undertreated cause of distress and impairment during a very vulnerable time of life, perinatal depression has been suggested being a subtype of depression with partially distinct biological underpinnings. Pregnancy and childbirth includes major fluctuations of numerous endogenous substances including, among others, reproductive hormones, oxytocin, cortisol, and prolactin.[94] It has been

hypothesized that abnormal changes in any of these substances may contribute to the development of perinatal depression, but so far results have been inconclusive.[94-96]

1.3 BIPOLAR DISORDER

In contrast to unipolar depression, bipolar disorder, as implied by the name, present with both periods of depressed mood and periods of elevated mood, as well as euthymic (normal) mood, and mixed mood states including both depressed and manic symptoms.[14] The elevated mood can further be categorized into either mania, a state of elevated mood that includes psychotic symptoms, or hypomania if the elevated mood lacks psychotic symptoms.[14,97] In the presence of mania, the bipolar spectrum disorder is defined as bipolar I disorder, whilst in the presence of hypomania and in the absence of mania, the bipolar spectrum disorder is defined as bipolar II disorder.[14,97] The prevalence of bipolar spectrum disorders has been estimated at 2.4%,[98] and it is the sixth-leading cause of disability according to the World Health Organization.[99] Due to the numerous potential manifestations of the disorder, many which are present in other psychiatric disorders, misdiagnosis is not uncommon.[100-103] Without knowledge of a patient's medical history, a treating physician could interpret a manic episode as schizophrenia, or an episode of bipolar depression as unipolar depression. This is further complicated as bipolar disorder is dominated by depression,[97] with episodes of depression being three times more common than episodes of elevated mood.[104-106]

1.4 PHARMACOLOGICAL TREATMENT OF PSYCHIATRIC DISORDERS

The introduction of the typical anti-psychotic drug chlorpromazine in the beginning of the 1950s was a fundamental event in the beginning of the modern pharmacological treatment of psychiatric disorders.[107,108] While amphetamines and opioids had been used for some conditions prior the 1950s, their effectiveness in more severe psychiatric conditions were limited, and the addictive properties was problematic.[109,110] A large number of drugs targeting mental illness was introduced following chlorpromazine, and the pharmacological treatments reshaped psychiatry and drastically reduced, or replaced, the use of therapies including insulin chock therapy, psychosurgery, and hydrotherapy, and was followed by a large reduction in psychiatric inpatient care.[107,111]

1.4.1 PHARMACOLOGICAL TREATMENT OF DEPRESSION

The modern day antidepressants emerged in the late 1950s with the introduction of the first tri-cyclic antidepressant imipramine, which was initially researched in an attempt to develop a more effective version of chlorpromazine.[112-114] Although the term "antidepressant" is well known today, at the time of their introduction, many of these newly discovered drugs targeted against depressive mood was rather described with other names, e.g. *thymoleptic* (imipramine),[115] or *psychic energizer* (iproniazid).[116] Following the tri-cyclic antidepressants came the selective serotonin re-uptake inhibitors (SSRI) that are selective for the serotonergic signaling system of the brain, as opposed to the tricyclic compounds that affect a wide variety of signaling pathways.[117] Fluoxetine, first described in 1974,[118] was the first major SSRI drug and was sold under the brand name Prozac. In comparison to the tri-cyclic antidepressants, the selective serotonin re-uptake inhibitors have fewer side effects and are safer for the patients, which also make them more tolerable.[31,119] A number of other antidepressant drugs have been introduced after the SSRIs, including the selective serotonin-norepinephrine re-uptake inhibitors (SNRI),[120] and bupropion.[121] The medication with antidepressants have seen a large increase over the last decades, with SSRIs making up the largest increase and constitute the most common antidepressant prescribed today.[122-126]

1.4.2 PHARMACOLOGICAL TREATMENT OF DEPRESSION DURING PREGNANCY

Pharmacological treatment of pregnant women is complicated by several factors. In 1957, the German pharmaceutical company Chemie Grünenthal introduced the sedative drug thalidomide that targeted anxiety, insomnia, an nausea.[127] The drug was sold under the name Contergan in Germany, and under the name Neurosedyn in Sweden, and was seen as particularly suitable for pregnant women because of the profile of the effects.[127,128] However, the use of thalidomide led to an international catastrophe due to the extreme side effects of teratogenic deformities in children prenatally exposed to the drug. It has been estimated that over 10,000 children was exposed during the few years the drug was marketed, of which a large portion did not survive.[127,128]Although the thalidomide catastrophe resulted in new stricter laws and directions to protect patients and offspring, it also led the American Food and Drug Administration (FDA) to expand the already existing ban on drug testing in pregnant women to include all "women of childbearing potential",[129] effectively making most women ineligible to participate in clinical trials of new drugs.[129]

Another complicating factor is the inability to use randomized controlled trials. In other groups, randomized controlled trials can be employed to test

the effects of a drug versus a placebo treatment. Studies on prenatal medication exposure instead have to be based on observational data. In this naturalistic setting, where all exposed women have been prescribed a medication due to a specific indication, the treated and non treated individuals will most likely be different in more aspects than the medication per se. For example, having or not having the disorder that led to the medication, which in turn can be affected by a certain genetic makeup or certain environmental exposures. It is possible that a factor underlying the medication fully or partially explains an observed association between a drug and an outcome. See the following sections 1.5, 1.6, and 1.7 for details about confounding, randomized controlled trials, and pharmacoepidemiology.

Today, antidepressant medication during pregnancy is not uncommon, and the prescriptions of SSRIs have increased among pregnant women just like it has increased in the general population.[130-132] But the use is not without controversy as there have been reports of many potential side effects. Studies of mice have reported smaller head size of mice prenatally exposed to SSRIs,[133] and abnormal wiring of the somatosensory cortex and the lateral geniculate nucleus in the brain in serotonin transporter knockout mice.[134] Studies of humans have shown that antidepressants pass the placenta,[135] and a large number of observational studies have reported associations between prenatal SSRI exposure and numerous adverse outcomes, including preterm birth,[136-138] persistent pulmonary hypertension,[139,140] septal heart defects,[141] lower birth weight,[138,142] lower gestational age,[136,142] malformations at birth,[143,144] fetal death,[138] reduced fetal head growth,[145] autism,[146,147] and anxiety.[148] However, with use of observational studies only, it is difficult to disentangle whether these associations are due to the drug per se, or due to other factors correlating with the medication.

1.4.3 PHARMACOLOGICAL TREATMENT OF BIPOLAR DISORDER

Pharmacological treatment of bipolar disorder is complex. The illness present with both elevated and depressed mood, which are generally targeted by different drugs. Mania or hypomania is effectively attenuated with mood stabilizers (lithium, valproic acid, and carbamazepine) or atypical anti-psychotics (quetiapine, lurasidone, and olanzapine).[149-151] However, except for quetiapine and olanzapine, these drugs have limited efficacy in treating bipolar depression. And even though the atypical antipsychotics quetiapine and olanzapine may be effective in attenuating both elevated and depressed mood, their numerous side effects make them less favorable as a long-term treatment option.[32] Instead antidepressants are usually prescribed to treat bipolar depression, and with depression being the most common abnormal mood state in bipolar disorder,[106] it is not surprising that antidepressants

constitute half of all psychotropic medication prescribed to patients suffering from this illness.[152]

But antidepressant treatment in bipolar disorder is also a controversial topic. Firstly, whereas evidence for the efficacy of antidepressants in treating unipolar depression is well documented,[153] this is not the case for bipolar depression and some advocate not using antidepressant drugs at all in bipolar disorder.[154,155] Secondly, already after the introduction of the first antidepressant imipramine in the 1950s, clinicians noted that some patients seemed to switch into a manic or hypomanic state following treatment initiation.[113,114] This treatment emergent mania has since been extensively studied,[156-165] and current guidelines caution against the use of antidepressant drugs in bipolar disorder because it is believed that such treatment increases the risk of a manic episode.[27,166] Guidelines further suggest adding a mood-stabilizer medication in conjunction to the antidepressant treatment if antidepressants have to be used, but whether mood-stabilizers protect against antidepressant induced switch has only previously been explored by a handful studies.[158,167-171]

1.5 CAUSAL INFERENCE AND CONFOUNDING

In epidemiological research, participants are studied in an observational setting. This means that exposures are not assigned randomly by a researcher, but rather follow an underlying non-random naturalistic pattern. An observational study may find an association between the exposure X and the outcome Y, but the association may not be causal. Instead, another factor, U, may underlie both the exposure and the outcome and is then known as a confounder. A somewhat silly example could be an association between ice-cream consumption and drowning accidents that in turn likely is confounded by warm weather that increases the chances of both ice-cream consumption and swimming and thereby drowning.

Other examples of confounding that are exceedingly difficult to adjust for in a standard approach are underlying genetics or previous environmental factors that are complicated to measure. An example is an association between hormone replacement therapy in women and several health benefits,[172] that in turn was shown confounded by an active and health conscious lifestyle - it turns out that women who pursued a healthy lifestyle also pursued the treatment that initially was believed to benefit health, but in reality increased the risk of for example breast cancer.[173,174] This example is important, as it highlights the problems with confounding in general, and the problems with adjusting for potential confounding factors in particular. Most, if not all,

epidemiological studies adjust for measured confounding factors. However, not all confounding factors will be known, leaving a lot of unmeasured confounders unadjusted for. Research has further shown that genes influence behavior and mood and that this is likely done through variation in thousands of genes,[8,9,16,20,21,175-177] It is therefor likely that the observational studies in the example with hormone replacement therapy were confounded by unmeasured genetics or unmeasured individual specific environment that could influence the health interest and thus affect both the willingness to use the medication perceived as healthy, and the outcomes related to better health.

A way to handle confounding from complex underlying factors could be by using a within-individual design that contrasts the studied outcome in a period of non-exposure, with a period of exposure, for example medication, in the same individual. This approach consequently adjusts for underlying unmeasured confounding like genetics. It also adjusts for any environmental factors the individual has been exposed to up until the start of follow up. However, this design has limitations. It may be difficult to adjust for factors that may change over time during the follow up, consequently making studies of long-term exposure and outcomes that are known to increase or decrease over time complicated. In the example of the hormone replacement therapy, it may prove difficult to discern causes from a therapy used over several years, as this exposure have to be contrasted to an equally long untreated period. Over these years, the individual inevitably grows older, which may affect the studied outcomes.

Another approach could be a family or sibling design, an approach that utilize the relatedness between siblings or family members and contrast an outcome in an exposed sibling to an unexposed sibling.[178] Full siblings share on average 50% of their segregating alleles, with the absolute majority sharing between 40-60%.[179] The design will therefor on average adjust for half of the underlying genetics, while offering the possibility to study an exposure that can only occur once, for example a prenatal exposure. However, this design also has limitations, including the inability to adjust for changes in behavior as a consequence of perceived consequences of exposure, and the potential of overestimating an association that is confounded by unshared environmental factors.[180] See chapter 5.6 for more details about these limitations.

1.6 RANDOMIZED CONTROLLED TRIALS

Results from adequately powered randomized controlled trials are commonly held as the most reliable scientific evidence and is referred to as the *golden standard*.[149,181,182] In this setting, a group of individuals are first screened for eligibility to participate in the study and then randomly assigned to either a treatment or control group.[183] Both groups are treated and followed in the same way, with the only difference being that the control group is not receiving the active compound or treatment being studied.[183] A pronounced outcome observed exclusively in the treated group of an adequately sized and randomized study can be assumed caused by the treatment, as both groups are treated in the same way and other potential factors that could influence the outcome will be randomly scattered and can be assumed to affect the two groups equally, thereby reducing or eliminating influence from confounding factors.

However, randomized controlled trials have limitations. Individuals prone to a side-effect may to a larger extent chose not to participate due to previous bad experiences of the studied treatment, consequently underestimating the potential side effects. On the other hand, more severely affected individuals may chose to join the study to a larger extent in hope of a new treatment, but may also be more susceptible to side-effects, consequently overestimating the side effects. Furthermore, this type of study takes a lot of time and involves a lot of people, consequently leading to very high costs.[184,185] This reduces the extent of the study through for example focus on a single treatment, in a specific setting, and with strict eligibility criteria of the participants, thereby limiting the generalizability - or the external validity - of the results.[186,187] Individuals suffering from a mental illness are often treated with multiple drugs, and the narrow setting of a single study may question the results validity in other settings.[187] Furthermore, the narrow eligibility criteria for participation often exclude individuals with a severe disorder, individuals with comorbidity, individuals with drug misuse problems, younger or elderly people, or women of childbearing age.[186] None of these situations are uncommon, particularly not in psychiatry, so even though results from randomized controlled trials have high reliability, the result may be applicable only to a small portion of patients.[187]

1.7 PHARMACOEPIDEMIOLOGY

Pharmacoepidemiology is the study of drug effects, both intended and side effects, in an observational setting using survey data on drug use, or data from a drug prescription register.[188] The latter commonly results in large-

scale datasets that has a number of strengths in comparison to randomized controlled trials. First, the approach is usually much less costly than a randomized controlled trial. The data also includes a lot more individuals, and the data is collected in a naturalistic setting that includes groups that would not be surveyed in randomized controlled trials, like children, the elderly, severely affected patients, and pregnant women.[188] The large scale also allows easier means of studying simultaneous medications, and can provide information on long-term treatment.[189,190] The information may further be used to study patterns of medication prescription and medication dispensation.[191,192]

However, by using observational data, pharmacoepidemiological studies are at the same risk of being confounded like normal epidemiological approaches. Moreover, by studying a particular treatment, pharmacoepidemiological studies may be affected by confounding by indication. That is, the indication that led to the medication might act as a confounder. This could for example be the case if the exposure is treatment with a mood stabilizing medication and the outcome is mania. If the rates of mania in mood stabilizer treated patients are contrasted to untreated patients, an increased level of mania will likely be observed among the treated patients. However, this will typically *not* reflect a mania inducing property of the mood stabilizing medication, but rather the underlying mania the medication was prescribed to treat. It will also likely reflect the fact that patients receiving a treatment in an observational setting are different from patients not receiving treatment, even though both patient groups have the same diagnosis. Another limitation of pharmacoepidemiological approaches is that the exact medication use is unknown, as there is no information on whether reported medication use, or prescribed and dispensed medication, was actually consumed. Instead, these studies have to rely on assumptions of medication use patterns.

2. AIMS

The overarching objective of this thesis was to gain better understanding of the mood disorders *bipolar disorder* and *depression*, and consequences of pharmacological treatment, with a special focus on the perinatal period.

Specifically, the aim of each study was as follows:

Study I: To explore the potential mania inducing properties of antidepressants among individuals with bipolar disorder, either when used alone or when used together with a mood stabilizing medication.

Study II: To estimate the heritability of perinatal depression and the heritability of non-perinatal depression, and to what extent these two definitions of depression overlap genetically.

Study III: To examine associations between maternal selective serotonin re-uptake inhibitor use during pregnancy and birth size related outcomes in the offspring.

Study IV: To investigate the patterns of healthcare utilization for depression in and around the perinatal period.

3. MATERIALS & METHODS

3.1 DATA SOURCES

The studies within this thesis rely on observational data obtained from national Swedish registers. These registers are managed by Swedish government agencies, e.g. the National Board of Health and Welfare (Socialstyrelsen), and Statistics Sweden (Statistiska Centralbyrån), which work together with, and collect data from, healthcare providers, pharmacies, and the Swedish Tax Agency (Skatteverket), among others. Although these national registers can be very comprehensive on their own, linking them together vastly expands the number of exposures and outcomes that can be investigated. A precise linkage can be facilitated through the use of the unique Swedish personal identification number that is provided at birth, or at immigration to the country.[193] On request by researchers, and after approval by an ethics board, and approval by the government agency, or agencies, responsible for the registers, linking of the data can be made. However, this procedure is completed by the governing agencies and when the data from these registers are delivered to research institutions, the unique Swedish personal identification number has been decoded and replaced with a unique sequence number.

Below follows descriptions of each register contributing data to the studies within this thesis.

3.1.1 THE NATIONAL PATIENT REGISTER

The Swedish National Patient Register (National Board of Health and Welfare) covers information on all admissions to inpatient hospital care since 1973, and all admissions to outpatient specialists since 2001.[35] The register, however, does not include information from the Swedish primary care. The register contains admission dates along with the main and secondary discharge diagnosis codes in accordance with the International Classification of Disease (ICD). In Sweden, every admission to hospital care, or healthcare provider visit, results in at least one diagnosis code.

3.1.2 THE SWEDISH PRESCRIBED DRUG REGISTER

The Swedish Prescribed Drug Register (National Board of Health and Welfare) holds information an all prescribed drugs that have been dispensed from a pharmacy in Sweden.[194] The register was initiated in July 2005 and currently represents one of the more recently established nation-wide registers in Sweden. Every entry in the register has, among other variables, a prescription date along with a corresponding dispensation date, the product name of the medication and generic name of the drug together with dose and package size, and a medication code in accordance with the Anatomical Therapeutic Chemical Classification System (ATC). However, the register

does not contain information on prescriptions that has not been dispensed from the pharmacies.

3.1.3 THE SWEDISH MEDICAL BIRTH REGISTER

The Swedish Medical Birth Register (National Board of Health and Welfare) covers 99% of all births since 1973.[195] The National Board of Health and Welfare collects data from antenatal care units, delivery units, and pediatric examinations of the newborn. Data from these different sources are combined into the register and every birth hold a large number of variables that are routinely reported by the health care professionals. These include, among many others, date of birth, gestational age, birth weight, birth length, birth head circumference, and parity.

3.1.4 THE MULTI-GENERATION REGISTER

The Swedish Multi-Generation Register (Statistics Sweden) contains information on first-degree relatives for persons born 1932 and later.[196] As of 2005, the register contained information on 9,371,000 index individuals, of which 82% were Swedish born. At this point, maternal information was available for 97% of the Swedish born, and for 27% of the individuals born outside Sweden. Paternal information was available for 95% of the Swedish born, and for 22% of the individuals born outside Sweden.

3.1.5 THE CAUSE OF DEATH REGISTER

The Cause of Death Register (National Board of Health and Welfare) was initiated 1961, is updated yearly, and provides information on all deaths among Swedish residents, including both Swedish citizens and non-citizens, and deaths occurring both in Sweden and outside Sweden. The register includes the date of death, and cause of death based on diagnosis codes according to the ICD system.[197]

3.1.6 THE TOTAL POPULATION REGISTER

The Total Population Register (Swedish tax Agency) contains information on place of birth, place of residence, marital status, and information on migration.[198]

3.1.7 THE SWEDISH TWIN REGISTRY

The Swedish Twin Registry (Karolinska Institutet) contains almost all Swedish twins born between 1886-1990, and is the largest population-based twin registry in the world [199,200] Information on twin births are provided by the National Board of Health and Welfare, and subsets of twins, or their parents, are approached by the Swedish Twin Registry and invited to participate in studies.

The Screening Across the Lifespan Twin study: the Younger (SALTY)

Twin data used in this thesis project mainly stems from the Screening Across the Lifespan Twin study: the Younger (SALTY). The SALTY study was conducted between 2009-2010 and included 11,372 twins from the Swedish Twin Registry with a median birth year of 1950 of whom 54.3% were female.[201] The SALTY study included an extensive self-report questionnaire that covered many different areas, including perinatal depression through a retrospective version of the Edinburgh Postnatal Depression Scale (EPDS).[58,76,202,203]

3.1.8 LONGITUDINAL INTEGRATION DATABASE FOR HEALTH INSURANCE AND LABOR MARKET STUDIES (LISA)

The longitudinal integration database for health insurance and labor market studies (LISA, Statistics Sweden) contains information on all individuals 16 years of age or above residing in Sweden.[204] The database started in 1990, contains information on education, family income, marital status etc. and is updated the 31st of December each year. Due to being updated once per year, changes between theses dates will not be detected.

3.1.9 SMALL AREA MARKETING STATISTICS (SAMS) REGISTER

Small Area Marketing Statistics (SAMS) Register is a geographical classification system including around 9,200 residential areas in Sweden, provided by Statistics Sweden.[205]

3.2 MEASURES

3.2.1 BIPOLAR DISORDER

The Swedish National Patient Register provides information on healthcare admissions with discharge codes for bipolar disorder according to the ICD system.[35] Due to the complicated nature of bipolar disorder there is a risk of misclassification. However, a validation of the bipolar disorder diagnoses in the National Patient Register by Sellgren and colleagues have resulted in a search algorithm yielding a positive predictive value of 0.93.[206] This algorithm requires at least two bipolar disorder diagnoses (ICD-8 296.00, 296.01, 296.03, 296.88, and 296.99; or ICD-9 296.0, 296.1, 296.3, 296.4, 296.8, and 296.9; or ICD-10 F30 and F31), or one diagnosis of bipolar disorder and one diagnosis of major depressive disorder (unipolar depression) according to ICD-8 296.20 or ICD-9 296.2. Further, this algorithm allows no more than one diagnosis of schizophrenia (ICD-8 295; or ICD-9 295; or ICD-10 F25). This algorithm was used for sensitivity analyses

in study II, while in study I, a modified version of this algorithm was used that 1) did not allow a diagnosis of unipolar depression to be counted towards the required two diagnoses, and 2) did not allow any diagnosis of schizophrenia.

3.2.2 MANIA

The outcome mania was specifically studied in study I, and was defined using hospital discharge diagnosis codes for mania. As the follow-up for study I was between 2005 and 2009 when ICD-9 was no longer used in Sweden, only ICD-10 codes were used (F30.0, F30.1, F30.2, F30.8, F30.9, F31.0, F31.1, and F31.2).

3.2.3 UNIPOLAR DEPRESSION

Similar to bipolar disorder, unipolar depression was defined using healthcare contacts in the National Patient Register with discharge code for unipolar depression (ICD-8 296.00, 296.40, 296.41, 790.20; ICD-9 296.2, 296.3, 296.9, 298.0, 300.4, 309.0, 309.1, and 311; or ICD-10 F32.0, F32.1, F32.2, F32.3, F32.8, F32.9, F33.0, F33.1, F33.2, F33.3, F33.4, F33.8, F33.9, F34.1, and F41.2). At least one admission with a discharge diagnosis for unipolar depression was used to define depression.

3.2.4 PERINATAL DEPRESSION

Using register data

Perinatal depression was defined as at least one admission with a discharge diagnosis for unipolar depression (defined above), within pregnancy or within a six-month postpartum period. Using the birthdate and gestational age provided in the Medical Birth Register, a conception date was calculated by subtracting the gestational age from the birthdate. The pregnancy period was then defined as the time between the conception date and the birthdate, allowing the pregnancy period to be dynamic and better represent the actual time the mother was pregnant. The six-month postpartum period was defined as the period making up the 183 days after childbirth.

Using the Edinburgh Postnatal Depression Scale

A lifetime version of the Edinburgh Postnatal Depression Scale was used to assess perinatal depression among the twin mothers in study II.[76] The Edinburgh Postnatal Depression Scale is the most widely used self-report assessment instrument for depressive illness during pregnancy of after childbirth in the world and has demonstrated good sensitivity and specificity in both depression during pregnancy and after childbirth.[58,202] The lifetime version of the Edinburgh Postnatal Depression Scale comprises the same ten

items used in the original instrument, see Figure 3.1 below, but is modified to assess previously experienced (or lifetime) perinatal depression.[76] A score of twelve or above on the scale is the acknowledged standard cut-off and has been extensively used in the literature.[202,203] Twin mothers neither reporting feeling depressed during the pregnancy, nor during the six-month postpartum period, were classified as non-depressed. The same applied to twin mothers reporting feeling depressed in either period, but getting a total score below 12 on the Edinburgh Postnatal Depression Scale, whereas twin mothers getting a score of 12 or above was classified as depressed. Reporting feeling depressed in either period but failing to complete every item of the Edinburgh Postnatal Depression Scale resulted in exclusion.

Figure 3.1. The ten items of the original Edinburgh Postnatal Depression Scale.

1. I have been able to laugh and see the funny side of things.
   □ As much as I always could
   □ Not quite so much now
   □ Definitely not so much now
   □ Not at all

2. I have looked forward with enjoyment to things.
   □ As much as I ever did
   □ Rather less than I used to
   □ Definitely less than I used to
   □ Hardly at all

3. I have blamed myself unnecessarily when things went wrong.
   □ Yes, most of the time
   □ Yes, some of the time
   □ Not very often
   □ No, never

4. I have been anxious or worried for no good reason.
   □ No, not at all
   □ Hardly ever
   □ Yes, sometimes
   □ Yes, very often

5. I have felt scared or panicky for not very good reason.
   □ Yes, quite a lot
   □ Yes, sometimes
   □ No, not much
   □ No, not at all

6. Things have been getting on top of me.
   □ Yes, most of the time I haven't been able to cope at all
   □ Yes, sometimes I haven't been coping as well as usual
   □ No, most of the time I have coped quite well
   □ No, I have been coping as well as ever

7. I have been so unhappy that I have had difficulty sleeping.
   □ Yes, most of the time
   □ Yes, sometimes
   □ Not very often
   □ No, not at all

8. I have felt sad or miserable.
   □ Yes, most of the time
   □ Yes, quite often
   □ Not very often
   □ No, not at all

9. I have been so unhappy that I have been crying.
   □ Yes, most of the time
   □ Yes, quite often
   □ Only occasionally
   □ No, never

10. The thought of harming myself has occurred to me.
    □ Yes, quite often
    □ Sometimes
    □ Hardly ever
    □ Never

Antenatal and postnatal depression

At least one hospital admission with a discharge diagnosis for unipolar depression within the pregnancy was defined as antenatal depression. Postnatal depression was defined as at least one hospital admission with a discharge diagnosis for unipolar depression within a twelve-month postpartum period. The postpartum time-window was expanded, from the

six months used in the definition of perinatal depression, to twelve months to allow inclusion of enough cases to allow heritability estimation in study II.

3.2.5 ANXIETY DISORDERS

Anxiety disorders were defined as at least one healthcare contact with the primary care, outpatient specialists, or an admissions to inpatient care with a discharge diagnosis code for an anxiety disorder according to any of the following codes: ICD-8 300, except 300.4; ICD-9 300, except 300.9; or ICD-10 F40, F41, F42, F44, F45, or F48.

3.2.6 PHARMACOLOGICAL TREATMENT

Medication prescriptions and dispensations were identified from the Swedish Prescribed Drug Register,[194] using the drug ATC codes and the dispensation dates from the pharmacies. In study I, a single dispensation of an antidepressant drug was used to define antidepressant medication. In the same study, mood stabilizer use was defined as at least two dispensations of lithium, valproic acid, or lamotrigine, over a certain period. See chapter 4.1 for details. In study III, medication with an SSRI was defined as at least two dispensations of an SSRI drug during pregnancy, or around the time of pregnancy. See chapter 4.3 for details. Therefor, the definition of antidepressant medication was different between study I, that only required one dispensation, and study III that required at least two dispensations. Reasons and implications of this difference is discussed in more detail in chapter 5.2

3.2.7 OFFSPRING BIRTH OUTCOMES

The birth data on gestational age in days, birth length in centimeters, birth weight in grams, and birth head circumference in centimeters, were all obtained from the Medical Birth Register. Preterm birth is defined as childbirth within the first 37 weeks of gestation,[207] and this cutoff was used to further dichotomize gestational age into preterm birth.

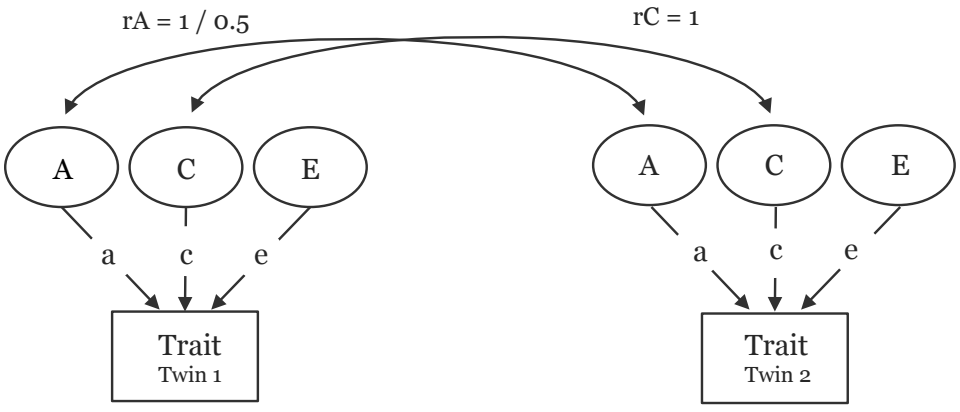
A deviation in gestational age will naturally affect any of the birth size variables, as a child born earlier has had less time to develop before birth. To handle this, the birth size outcomes were standardized by gestational age by using the mean and standard deviation among children born within the same gestational week. The resulting standardized birth size outcomes do therefor not represent the exact value, but rather the deviation from the normal at a specific gestational week.

3.3 QUANTITATIVE GENETICS

The classical twin model

The classical twin model can be used to estimate the heritability of a trait and rely on the differing genetic within pair similarity between monozygotic twins and dizygotic twins. Monozygotic - or identical twins - share all of their genes, whereas dizygotic twins share on average half of their segregating genes. In other words, dizygotic twins, just like other siblings, may be more or less similar genetically due to the stochastic nature of segregation and recombination. However, the model assumes that if a large enough group of siblings were tested, the average percentage of segregating genes would be 50%, which has also been experimentally confirmed.[179] The model further relies on the assumption that both types of twins share environment to similar extent, and that there is no assortative mating. If genes influence a trait, there will be more pronounced twin similarity within monozygotic than within dizygotic pairs. By modeling twin covariance structures in monozygotic and dizygotic pairs, the variation in a phenotype is decomposed into additive genetics (A) - or narrow sense heritability, shared environment (C), and non-shared environment (E), where the latter captures remaining measurement error. This is also referred to as an ACE model. See Figure 3.2.

Figure 3.2. Path diagram of the classical twin model*



* The variance in the trait of each twin is explained by the variance components additive genetics (A), shared environment (C), and non-shared environment (E). The magnitude of the associations between the variance components and the trait can be given as standardized regression coefficients (a, c, and e). Monozygotic twins are assumed to share all their genes, whereas dizygotic twins are assumed to share on average half of their segregating alleles. Both monozygotic and dizygotic twins are assumed to share environment to similar extent.

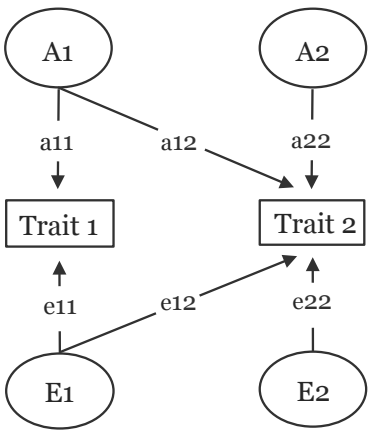
Sibling model

In a similar way, the genetic and environmental relationship between full-siblings and half-siblings can also be used to estimated the variance due to genetic or environmental factors. In a sibling model, monozygotic and dizygotic twins are assumed to share 100% and 50% of their additive genetic factors, whereas the corresponding values are 50% for full siblings, and 25% for half siblings. The shared environment is assumed to be completely shared by all sibling types except by paternal half siblings, that instead is assumed unshared because Swedish half siblings are much more likely to live with their mother.[208]

Multivariate models

Estimating the heritability using these models can be done for a single trait, i.e. a univariate model, or for multiple traits, i.e. multivariate models. A bivariate model is a multivariate model using two traits, and can be used to account for genetic and environmental overlap between two traits. One of many multivariate parameterization techniques is the Cholesky decomposition approach that enables the estimation of the phenotypic correlations between traits, as well as the genetic and environmental contributions to the correlations.[209] See Figure 3.3.

Figure 3.3. Path diagram of a Cholesky decomposition*



* The example only includes A and E factors. The variance in trait 2 is explained by additive genetics that also explain trait 1 (A1), and additive genetics that is unique for trait 2. The magnitude of the contribution is given by a11, a12, and a22. The same applies for non-shared environment (E1 and E2).

4. STUDY DESIGNS

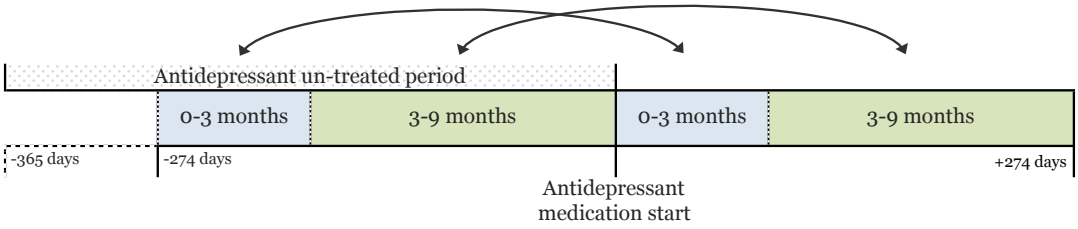
4.1 STUDY I

We identified individuals with bipolar disorder in the National Patient Register using a validated algorithm,[206] and linked these individuals to the Swedish Prescribed Drug Register to identify incidences of dispensed prescriptions of antidepressant drugs (SSRIs, SNRIs, tricyclic- and tetracyclic antidepressants, and bupropion), and mood stabilizing drugs (lithium, valproate semisodium, and lamotrigine). To be included, we required an individual with bipolar disorder to have at least one prescription and dispensation of an antidepressant drug without any dispenses during the preceding year, consequently securing that this dispense signified the start of a treatment period.

Antidepressant medication was the main exposure, and patients were stratified based on the simultaneous medication with mood stabilizers. To be categorized as a minimally adequate course of treatment with a mood stabilizer, an individual with bipolar disorder had to have dispensed a mood stabilizing drug at least two times in the year preceding the antidepressant treatment, of which at least one had to have been dispensed between 4 and 12 months prior the antidepressant treatment start. To be categorized as not using a mood stabilizer, an individual with bipolar disorder was required not have any dispenses of mood stabilizers in the year preceding the antidepressant treatment start. If an individual in the antidepressant monotherapy group was prescribed a mood stabilizer, the follow-up was censored at the time of prescription. The occurrence of mania among the patients was obtained using discharge diagnosis codes for mania from the National Patient Register during the follow up from July 2005 through 2009.

The association between antidepressant medications and the outcome mania were estimated by cox proportional hazards regression analyses where all patients serve as their own control, i.e. a within-individual model, thereby reducing confounding by differences between patients in genetic makeup, severity of the disorder, and environmental factors up until the start of follow up. We compared the individuals during, 1) a 9-month time period prior the treatment start, with 2) a 9-month time period following treatment initiation. See Figure 4.1. We accounted for deaths and migrations, and if the patient died, emigrated, or was diagnosed with schizophrenia during the second (treated) period, the follow up was censored at this time. To allow for assessment of both acute and long-term effects, interaction terms with split follow-up time (0-3 months, 3-9 months) was included in the statistical model. In a second analysis, we added mood stabilizer medication as an additional interaction term to establish differences depending on simultaneous mood stabilizer use.

Figure 4.1. Design of Study I*



* The design permits within-individual comparisons of mania after initiation of an antidepressant treatment with a preceding non-treatment period. The follow-up time is divided into 0–3 months and 3–9 months to assess acute (switch) effects and longer-term effects.

4.2 STUDY II

Classical twin study

We initially identified twin mothers who reported having given birth to a living child, and who completed the lifetime Edinburgh Postnatal Depression Scale in the Screening Across the Lifespan Twin study: the Younger (SALTY). Mood symptoms both during pregnancy and within six months postpartum were assessed using the lifetime version of the Edinburgh Postnatal Depression Scale, and a score of 12 or above was used to define a binary outcome of perinatal depression. The variance in perinatal depression due to genetic or environmental factors was estimated using the classical twin methodology and a univariate model. Since shared environment, the C component, was found to be statistically insignificant, an AE model where C was fixed at zero was fitted instead of an ACE model.

Sibling design

A population-based sample from Swedish national register data was further included to assess variance in perinatal depression and non-perinatal depression due to genetic and environmental factors in a larger and more generalizable setting. The sample included all parous women who had given birth to their first child after 1973, and fulfilled the criteria of being born in Sweden, not having emigrated and moved back to Sweden more than once, and had to have at least one sister fulfilling the same criteria. A design that included up to four full or half-siblings per nuclear family was used. The sample included monozygotic and dizygotic twins, full siblings, and maternal and paternal half-siblings. Depression was assessed using treatment contacts for depression. The conception date was calculated using the birthdate of the child and gestational age at delivery, both retrieved from the Medical Birth Register, and the perinatal period was defined as any point from estimated

date of conception through six-months postnatally. Perinatal depression was further defined as at least one inpatient or outpatient treatment contact for depression according to the above listed diagnosis codes within a perinatal period, whereas non-perinatal depression was defined as depression at any other time of life. We further separated perinatal period into an antenatal period covering the pregnancy, and a postnatal period of 12 months to allow heritability estimation of these separate periods.

The relative importance of genetic and environmental effects was estimated in up to four female siblings simultaneously in family clusters. The family clusters included siblings who shared at least one parent, permitting both full and half-siblings within a single family. No known sibling relations existed between clusters and the individual sisters were not included in more than one cluster. If individuals were belonging to half-sibships in more than one family, only the largest family was included to avoid duplicate entries. Any family consisting of more than four individuals was reduced to four individuals through random selection.

Similarly as in the classical twin design, monozygotic and dizygotic twins were assumed to share 100% and 50% of their additive genetic factors, and the corresponding values were 50% for full siblings, and 25% for half siblings. The shared environment was modeled to be completely shared by all sibling types except paternal half siblings, were it was assumed unshared because Swedish half siblings are much more likely to live with their mother.[208] Individual environmental factors were assumed unique to each individual. These assumptions formed the basis on which we could determine the expected correlation structures for each specific type of family cluster depending on the sibling types included. We fitted univariate models where the variance in each disease was modeled separately to be due to additive genetics, shared environment, and non-shared environment. Similar to the twin model, shared environment in perinatal depression, or the C component, was found statistically insignificant whereby an AE model instead was fitted where the C component was fixed at zero. We further fit bivariate models where the variance and covariance in each trait were simultaneously modeled to be due to additive genetics, shared environment, and non-shared environment. A Cholesky decomposition approach was used to estimate how much of the variance in one disorder that could be attributed to each of the factors in common with the other disorder, and factors unique to perinatal depression.[209] As this was modeled in a regression framework, we adjusted the prevalences for whether the family included half-siblings as well as for birth year (both linear and squared), and further adjusted non-perinatal depression for time at risk (linear and squared), and perinatal depression for number of offspring.

4.3 STUDY III

We identified live and non-twin childbirths from April 1st 2006 to the end of 2009 from the Swedish Medical Birth Register. The register contains the birthdate and the gestational age, and this information was used to estimate the conception date. The cohort was further linked to the Multi-Generation Register to create a within-family sub-sample through identification of both parents of each child, consequently allowing identification of full-sibling relationships. To allow informative within-family comparisons, the full-siblings had to be discordant for the SSRI exposure.

Exposures

Treatment with SSRIs was determined by linking the cohort to the Swedish Prescribed Drug Register and allowed identification of all Swedish prescribed and dispensed prescription drugs since July 1st 2005. Using the Anatomical Therapeutic Chemical Classification System (ATC), we identified dispensations of SSRI medication around the time of pregnancy. A dichotomous exposure variable was created based on SSRI dispensation patterns: 1: no dispensations from three weeks before pregnancy until the childbirth (no SSRI exposure), and 2: more than one dispensation between conception and childbirth, or one dispensation within the pregnancy period and at least one more dispensation within 6 months before or after the dispensation during pregnancy (SSRI exposure). Depression was identified in the National Patient Register that provides information on Swedish psychiatric specialist inpatient care and outpatient care. Depression was defined as at least one treatment contact for depression between conception and delivery. A categorical exposure variable was produced based on SSRI treatment and hospital care for depression (0: No SSRI exposure, and no hospital care for depression during pregnancy. 1: SSRI exposure. 2: At least one treatment contact for depression during pregnancy, and no SSRI medication).

Outcomes

We used information from the Medical Birth Register to create the outcome variables studied. This included gestational age at birth (days) and preterm birth (gestational age at birth below 259 days) calculated through standardized ultrasound measurements at pregnancy week 16-18, birth weight (grams), birth length (centimeter), and birth head circumference (centimeter). Since there is a strong correlation between birth size and the gestational age at birth, the growth outcomes were standardized by gestational age at birth using the mean and standard deviation of children in the cohort born within the same gestational week. The standardized values of birth weight displayed a correlation of 0.98 with a previous method based on

ultrasound measurements at different gestational ages during pregnancy in healthy children.[36]

We adjusted the analyses for factors that may confound the associations. The body mass index (BMI) of the mother was calculated (weight in kilograms divided by height in meters squared) based on weight and height measured at the first antenatal care visit and provided by the Medical Birth Register, and was divided into four categories (<18.5, 18.5-25, 25-30, >30). The height of the mother was also used as a separate covariate. The birth order was included as a covariate since there may be systematical differences for using SSRI depending on the mother's parity at the specific pregnancy. Previous psychiatric history was established using any hospital contact with a psychiatric diagnosis from the National Patient Register prior the specific childbirth using ICD 7-10 revisions. The mother's age at delivery (years), and smoking status (1: no smoking. 2: 1-9 cigarettes per day. 3: >9 cigarettes per day) at first antenatal care visit, was obtained from the Medical Birth Register. The highest completed education (1: compulsory school. 2: upper secondary school. 3: post secondary education less than three years. 4: university three years or more) at the time of delivery was obtained by linking the subjects to the Swedish longitudinal integration database for health insurance and labour market studies.

In the full cohort, the association between prenatal exposure of SSRI treatment, or depression without SSRI treatment, and the continuous variables birth weight, birth length, birth head circumference, and gestational age at birth were estimated by linear regression analyses, while the binary outcome preterm birth was analyzed by logistic regression. Children without SSRI or depression exposure was used as the reference group and the analyses were adjusted for all the covariates. Robust standard errors were used, as several children from the same mother were included in the analysis. The within-family analyses were done by estimating models with a fixed effects regression estimator (STATA xtreg statement, within mother) for continuous variables and conditional logistic regression for preterm birth. This design allows automatic adjustments for all covariates that did not change between the births, consequently adjusting for a wide range of unmeasured confounding factors that are shared within the family. In these analyses we included all families with at least two siblings discordant for SSRI exposure, but if more than two siblings were identified they were also included. The children not exposed to depression or SSRI was used as the reference group.

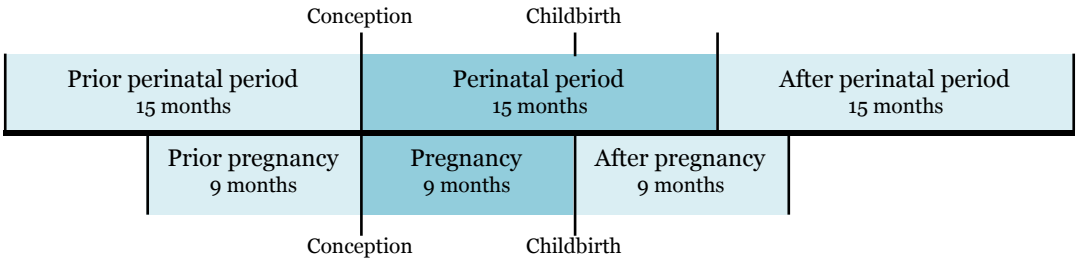
4.4 STUDY IV

We established a nation-wide cohort of all mothers and childbirths over a 37-year period in Sweden using the Medical Birth Register. Fathers are not included in the Medical Birth Register, but were identified by linking the cohort to the Multi-generation Register. Primary care data was only available for Stockholm County, and only covered a six-year period. Therefor, a sub-sample of Stockholm County residents was created by linking the full cohort with the Small Area Marketing Statistics (SAMS) register that contain annual information on residential area. Only individuals living in Stockholm County throughout the six-year period was included to reduce the risk of misclassification.

All individuals in the cohort, including both mothers and fathers, were linked to the National Patient Register, allowing identification of healthcare contacts. At least one treatment contact with a diagnosis code for depression, anxiety disorders, or any psychiatric disorder was used.

Patterns of healthcare around the perinatal period, and compared to other periods of life, were studied using two approaches. First, the occurrence during a period (pregnancy, or the whole perinatal period) was contrasted to the occurrence during adjacent periods before and after of equal length as the period compared. If an adjacent period overlapped with the period belonging to a sibling, the period was not used. See Figure 4.2.

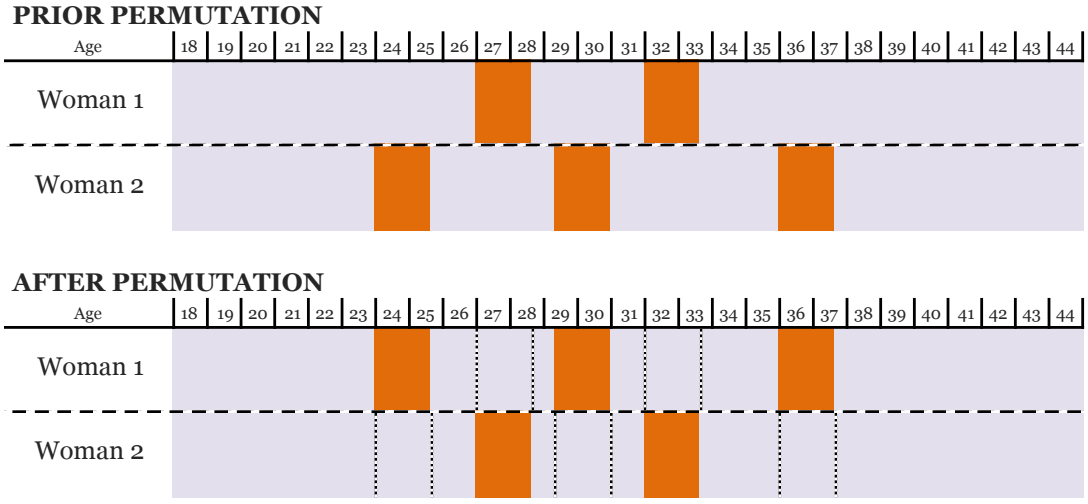
Figure 4.2. Comparisons of adjacent periods in Study IV*



* The occurrence during a period was compared to adjacent periods of equal length before and after. This was done for the pregnancy, which was contrasted to an equally long period prior conception, and after childbirth, and for the whole perinatal period, which was contrasted to a period equally long as the whole perinatal period prior conception, and after the perinatal period - thus starting six months postpartum. The given 15 and 9 months in this figure is an approximate and could vary between individual pregnancies.

A second approach was applied to avoid the inherent problem of potential influences by the fixed calendar time order of adjacent periods before and after. This approach was used to study the whole perinatal period only, and each subject was grouped with the other subjects in the cohort matched on birth year and sex, and the perinatal period(s) belonging to each subject were permutated, i.e. randomly swapped between subjects. This provided each parent the perinatal time period(s) belonging to an age and sex matched, but otherwise randomly selected parent. These permuted periods covered time-periods at random, but as opposed to simply providing each parent randomized periods, the permuted periods originate from another individual and represent the time of life were other individuals born the same year would have children. Furthermore, by maintaining the natural patterns of childbirth, the permuted periods represent a biologically possible distribution, as opposed to randomized periods that could overlap in biologically impossible ways. See Figure 4.3. Using this procedure, the occurrence of diagnoses within the perinatal period(s) could be contrasted to that of non-perinatal period(s) in the same person, as opposed to using a control group that could have a totally different liability. Differences in occurrences were described descriptively, and tested using logistic regression with robust standard errors clustered on the parent (adjacent periods), by chi-squared tests (permuted periods).

Figure 4.3. Example of permutation of perinatal periods*



* Woman 1, born 1955, has been pregnant two times: the first time at age 27 and the second time at age 32. After permutation, she has randomly been assigned the perinatal periods of woman 2. Woman 2 is also born 1955 but has been pregnant three times, at age 24, 29, and 36. This gives woman 1 three perinatal periods, or permuted periods, originally belonging to woman 2, and none of these overlap with her original perinatal periods. However, they are still within the age range where most women born that year get pregnant.

5. RESULTS AND DISCUSSION

5.1 STUDY I RESULTS

We identified 31,916 individuals that met our criteria for bipolar disorder, where 22,339 individuals (70%) had an antidepressant drug dispensed between the 1st of July 2005 and the 31st of December 2009. Among these subjects, 3,240 individuals passed the criteria for initiating an antidepressant treatment during the follow up. The mean age of the included individuals was 52 years and 61% were women.

Table 5.1. Characteristics of the patients at baseline (n=3,240).

Characteristic	N	%
Female	1,270	60.8
Living in a metropolitan area	1,555	48.1
Civil status		
Unmarried	1,222	38.2
Married	945	29.5
Divorced	873	27.2
Widowed	163	5.1
Employed	1,068	33.3
In school	172	5.4
Age group		
< 25 years	197	6.1
25-39 years	651	20.1
> 39 years	2,384	73.8

5.1.1 ANTIDEPRESSANTS AND THE RISK OF MANIA

We initially analyzed the full cohort of 3,240 bipolar disorder patients, placing the patients treated on an antidepressant monotherapy and those on a combined therapy of an antidepressant and a mood stabilizer together. This revealed no increased risk of mania within the first three months of treatment (the hazard ratio [HR] for the 0- to 3-month period was 0.91, 95% confidence interval [CI] 0.69 - 1.21; non-significant). For the long-term period, a decreased risk of mania was observed (HR 0.68, 95% CI 0.50-0.92; p=0.01).

5.1.2 MOOD STABILIZER TREATMENT

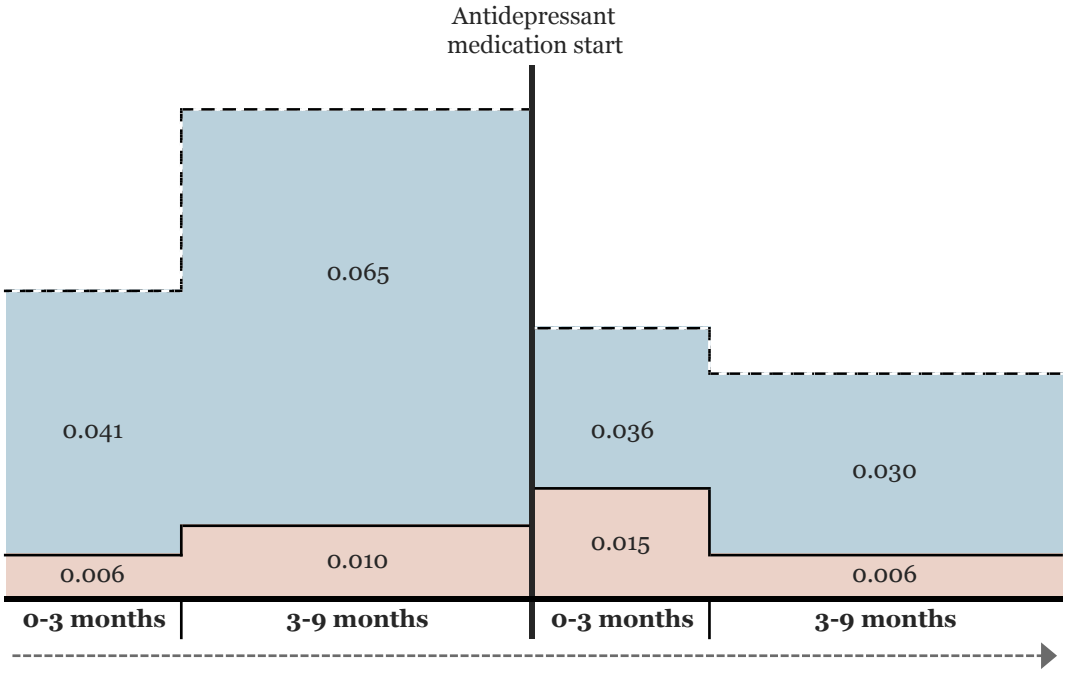
Next, we separated out the 1,117 patients in the full cohort that had received an antidepressant monotherapy (34.5%). In this sub-sample the risk of mania was significantly increased within the first three months of treatment (HR 2.83, 95% CI 1.12-7.19, p=0.028), but not in the long-term period (HR 0.71, 95% CI 0.23-2.26, p=0.57).

Among the remaining patients, 1,641 (48%) had received a mood stabilizer in conjunction with the antidepressant according to our criteria. Contrary to the monotherapy treated patients, these patients did not display an increased

risk of mania within the first three months of treatment (HR 0.79, 95% CI 0.54-1.15, p=0.214), and a decreased risk of mania in the long-term period (HR 0.63, 95% CI 0.42-0.93, p=0.020).

We also observed differences in mania rates, i.e. number of mania events divided by number of individuals in the specific group, between the separated groups. The antidepressant monotherapy treated patients had lower rates altogether; without antidepressant: 0.006 and 0.010 in the 0-3 months and 3-9 months respectively; with antidepressant: 0.015 and 0.006 in the 0-3 months and 3-9 months respectively, while the patients on a combined treatment of an antidepressant and a mood stabilizer displayed higher rates; without antidepressant: 0.041 and 0.065 in the 0-3 months and 3-9 months respectively; with antidepressant: 0.036 and 0.030 in the 0-3 months and 3-9 months respectively. See Figure 5.1.

Figure 5.1. Rates of mania among individuals with bipolar disorder*



* Mania rate is calculated for each group by dividing no. of mania diagnoses by no. of patients in the specified group. Patients treated with an antidepressant monotherapy is represented by the lower part under a full line, and the patients with an antidepressant in conjunction with a mood stabilizing medication is represented by the upper and lower part combined under a dotted line. Here, all mania diagnoses are considered, in contrast to the COX regression analysis where only the first diagnosis in each period is considered. The COX regression further considers time to event in the estimation of the hazard ratio, which is not described by this figure.

Table 5.2. Specific antidepressants dispensed[a]

	Full sample (N=3,240)		Antidepressant monotherapy group (N=1,117)		Antidepressant + mood stabilizer group (N=1,641)	
Name	N	%	N	%	N	**%**
Citalopram	519	18.8	244	21.8	275	16.8
Sertraline	456	16.5	184	16.5	272	16.6
Mirtazapine	444	16.1	199	17.8	245	14.9
Escitalopram	358	13.0	104	9.3	254	15.5
Venlafaxine	189	6.9	76	6.8	113	6.9
Duloxetine	176	6.4	69	6.2	107	6.5
Fluoxetine	158	5.7	59	5.3	99	6.0
Amitriptyline	140	5.1	65	5.8	75	4.6
Bupropion	140	5.1	43	3.9	97	5.9
Paroxetine	66	2.4	31	2.8	35	2.1
Mianserin	50	1.8	12	1.1	38	2.3
Clomipramine	46	1.7	20	1.8	26	1.6
Nortriptyline	7	0.3	4	0.4	3	0.2
Maprotiline	4	0.2	4	0.4	0	0.0
Imipramine	2	0.1	0	0.0	2	0.1
Trimipramine	2	0.1	2	0.2	0	0.0
Fluvoxamine	1	0.05	1	0.1	0	0.0

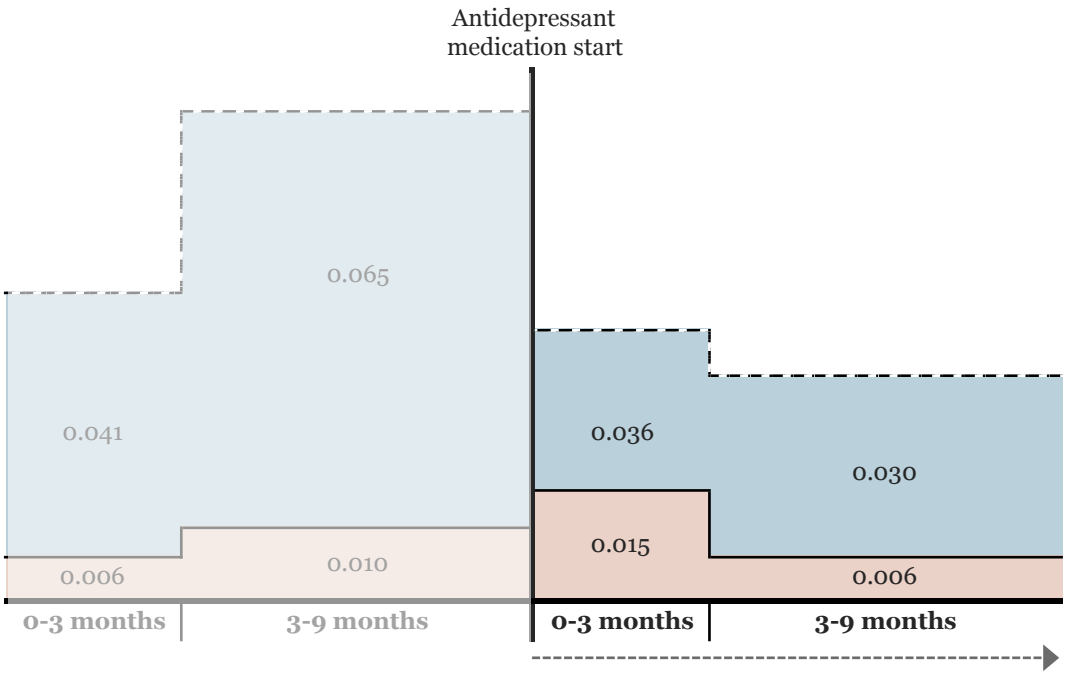
[a] The specific antidepressants and the number and percent of individuals with the specific antidepressant dispensed at the start of the treatment period. Due to strict inclusion criteria to classify patients as being on a concurrent mood stabilizer treatment or not, 482 patients from the full sample with ambiguous mood stabilizer use were not classified as either on monotherapy, nor concurrent mood stabilizer treatment.

5.2 DISCUSSION OF STUDY I

The results from this study suggests that antidepressant induced switching may be confined to patients on an antidepressant monotherapy. Patients on a concomitant mood stabilizing treatment instead displayed a decreased rate of mania after antidepressant medication. By surveying the overall rate of mania in these two groups, we observed more mania among the mood stabilizer treated patients overall. Nonetheless, we observed no *increase* in mania occurrence after the antidepressant medication start in this particular group, even though this patient group clearly exhibited a higher occurrence of mania. This is in line with many previous studies that have found an association between antidepressant monotherapy and manic switching,[156,158,160-162,210] and lends support to recent recommendations that caution against the use of an antidepressant monotherapy in bipolar disorder patients.[27,166] The study also demonstrate that antidepressant medication is common among Swedish bipolar disorder patients, with 70% of all identified patients nation-wide having received an antidepressant medication anytime during the total 4.5 years of follow up. Furthermore, half of these received an antidepressant alone and not in combination with a mood stabilizing treatment.

The study also demonstrates that the underlying differences between patients with the same diagnosis but on different medication can be pronounced. See Figure 5.1. This is important, as it demonstrate that a pharmacoepidemiological approach that does not take the disorder history into account may risk drawing incorrect conclusions. If we would only survey the occurrence of mania after the antidepressant medication initiation, we would end up observing more mania among the patients being treated with a mood stabilizer in combination with the antidepressants, as compared to the patients on an antidepressant monotherapy. See Figure 5.2 below. However, this is a classic case of confounding by indication, where the patients on the double therapy are being treated with a mood stabilizer medication just because they likely suffer from more mania overall. This may have been the case in a big meta-analysis by Tondo et al. where patients on a mood stabilizing treatment were found to have equally or more mania than patients not treated with a mood stabilizer.[211] By allowing our study to compare the rate of mania in periods prior the antidepressant treatment start with periods after the initiation, we expand our view and allow the model to take the disorder history into account. Moreover, by doing this within-individual framework, we further take individual-specific variation into account and automatically adjust for several otherwise unmeasured confounding factors.

Figure 5.2. Rates of mania among individuals with bipolar disorder*



* If only the time after medication start is considered, one may conclude that mania is more common among mood stabilizer treated individuals. However, in an observational setting individuals with a mood stabilizer treatment is likely more prone to suffer from elevated mood. If a preceeding period is taken into account, it is apparent that the mood stabilizer treated group has overall more mania, and that mania is reduced after antidepressant treatment initiation.

Switching in bipolar disorder is a controversial topic and these findings were not received without some debate. Ostacher et al. sent a letter to the editor of the American Journal of Psychiatry, questioning a number of aspects of the study and the reported observations.[212] We were allowed to respond to Ostacher et al. in a response letter also published in the *Journal*,[213] and even if we did not agree to some of the points made by the authors of the letter, the letter and our response allowed a public discussion of important topics and considerations that were not clear in the initial publication.[214] Firstly, Ostascher et al. pointed out that the hazard ratio among the antidepressant monotherapy treated patients was supported by a low event rate, that there were few patients that actually switched, and that out of a hundred antidepressant monotherapy treated patients only one would experience a manic switch. Based on this, Ostacher et al. proclaimed that they did not agree with our conclusions, and particularly not that antidepressants are associated with mania. However, as we also pointed out in our response letter, the antidepressant monotherapy treated patients have a different underlying mania rate, and likely a different risk of manic switching. In this observational setting, this is an example of confounding by indication, and the monotherapy group is not representable for all bipolar disorder patients. That is, it is not likely that a similar hazard ratio would be observed if the patients with more mania, and therefor a mood stabilizing treatment, were denied their concomitant mood stabilizer medication and put on an antidepressant monotherapy. These patient with a higher risk of mania would likely experience more switching, thereby increasing the hazard ratio.

The letter further allowed us to point out an important detail of our study that for a number of reasons did not make it to the final publication. Due to the observational nature of the study, we were very cautious of potential interpretations and assumptions. This led to strict inclusion criteria, and hence excluded a large number of potential subjects. One of these potential interpretations was with regards of dispensations of mood stabilizer treatment after antidepressant medication initiation in the monotherapy group. This group was formed based on the criterion of having no mood stabilizer treatment in the year preceding the antidepressant medication start. As these patients were followed after the initiation of the antidepressant treatment, some of them would develop mania and be censored at that time. However, quite a lot of these patients would dispense a mood-stabilizing drug in this antidepressant treated period, without receiving a mania diagnosis. This could be interpreted either as a cautionary measure by a treating clinician to prevent elevated mood. But it could also signify that the patient indeed was experiencing mood elevation, and that the sudden prescription and dispensation of this extra medication was an indication of a manic switch. We felt that this was too speculative and did not

want to make such an assumption. Instead, all patients in the monotherapy group were censored if they received a mood stabilizer medication after antidepressant treatment start. If, however, the sudden prescription and dispensation were to be classified as a manic switch, the hazard ratio would have risen to 16.3 (95% CI=7.2–37.2) in the 0- to 3-month period and to 11.7 (95% CI=5.1–26.9) in the 3- to 9-month period after the antidepressant treatment start.

Moreover, as we also point out in the response letter, we lack primary care data for these patients, and therefor may fail to detect episodes of elevated mood diagnosed in a primary are setting exclusively, although the extent of this happening is not known at the moment. It is also important to note that just like a sudden dispensation of a mood stabilizing treatment may signify elevated mood even without a mania diagnosis, there could also be a number of patients that experienced elevated mood and stopped the antidepressant treatment, without neither getting a mood stabilizing treatment, nor a mania diagnosis.

Another important limitation in this setting is that of adherence. Our study relies on prescription and dispensation data, and we define the start of an antidepressant treatment as at least one dispensation. This dispensation has to be preceded by a year of no dispensations, thereby indicating that this is indeed the start of a new treatment. However, we have no way to knowing whether the medication was actually consumed. In other settings, a continuous pattern of dispensations may be used, as antidepressants are commonly used over longer periods of time.[215-217] It is therefore more likely that a continuous dispensation pattern denotes consumption, as compared to a single dispensation. In our study setting, however, requiring a continuous pattern creates selection bias, as this criterion effectively excludes anyone that would chose to end the medication prior having the chance to dispense a second prescription. Therefor we have to rely on a single dispensation, and there is a possibility that this dispensed drug was not consumed, thereby making an antidepressant induced manic switch impossible and potentially underestimate the risk.

All these things considered, it is likely that the low rate of manic switch that is pointed out in the letter is a conservative estimate, and that the actual risk is higher. But even if the actual number is higher than our study estimates, Ostascher et al. points out an important issue. Whether or not to prescribe a concurrent mood stabilizing treatment with an antidepressant medication to bipolar disorders patients is still complicated. Lithium and valproaic acid have numerous side-effects,[218,219] and adding these drugs to an antidepressant medication may induce further side-effects through interactions. It is possible that switching is confined a subset of bipolar

disorder patients, and that there are patients that would never switch, but that would suffer from a mandatory addition of a mood stabilizing medication in combination with the antidepressant. However, as there are currently no ways to distinguish these patients, and switching is associated with worse disorder outcomes,[220] whether to prescribe this double treatment or not remains complicated.

Another limitation of this study is the grouping of different antidepressant drug categories. It is possible that a specific category is causing all or a majority of the switches. We tried to address this, but groups based on specific drug prescriptions yielded sample sizes that were too small. Most patients received SSRIs and too few patients were treated with SNRIs, TCAs, tetracyclic antidepressants, or bupropion to allow for meaningful comparisons. Similarly, the lack of statistical power prevented us from conducting meaningful analyses of the type of mood stabilizing drugs separately, and just like the example above with antidepressants, it is possible that a specific type of mood stabilizer is possessing all or a majority of the switch preventing properties. Another aspect of the mood stabilizing drugs studied is the lack of atypical antipsychotics like quetiapine or olanzapine in the study. These drugs have anti-manic properties and are also used to treat mania. However, due to their side-effect profile, these drugs may not be suitable for long-time treatment, and this was also reflected in our data. If we singled out the patients in the cohort whose mood-stabilizing treatment only consisted of atypical antipsychotics (N=112), we noted a large rise in mania just prior the antidepressant treatment start. This indicated that these patients were different and that the atypical antipsychotic medication likely reflected an acute treatment. Because of the deviation of this group, we chose not to allow mood-stabilizing treatment to be defined based on atypical-antipsychotic use. However, to not create a selection effect, we did not prohibit the mood-stabilizer treated patients from also having atypical antipsychotics dispensed.

Furthermore, it can be worth noting that our study did not survey the efficiency of antidepressants in treating bipolar depression. This is another related controversial topic,[154,155] and we initially discussed including this during the planning of the study, but reached the conclusion that it is not possible to address this question with the current design. The problem lies in the nature of how depression diagnoses are used in our healthcare system: When prescribed an antidepressant, the patient will be diagnosed with the indication for the drug - in this case depression. We would then require a time point at which the patient is recovered. But time to follow up visits depends on several other factors than the response to the drug: resources, the individual doctor, the type of drug prescribed, to name a few. Also, the

diagnosis that indicates remission, F31.7: bipolar disorder without current affective symptoms, is rarely used and patients tend to continue on the bipolar depression diagnosis, F31.3-4, as long as they receive antidepressant treatment despite recovering. This is opposite to how we use the mania diagnosis in this study where we know that that the patient has received an antidepressant most likely for depression. The follow up visit should hence not routinely lead to a mania diagnosis.

5.3 STUDY II RESULTS

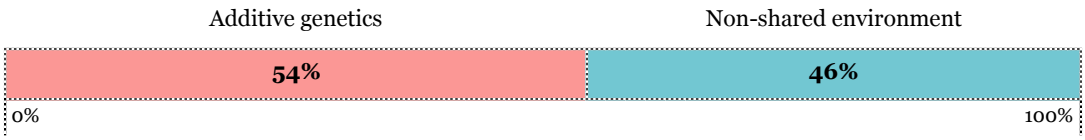
5.3.1 THE TWIN COHORT

We identified 3,427 twin mothers that had completed the lifetime version of the Edinburgh Postnatal Depression Scale. Among these, 1,517 were monozygotic twins and 1,991 were same-sex dizygotic twins. In the twin cohort, where perinatal depression had been assess with the lifetime version of the Edinburgh Postnatal Depression Scale, we observed an lifetime occurrence of perinatal depression of 7.6%.

Univariate heritability

After initially fitting an ACE model that revealed the variance due to shared environment statistically insignificant, we instead fitted an AE model where the C-component was fixed at zero. Based on the lifetime version of the Edinburgh Postnatal Depression Scale, the heritability of perinatal depression among the twin mothers were estimated at 54% (95% CI 35-70%), with the remaining variance explained by non-shared environment (46%, 95% CI 31-65%). See Figure 5.3. We observed a tetrachoric correlation of 0.55 (standard error: 0.09) among the monozygotic twins, and a tetrachoric correlation of 0.22 (standard error: 0.14) among the dizygotic twins.

Figure 5.3. Variance in perinatal depression using the classical twin model



5.3.2 THE SIBLING COHORT

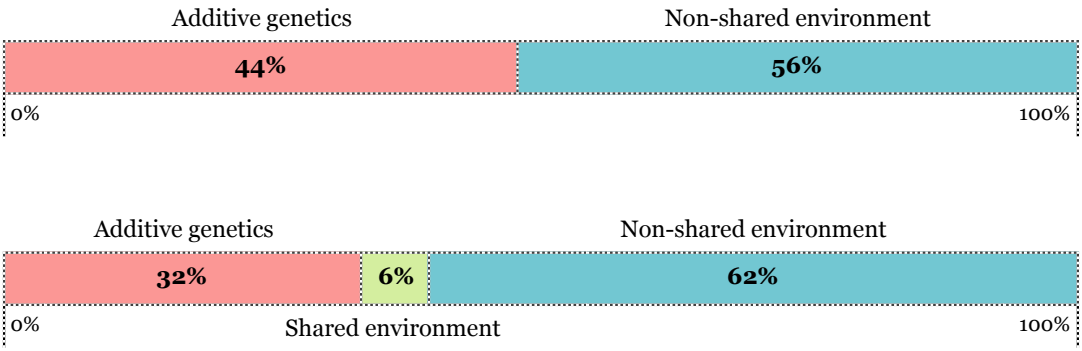
By linking Swedish national registers, we identified 580,006 female siblings that had given birth to at least one child between the beginning of 1973 and

the end of 2009. These siblings stemmed from 260,384 unique families and included 313,632 pairs of full-sisters, 33,931 pairs of paternal half-sisters, 28,568 pairs of maternal half-sisters, 2,225 pairs of monozygotic twin sisters, and 2,104 pairs of dizygotic twin sisters. We identified 1,572 twin sisters that overlapped between the twin cohort and the sibling cohort. The observed occurrence of perinatal depression in the sibling cohort, using treatment information rather than a questionnaire, was 0.6%.

Univariate heritability

Just like in the twin model, the variance in perinatal depression due to shared environment was statistically insignificant, and an AE model where the C-component was fixed at zero was fitted. Using the sibling cohort and treatment information data, we estimated the heritability of perinatal depression at 44% (95% CI, 35-52%), with the remaining variance explained by non-shared environment only. In the same sample, we estimated the heritability of non-perinatal depression at 32% (95% CI, 24-41%), with the remaining variance explained by shared environment (6%; 95% CI, 2-10%), and non-shared environment (62%; 95% CI, 57-66%). See Figure 5.4.

Figure 5.4. Variance in perinatal depression (upper) and non-perinatal depression (lower) using the sibling model



Dividing the perinatal period revealed little difference between antenatal depression, with a heritability estimated at 37% (95% CI, 27-47%) and remaining variance due to non-shared environment, and postnatal depression, with a heritability estimated at 40% (95% CI, 31-49%) and similarly the remaining variance also due to non-shared environment.

Bivariate heritability

We used a multivariate model to estimate the overlap between the two types of depression. When applying this model to explain the variance in perinatal depression, the C-parameters, except C unique for non-perinatal depression, was estimated close to zero and did not provide a significant contribution to the variance. We instead fitted an AE model where these parameters were set to zero, and estimated that 14% of the total variance (or 33% of the genetic variance) in perinatal depression was unique for perinatal depression and not in common with non-perinatal depression. See Figure 5.5.

Figure 5.5. Variance in perinatal depression due to factors unique for perinatal depression, and due to factors in common with non-perinatal depression*

* No contribution from shared environment.

5.4 DISCUSSION OF STUDY II

This study is the largest and most comprehensive genetic epidemiological study of perinatal depression yet reported. But more importantly, it is the first bivariate heritability study that explores the genetic overlap between depression specifically around the time of pregnancy with depression at any other time, and the second ever study to estimate the heritability of depression at this particular time.[221] As such, the study estimated the heritability of perinatal depression at 54%, using the classical twin model and the lifetime Edinburgh Postnatal Depression Scale, and at 44% when the sibling model and healthcare data were used. Moreover, the sibling model using treatment data estimated the heritability of non-perinatal depression at 32%, and a bivariate approach demonstrated that a third of the genetic contribution is unique to perinatal depression and not shared with non-perinatal depression. This implies only partially overlapping genetic etiologies for perinatal depression and non-perinatal depression, and may indicate that depression treated in the perinatal period is not only different based on when in life the depression is diagnosed, but may also constitute a subtype of depression with slightly different genetic underpinnings.

Differences regarding timing of onset of depressive symptoms in pregnancy (antenatal depression) versus postpartum (postnatal depression) has been a

central topic in recent work.[222] Our study allowed division of the perinatal period into an antenatal period and a postnatal period. However, to allow meaningful comparisons, the postnatal period had to be extended to incorporate enough cases to permit the heritability to be estimated. Using this approach, the heritability of antenatal depression was estimated at 37% and the heritability of postnatal depression was estimated at 40%. Furthermore, the variance of both antenatal and postnatal depression separately displayed a similar pattern as the variance of perinatal depression as a whole, with variance explained by additive genetics and non-shared environment of similar size, without contribution of shared environment.

However, in the sibling model, the definition of perinatal depression, antenatal depression, and postnatal depression is based on timing of diagnosis. A diagnosis within the timeframe of any of these periods is used to define the type of depression, and this somewhat blunt definition constitutes a limitation of the study. It is, for instance, possible that a woman had depression prior becoming pregnant, and that the a depression diagnosis that arose from a planned revisit with the treating clinician is defined as perinatal depression and assumed different from non-perinatal depression in our study. This topic was investigated during the development of the study, and we tried to build an algorithm that would take patterns of previous healthcare contacts into consideration. However, we realized that without a proper validation study, it would be difficult to justify the use of this algorithm, which could potentially introduce bias. Instead we opted to keep the blunt definition, even though the actual depression onset was not known. But, even if a depression diagnosis is the first one in a long time, preceded by years of no diagnoses, the diagnosis date may still not represent the date of the onset, as a number of factors could act as barriers to healthcare seeking during this period of life and thereby delay treatment.[72,87,88,92,93,223] Therefor, hurdles to treatment seeking may delay healthcare until after the postnatal period, and consequently define perinatal depression as non-perinatal depression. Conversely, a depression diagnosis within the perinatal period may in reality originate from a non-perinatal period and also be mis-classified. Furthermore, depression can occur anytime throughout life and appears to have numerous underlying mechanisms,[9,51] making it is possible that a depression starting within a perinatal period has underlying causes that are not connected to the pregnancy or childbirth in any other way than occurring during this specific timeframe, and that stochastic variation influenced the real underlying causes to coincide with the perinatal period. Nonetheless, we do detect differences between our two main definitions of depression, suggesting that at least a portion of the individuals with a depression diagnosis within the perinatal period may have had an onset

during this timeframe, and that this onset could denote a subtype of depression.

This also puts the observed difference into perspective. Due to the potential misclassification of perinatal depression that originated in a non-perinatal period, our estimates may be diluted. If a more precise method of definition existed that allowed less misclassification, the observed difference may be larger. Furthermore, this potential misclassification between definitions due to timing of onset is likely affecting our division of antenatal and postnatal depression, and more precise information on onset in either period may reveal larger differences between the two periods.

The study also estimated the heritability of perinatal depression at different sizes depending on the type of model used. In the classical twin model using the lifetime Edinburgh Postnatal Depression Scale, the heritability was estimated at 54%, whereas in the sibling model using healthcare data the heritability was estimated at 44%. The two designs also display marked difference in observed occurrence of perinatal depression with 0.6% in the sibling model and 7.6% in the twin model. However, the heritability estimates are similar and the confidence intervals overlap, and both estimates follow the same pattern with variance only due to additive genetics (A) and non-shared environment (E), as opposed to the variance in non-perinatal depression that was also affected by shared environment (C). This is consistent with that both approaches capture the same underlying liability for perinatal depression. The different methodologies likely explain the different observed occurrence rates; self-report in the twin model, and register based healthcare contacts in the sibling model. Therefor, the sibling design did not include women who did not seek treatment for perinatal depression but who would report symptoms on a self-report questionnaire.

Additionally, it may be argued that the depression captured using the Edinburgh Postnatal Depression Scale and depression captured from specialist healthcare are of different severity. However, if the assumption of normally distributed liability and equal-environments hold true, this should not affect the estimates. That is, if the risk for a trait studied is normally distributed, different cut-offs on a scale that measures this risk will result in corresponding cut-offs in the normal distribution and capture the same underlying liability. Key assumptions of normally distributed liability and equal-environments have strong empirical support.[224]

The definition of perinatal depression among the twin mothers in the twin model was based on a score of 12 or above on the lifetime version of the Edinburgh Postnatal Depression Scale, which is a commonly used cutoff.[76,202,225,226] If a low score on the scale, and thus few depressive

symptoms, is the most common state in a population then the start of this scale will likely begin around the center of the bell curve. For every step up on the scale, i.e. increased depression severity, fewer individuals will be detected and the bell curve gets flatter. If the assumption of normally distributed liability holds true, then adjusting the cutoff should not affect the heritability estimate, as we should capture the same liability. Increasing or decreasing the cut-off still implies comparison of less depressed individuals with more depressed individuals.

Table 5.3 below provides results from analyses using both decreased and increased thresholds on the Edinburgh Postnatal Depression Scale. If the assumption of underlying normally distributed liability hold true, the heritability estimates should not change, which is what we observe. This further support that potential differences in disorder severity between the two models different perinatal depression definitions does not constitute a barrier to capture the same underlying liability.

Table 5.3. Univariate heritability estimates of perinatal depression with different Edinburgh Postnatal Depression Scale cut-offs using classical twin design (N=3,427)*

			Estimated Variance (95% CI)			Tetrachoric Correlation (SE)	
				Environment			
Model	Cut-off	Observed Outcome Occurrence	Additive Genetic (A)	Shared (C)	Non-shared (E)	Monozygotic Twins	Dizygotic Twins
AE[b]	≥8	13.6%	0.49	NA	0.51	0.51	0.19
			(0.34-0.63)		(0.37-0.66)	(0.08)	(0.10)
AE[b]	≥10	10.6%	0.54	NA	0.46	0.59	0.11
			(0.38-0.69)		(0.31-0.62)	(0.08)	(0.12)
AE[b]	≥12	7.6%	0.54	NA	0.46	0.55	0.22
			(0.35-0.70)		(0.31-0.65)	(0.09)	(0.14)
AE[b]	≥14	5.2%	0.53	NA	0.47	0.54	0.29
			(0.32-0.70)		(0.30-0.68)	(0.10)	(0.16)
AE[b]	≥16	3.3%	0.51	NA	0.49	0.53	0.15
			(0.20-0.74)		(0.26-0.80)	(0.14)	(0.23)
AE[b]	≥18	1.6%	NA	NA	NA	0.56	Na[c]
						(0.18)	

Abbreviations: CI, confidence interval. SE, standard error. NA, not applicable.

* Different cut-offs on the Edinburgh Postnatal Depression Scale was used to define a binary outcome variable of perinatal depression. A score of ≥12 is the widely used cut-off to define a depressive illness.

[b] An AE model, were the C parameter was fixed at zero, was considered as the estimate of C was statistically insignificant in the ACE model.

[c] No concordant dizygotic twins.

The difference in the heritability estimates of perinatal depression between the twin model and the sibling model may instead be due to differences in samples and methodology. The twin model only incorporate twins, and they are born the same day and are assumed to share their childhood environment. However, this is not the case in siblings that can be born many years apart. Our sibling model handled this and other differences by

adjusting the prevalences for whether the family included half-siblings, as well as for birth year (both linear and squared) and non-perinatal depression was additionally adjusted for time at risk (linear and squared) and perinatal depression for number of offspring. The register based methodology for detection may have a lower precision, which may decrease the overall heritability estimates, which could further explain why non-perinatal depression also was estimated lower in our study than in previous studies.[51]

Another novel finding from this study was that perinatal depression and non-perinatal depression have partially different genetic etiologies. One third of the genetic variance in perinatal depression was unique for the type of depression, and not seen in non-perinatal depression. In line with the previous discussion, this may be affected by potential miss-classification and could be larger if an exact definition of perinatal depression and non-perinatal depression existed. This difference is interesting and important, as it suggest that within the current heterogeneous definition of depression, there are potentially distinctive sub-types. It is, however, important to note that this is a quantitative genetic approach that and cannot distinguish the exact genes and corresponding functional biology. It is possible that this unique genetic portion is related to the female specific fluctuations during pregnancy and childbirth, but this has to be explored further.

Moreover, when separating depressive illness into perinatal depression and non-perinatal depression, we only permit perinatal depression to occur during perinatal periods whereas non-perinatal depression can occur at any time of life (excluding perinatal periods). Pregnancy tends to be clustered around a specific age in women, and this generates a possibility that the discrepancy observed between perinatal depression and non-perinatal depression could be caused by a factor related to the different ages when depression was experienced, rather than by the actual pregnancy or childbirth. One way to study this is through permutation where women born the same year are randomly assigned each other's perinatal periods. For example, woman 1, born 1955, has been pregnant two times: the first time at age 27 and the second at age 32. After permutation, she has randomly been assigned the perinatal periods of woman 2. Woman 2 is also born 1955 but has been pregnant three times, at age 24, 29 and 36. This gives woman 1 three perinatal periods originally belonging to woman 2, and none of these overlap with her original perinatal periods. However, they are still within the age range where most women born that year get pregnant. See Figure 4.3 for a graphical representation of the permutation procedure.

Applying this permutation approach assigned 84.4% of the women in the cohort to permuted periods that did not overlap with their own real perinatal periods. Using these permuted periods, depressive illness was then separated

into perinatal depression and non-perinatal depression just like before. However, this time perinatal depression would not actually denote depression in a perinatal period in 84.4% of the women, but rather a non-perinatal period at the same age range where most women born that year would be pregnant. Bivariate analysis revealed that the variance in the permuted perinatal depression was explained completely by genetic factors in common with non-perinatal depression, without any genetic factors unique for the permuted perinatal depression. In other words, when perinatal depression was defined as depression around the "childbearing age", but not during the real perinatal periods, no unique genetic component was observed. This lends support to an association between the unique genetic component originally observed in perinatal depression and the actual pregnancy or childbirth.

We further tested if the unique additive genetics seen in perinatal depression was explained by bipolar disorder or schizophrenia. However, excluding all individuals in the sibling design with at least one hospital admission with a discharge diagnosis code for bipolar disorder or schizophrenia (N=6,817) did not alter the results.

Overall, the results from this study may provide clinicians with important information that will assist counseling patients regarding the prognosis and risk of perinatal mood disorders. The heritability of a disorder can have a direct translational impact in dialogues between treating clinicians and patients. Patients commonly ask questions as to “why am I affected by perinatal depression?”, “is it my fault?”, “will it happen the next time?”. The results underline the need for clinicians to obtain detailed information concerning the patient’s personal and family history of mental illness that started during the perinatal period. Integration of genetic risks with environmental factors is central for the proper tailoring of individual treatment and discussions of prognosis.

Moreover, perinatal depression may represent a form of unipolar mood disorder that could be prioritized for genomic discovery efforts. Adequately powered studies of perinatal depression could provide genomic findings important to disentangling the disorder specific etiology and potential relevance to depressive illness in general. Finally, enhanced identification of women at risk for perinatal depression could result in targeted interventions to prevent, identify, and treat perinatal depression.

5.5 STUDY III RESULTS

5.5.1 FULL POPULATION SAMPLE

Using information from the Swedish Medical Birth Register, we were able to identify 392,029 children born between April 1st 2006 and December 31st 2009. Among these children, 6,572 (1.7%) had a mother with several dispensations of an SSRI, while 1,625 (0.4%) of the children had a mother with a treatment contact for depression during pregnancy, but no SSRI medication.

Table 5.4. Descriptive characteristics of the full population sample

Characteristic	Reference Group	SSRI Exposed	Depression Without SSRI Exposed	Total
Number of children (%)	383,832 (97.9)	6,572 (1.7)	1,625 (0.4)	392,029
Mother's education, %				
Compulsory school	10.8	15.8	25.0	11.0
Upper secondary school	39.8	42.9	45.4	39.9
Post secondary education less than 3 years	12.4	12.2	9.9	12.4
University 3 years or more	36.9	29.2	19.7	36.7
Mother characteristics, mean (SD)				
BMI	24.6 (4.5)	25.6 (5.2)	25.4 (5.1)	24.6 (4.5)
Height (cm)	166.4 (6.4)	166.8 (6.2)	165.7 (6.5)	166.4 (6.4)
Age at pregnancy	30.3 (5.2)	31.0 (5.4)	30.0 (5.8)	30.4 (5.3)
Caesarean section, %				
Elective	7.3	10.4	10.7	7.3
Acute	9.2	12.3	11	9.3
Previous psychiatric history, %	7.7	52.1	64.9	8.7
Smoking, first visit at maternal care, %				
Does not smoke	93.2	84.9	80.1	93.0
1-9 cigarettes / day	5.3	10.5	13.4	5.4
>9 cigarettes / day	1.5	4.6	6.4	1.6

Abbreviations: SSRI, selective serotonin reuptake inhibitor. BMI, body mass index (weight in kilograms divided by height in meters squared).

Comparing children between different groups revealed children prenatally exposed to SSRIs having lower birth length and smaller birth head circumference, shorter gestational age at birth, and a higher probability of preterm birth. See Table 5.6.

5.5.2 WITHIN-FAMILY SAMPLE

From the full population sample, we identified 1,007 full siblings from 496 families where the siblings were discordant for SSRI exposure.

Table 5.5. Descriptive characteristics of the within-family sub-sample

Characteristic	Reference Group		SSRI Exposure Group	
	N	%	N	%
Number of children	506	50.3	501	49.7
Birth order among included siblings				
First	315	63.5	181	36.5
Second	185	37.3	311	62.7
Third	5	35.7	9	64.3
Fouth	1	100	0	0
Parity				
First	198	59.1	137	40.1
Second	210	49.0	219	51.0
Third	55	39.6	84	60.4
Fourth	21	36.2	37	63.8
Fifth	11	42.3	15	57.7
Sixth	8	80.0	2	20.0
Seventh	1	20.0	4	80.0
Eighth	1	33.3	2	66.7
Ninth	1	50.0	1	50.0
Caesarean section				
Elective	32	6.3	37	7.4
Acute	44	8.7	46	9.2

Abbreviations: SSRI, selective serotonin reuptake inhibitor.

The associations between SSRI exposure and birth length, birth head circumference, and birth weight observed in the full cohort were all diminished in the within-family analyses. Gestational age at delivery was lower (-2.27 days; 95% CI -3.79 to -0.75; *P*=0.004) in the SSRI exposed group of children, and the odds ratio for preterm birth was similar as in the population cohort, although with confidence intervals overlapping zero. See Table 5.6.

This remaining difference may be due to the depression underlying the medication. Therefore we compared children exposed to depression (without prenatal SSRI exposure) with children of mothers without either a diagnosis of depression or SSRI medication. These children had also lower gestational age (-1.69; 95% CI -2.51 to -0.86; *P*<0.001) and higher probability of preterm birth (odds ratio 1.31; 95% CI 1.07 to 1.60; *P*=0.009). See Table 5.6.

Table 5.6. Results from study III

	Population analysis (N=392,029)		Within-family analysis (N=1,007)	
Characteristic	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
Birth Length[a,b]				
SSRI Exposure	-.14	-.16 to -.11	.01	-.1 to .11
Depression without SSRI exposure	.06	.01 to .11	NA	NA
Birth Head Circumference[a,b]				
SSRI Exposure	-.08	-.10 to -.05	-.03	-.14 to .08
Depression without SSRI exposure	.05	-.01 to .10	NA	NA
Birth Weight[a,b]				
SSRI Exposure	-.01	-.04 to .02	.05	-.05 to .14
Depression without SSRI exposure	.03	-.026 to .01	NA	NA
Gestational Age at Delivery[a]				
SSRI Exposure	-3.12	-3.53 to -2.70	-2.27	-3.79 to -.75
Depression without SSRI exposure	-1.69	-2.51 to -.86	NA	NA
Preterm Birth[a]				
SSRI Exposure	1.45	1.31 to 1.61	1.36	.77 to 2.42
Depression without SSRI exposure	1.31	1.07 to 1.60	NA	NA

Abbreviations: SSRI, selective serotonin reuptake inhibitor. CI, confidence interval. NA, not applicable.

[a] The population analyses were adjusted for the mother's education, the mother's BMI (<18.5, 18.5-25, 25-30, >30), the mother's height (cm), parity, the mother's age at pregnancy (years), the mother's previous psychiatric history (yes/no), the mother's smoking at first visit to maternal care (1: no smoking. 2: 1-9 cigarettes/day. 3: >9 cigarettes / day). The population analyses used robust standard errors to account for several children from the same mother. The within-family analyses were adjusted for parity.

[b] The outcome variable is a standardized value adjusted for gestational age (see Methods). Standardized values for birth weight, birth length, and birth head circumference above or below five standard deviations from the sample mean (N=465) were considered outliers and excluded from the analyses.

5.6 STUDY III DISCUSSION

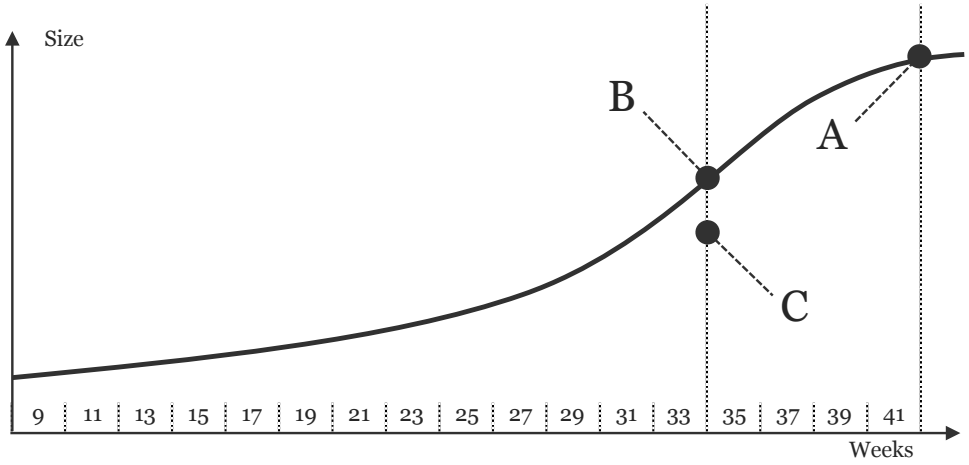
In this study, we initially observed associations between prenatal SSRI exposure and a number of birth size related outcomes, similar to previous studies.[138,142,145] However, this was when a classic epidemiologic approach was used that adjusted for several measured confounding factors, but not for potential unmeasured familial confounding. When a within-family approach was used where full siblings with discordant SSRI exposure were compared, the associations between SSRI exposure and birth size related outcomes were no longer observed. This could suggest that the associations between SSRI exposure and birth size outcomes initially observed was due to unmeasured familial confounding, i.e. parents genetics or environmental exposures preceding the pregnancies, which the measured confounding factors could not properly adjust for. In other words, the children exposed to SSRIs during gestation in the initial analysis had indeed impaired growth, but the within-family approach demonstrated that there were no difference between an exposed and an unexposed sibling, suggesting that the impaired growth was due to other underlying genetic or environmental factors shared by the siblings.

On the contrary, a shorter gestational age was observed both when using the classic epidemiological approach, and when using the within-family approach. Although there have been no family or sibling studies of prenatal SSRI exposure and gestational age, our results are in line with those of studies using a classic epidemiological approach.[136,138,142] The estimate size of this association was 3.1 fewer days of gestation in the classical approach, and 2.3 fewer days in the within-family approach. This finding is interesting and could have several conceivable explanations. Firstly, the association may denote a causal effect of the SSRI on gestational age. Another explanation may be that the underlying disorder, depression, leading up to the antidepressant treatment is causing the association. A third possibility would be that the association is due to the liability underlying both the depression and the consequent antidepressant treatment.

To test these potential explanations, we contrasted women having at least one treatment contact with a discharge diagnosis code for depression but no SSRI medication during pregnancy, with women not having a treatment contact for depression or SSRI medication during pregnancy. The analyses showed that women with a depression diagnosis only were more likely to have both shorter gestational age and preterm birth offspring compared with women without a healthcare contact for depression or a SSRI medication during pregnancy. If the liability for depression were the only influence on gestational age, the association would likely be attenuated in the within-family analyses, as both siblings have the same parents. However, an association was seen, indicating influence from factors other than the liability, for example the medication, or the depression leading to the medication.

To continue discuss these results, it is important to remember that the birth size outcomes in this study were standardized based on gestational age. This is, as previously mentioned, because time in gestation is strongly correlated with the size at birth - a child allowed less time to grow will correspondingly be born smaller.[227] Without this standardization, it would be difficult to survey deviation in growth, and whether a potential association was targeting the growth, or just shorter gestational time that produces a child that has been allowed less time to grow and consequently are smaller. See Figure 5.6 below.

Figure 5.6. Intra-uterine growth curve example*



* This curve represents the intra-uterine growth of a child during pregnancy. In this figure, A represents a child born with a normal gestational age, and with a normal size for that age. B on the other hand is smaller, but this is likely due to being born earlier and consequently not having been allowed equal amount of time to grow as A, rather than having impaired growth. Both A and B follow the intra-uterine growth curve, and with birth size outcomes standardized for gestational age, a comparison of B and A would not reveal a difference, as they both are within the size expected for their gestational age. On the contrary, C has the same gestational age as B, but is also smaller than what is expected. Therefor, a comparison between C and A would reveal a difference and would indicate impaired growth of C.

In the within-family model, the SSRI exposed child has on average 2.3 fewer days in gestation compared to the unexposed sibling. However, neither the exposed, nor the unexposed child display any changes in gestational age adjusted size outcomes. In other words, the SSRI exposed child has shorter time in gestation, which in turn reduces the birth size, but it does not seem to cause growth impairment. This in turn could be due to both siblings not deviating from the growth curve, or that both siblings deviate in similar ways.

Another aspect is the growth during gestation and the shape of normal intra-uterine growth curves. The curves displays sigmoidal shapes that commonly starts plateau at around week 38. After this, there is less pronounced growth, and if both siblings are born after week 38, the 2.3 fewer days of gestation potentially caused by the SSRI exposure may not produce pronounced differences in size between the exposed and unexposed sibling.

Alternately, the observed shorter time of gestation in the SSRI exposed child could be fully or partially due to other types of confounding. The within family analysis does not adjust for changes in behavior as a consequence of perceived consequences of exposure. That might be the case if a first pregnancy is exposed, and the child is born with a certain outcome due to causes other than the exposure, and this outcome of the first child in turn results in changes in both exposure and relevant behavior associated with the real cause. This could result in a within-family association between an

exposure and an outcome, which may in reality be affected by another underlying factor. This is sometimes called a carry over effect, and it has been shown very complicated to adjust for.[180]

Another potential explanation would be if an association between an exposure, e.g. SSRI medication, and an outcome, e.g. shorter gestation, were confounded by a factor that is unshared between the siblings, e.g. an automobile accident (assuming that this automobile accident is not due to a trait underlined by genetics like attention deficit,[228,229] but rather unrelated in a type of a-piece-of-a-passing-airplane-suddenly-falls-into-the-road way). In the within-family model, only siblings that are discordant for the exposure are informative. If we assume that automobile accidents are associated with depression and thereby SSRI medication, and also that that automobile accidents cause some sort of reaction that reduces the time of gestation. Then the other sibling, which will not be exposed to an SSRI medication due to the study design, will also be less likely to have been exposed to a mother in an automobile accident during pregnancy (due to this made-up correlation between automobile accidents and SSRI medication), and consequently the automobile accident-specific reduction of gestation time would not affect this sibling.

In the end, whether to use a within-family design or not becomes a balance between potential gains from controlling for unmeasured shared confounding like genetics and parental environmental factors, and potential problems caused by unshared confounders. If unshared confounding is assumed a major problem for the studied exposure and outcome, a within-family design may not be suitable. However, based on previous literature on psychiatric genetics,[8,9,16,21,175-177] and the results from Study II,[230] we assume that depression around the time of pregnancy is a trait with considerable influence by genetics. We therefore consider the studied variables well suited for the within-family design. As such, we conclude that these study results indicate that prenatal SSRI exposure may not be causally related to offspring birth size. Rather, our analyses imply that the associations between prenatal SSRI exposure and the studied birth size outcomes may be due to other underlying factors that are adjusted for in a within-family analysis. Depression is considered a complex and highly polygenic trait, much like most other psychiatric disorders studied with genome-wide association studies.[16,25] Growth is also a complex polygenic trait,[231,232] and it is not unthinkable that shared additive genetics exists behind psychiatric disorders and outcomes related to growth, such as birth size. Further, runs of homozygosity have been associated both to reduced height and to complex disorders such as Alzheimer's disease and schizophrenia,[233,234] and may serve as a common causal pathway to both depression and reduced growth.

Although the study did find an association between maternal SSRI medication and shorter gestation, this reduction of gestational age was minor and could either be due to the exposure of the antidepressant, or due to factors varying between the pregnancies. While the study cannot rule out a causal effect of SSRI medication on shortened gestational age, the association was reduced between the classical epidemiological approach and the within-family approach, and the associations to the birth size related outcomes were attenuated. This is important, as it could indicate that many of the numerous reported associations between antidepressant treatment during pregnancy and outcomes in the offspring, several which fail replication, may be due to factors other than the medication.

5.7 STUDY IV RESULTS

In total, from 1973 through 2009, we identified 1,857,043 mothers giving birth to 3,637,895 children, and 1,835,602 fathers to 3,589,251 children (98.7%). Using data from this cohort, we created a sub-sample of parents living in Stockholm County having at least one child between the beginning of 2004 and the end of 2009. This included 101,671 mothers and 92,974 fathers.

Table 5.7. Descriptive statistics of the nation-wide cohort and the Stockholm County sub-sample

	Nation-wide cohort 1973-2009				Stockholm County sub-sample 2004-2009			
	Mothers N = 1,857,043		Fathers N = 1,835,602		Mothers N = 101,671		Fathers N = 92,974	
Characteristic[a]	No Perinatal Depressive Illness	Perinatal Depressive Illness	No Perinatal Depressive Illness	Perinatal Depressive Illness	No Perinatal Depressive Illness	Perinatal Depressive Illness	No Perinatal Depressive Illness	Perinatal Depressive Illness
Number of perinatal periods	3,626,766 (99.7%)	11,129 (0.3%)	3,584,066 (99.9%)	5,185 (0.1%)	135,050 (96.6%)	4,809 (3.4%)	125,428 (97.7%)	2,958 (2.3%)
Age at pregnancy, %								
- 24	23.7	18.7	9.4	9.4	8.4	8.7	2.6	3.0
25 - 34	63.0	59.1	61.2	48.4	62.8	58.3	47.3	44.5
34 -	13.3	22.1	29.4	42.2	28.8	32.9	50.0	52.5
Mean BMI of mother (SD)	23.6 (4.1)	25.1 (5.0)	23.6 (4.1)	24.8 (5.0)	23.9 (4.1)	24.5 (4.6)	23.8 (4.1)	24.4 (4.5)
Mother's smoking, first visit at maternal care, %								
Does not smoke	82.0	78.8	82.06	77.37	94.6	89.1	94.9	91.8
1-9 cigarettes / day	12.0	13.1	11.54	14.82	4.1	7.9	3.9	5.9
>9 cigarettes / day	6.5	8.1	6.41	7.81	1.3	3.1	1.2	2.3
Caesarean section of mother, %								
Acute	2.2	8.1	2.2	6.6	10.9	13.5	10.7	12.1
Planned	1.9	8.1	1.9	5.1	9.8	12.7	10.0	11.5
Preterm birth, %	6.1	9.6	5.8	7.0	5.7	7.8	5.6	6.5
Parity[b]								
First	42.0	43.5	51.2	44.9	43.3	40.8	43.8	38.3
Second	36.6	31.8	33.2	31.0	38.2	35.8	37.5	37.7
Third	15.1	15.3	11.5	14.9	13.7	15.7	13.4	16.1
Fourth and up	6.3	9.4	4.1	9.2	4.8	7.7	5.3	7.9

Abbreviations: SD,Standard deviation.

[a] Numbers are rounded to one decimal

[b] Exact parity information is not available for the fathers. Here, parity represents the order or births within the Medical Birth Register. Births prior to 1973, or among the 1 % not in the register, will not be included.

In the nation-wide cohort we observed perinatal depressive illness among 10,465 mothers (0.56%), perinatal anxiety disorders among 8,946 mothers (0.48%), and 3,633 mothers having both disorders. Among the fathers, 4,864 (0.26%) had perinatal depressive illness, 4,379 (0.24%) had a perinatal anxiety disorder, and 1,189 of the fathers had both. See Table 5.8. In the Stockholm County sub-sample, a majority of the diagnoses came from primary care and only 13-16% of the diagnosed parents had been in contact with both primary and specialist care. See Table 5.9. In this sub-sample, 1,956 mothers (1.92%) had perinatal depressive illness, 1,490 (1.47%) had a perinatal anxiety disorder, and 475 mothers had both disorders. Among the fathers, we observed 1,267 (1.36%) with perinatal depressive illness, 914 (0.98%) with a perinatal anxiety disorder, and 256 with both disorders. See Table 5.9.

Table 5.8. Nation-wide occurrence of depression and anxiety disorders during perinatal periods and during permuted periods[a]

Parent	Disoder	N parent	N children	Occurrence (%) perinatal periods	Difference[b]	Occurrence (%) permuted periods	Overlapping periods[c]	Mean days between (SD)[d]
Mother	Depression	1,857,043	3,637,895	10,465 (0.56)	-21,8% ***	13,381 (0.72)	29.7 %	1,975 (1,564)
	Anxiety	1,857,043	3,637,895	8,946 (0.48)	-18,8% ***	11,023 (0.59)	29.7 %	1,975 (1,564)
	Depression & anxiety	1,857,043	3,637,895	15,778 (0.85)	-14,7% ***	18,505 (1.00)	29.7 %	1,975 (1,564)
Father	Depression	1,835,602	3,589,251	4,864 (0.26)	-33,6% ***	7,326 (0.40)	27.8 %	2,183 (1,797)
	Anxiety	1,835,602	3,589,251	4,379 (0.24)	-23,5% ***	5,723 (0.31)	27.8 %	2,183 (1,797)
	Depression & anxiety	1,835,602	3,589,251	8,054 (0.44)	-28,0% ***	11,193 (0.61)	27.8 %	2,183 (1,797)

[a] The percentual occurrences are based on the number of parents.

[b] The difference in occurrence during the perinatal periods compard with the permuted periods expressed as percentualdifference. I.e. the occurrence during perinatal periods divided by the occurrence during the permuted periods.The differences in occurrence between the studied periods were analyzed using chi-squared tests, and the resulting p-values are given with each percentual change as follows: ns (non-significant) denotes P > 0.05, * denotes P ≤ 0.05, ** denotes P ≤ 0.01, and *** denotes P ≤ 0.001.

[c] The percent of permuted periods that completely or partially overlap with a parents real perinatal period. A higher figure will cause the difference between permuted and perinatal periods to be less prononced.

[d] The mean number of days between permuted periods and the real perinatal periods. E.g. a number of 365 would indicate that, on average, a permuted period covers a time window a year prior or after the perinatal period.

Table 5.9. Occurrence of depression and anxiety disorders during perinatal periods and permuted periods in the Stockholm County sub-sample[a]

A: Specialist care and primary care combined

Parent	Disoder	N parent	N children	Occurrence (%) perinatal	Difference[b]	Occurrence (%) permuted	Overlapping periods[c]	Mean days between (SD)[d]
Mother	Depression	101,671	139,859	1,956 (1.92)	-29,6% ***	2,780 (2.73)	50.1 %	734 (536)
	Anxiety	101,671	139,859	1,490 (1.47)	-31,7% ***	2,181 (2.15)	50.1 %	734 (536)
	Depression & anxiety	101,671	139,859	2,971 (2.92)	-30,7% ***	4,289 (4.22)	50.1 %	734 (536)
Father	Depression	92,974	128,386	1,267 (1.36)	-12,6% ***	1,449 (1.56)	50.0 %	738 (535)
	Anxiety	92,974	128,386	914 (0.98)	-11,4% **	1,032 (1.11)	50.0 %	738 (535)
	Depression & anxiety	92,974	128,386	1,925 (2.07)	-12,3% ***	2,195 (2.36)	50.0 %	738 (535)

B: Specialist care and primary care separated[e]

Parent	Disoder	Occurrence (%) specialist care	Difference[f] specialist care	Occurrence (%) permuted specialist care	Occurrence (%) primary care	Difference[g] primary care	Occurrence (%) permuted primary care	Overlap[h] (%) specialist and primary care
Mother	Depression	937 (0.92)	-1,1% [ns]	947 (0.93)	1,296 (1.27)	-42,1% ***	2,237 (2.20)	277 (14.2)
	Anxiety	794 (0.78)	0,5% [ns]	790 (0.78)	931 (0.92)	-46,5% ***	1,741 (1.71)	235 (15.8)
	Depression & anxiety	1,388 (1.37)	1,1% [ns]	1,373 (1.35)	2,046 (2.01)	-42,5% ***	3,557 (3.50)	463 (15.6)
Father	Depression	513 (0.55)	-12,6% *	587 (0.63)	932 (1.00)	-11,2% **	1,050 (1.13)	178 (14.0)
	Anxiety	293 (0.32)	-10,4% [ns]	327 (0.35)	756 (0.81)	-10,6% *	846 (0.91)	135 (14.8)
	Depression & anxiety	669 (0.72)	-12,7% *	766 (0.82)	1,512 (1.63)	-11,4% ***	1,707 (1.84)	256 (13.3)

[a] The differences in occurrence between the studied periods were analyzed by chi-squared tests, and the resulting p-values are given with each percentual change as follows: ns (non-significant) denotes P > 0.05, * denotes P ≤ 0.05, ** denotes P ≤ 0.01, and *** denotes P ≤ 0.001. The percentual occurrences are based on the number of parents.

[b] The percentual difference in occurrence between the permuted period and the perinatal period. I.e. the occurrence during perinatal period divided by the occurrence during the permuted period. Including data from both specialist care and primary care.

[c] The percent of permuted periods that completely or partially overlap with a parents real perinatal period. A higher figure will cause the difference between permuted and perinatal periods to be less prononced.

[d] The mean number of days between permuted periods and the real perinatal periods. E.g. a number of 365 would indicate that, on average, a permuted period covers a time window a year prior or after the perinatal period.

[e] The (B) table with specialist care and primary care is based on the same number of parents and children, the same portion of overlapping periods, and the same mean days between perinatal and permuted periods, as reported in (A).

[f] The percentual difference in occurrence between the permuted period and the perinatal period. I.e. the occurrence during perinatal period divided by the occurrence during the permuted period. Including data from specialist care only.

[g] The percentual difference in occurrence between the permuted period and the perinatal period. I.e. the occurrence during perinatal period divided by the occurrence during the permuted period. Including data from primary care only.

[h] The number of perinatal periods where a subject received both specialist and primary healthcare.

When the pregnancy was compared to adjacent periods, a lower occurrence of depression, and anxiety disorders, were observed among the mothers compared both to the period prior and after pregnancy. The largest occurrence was observed in the postnatal period. See table 5.10. A similar pattern was observed for depression among the fathers in the nation-wide cohort with lower occurrence during pregnancy than both prior conception and after childbirth. However, the occurrence of depression in the Stockholm County cohort, and the occurrence of anxiety disorders in both cohorts, displayed a step-wise pattern with the lowest occurrence prior conception and highest after childbirth. See Table 5.10. When the whole perinatal period were compared to periods of equal length (i.e. roughly 15 months) prior conception, and after six months postpartum, lower occurrence prior conception and higher occurrence in the period following the perinatal period were observed among both mothers and fathers, but with higher estimates among the fathers in the nation-wide cohort than among the mothers. See Table 5.10.

After permutation, 28-30% of the permuted periods overlapped with original perinatal periods in the nation-wide cohort. The occurrence in the perinatal periods compared to the permuted periods were 21.8% lower for depression, and 18.8% lower for anxiety disorders among the mothers. See Table 5.8. The occurrence of diagnoses for fathers in the perinatal periods compared to the permuted periods were 33.6% lower for depression, and 23.5% lower for anxiety disorders. See Table 5.8. After permutation of the Stockholm County sub-sample, 50% of the permuted periods overlapped with perinatal periods. In this sub-sample, the occurrence in the perinatal periods compared to the permuted periods was 29.6% lower for depression, and 31.7% lower for anxiety disorders among the mothers, with limited contribution to the difference from specialist care, but major contribution from primary care. See Table 5.9. The occurrence among the fathers in the perinatal periods compared to the permuted periods were 11.4% lower for depression, and 12.3% lower for anxiety disorders, with equal contribution to the difference from both specialist care and primary care. See Table 5.9.

Table 5.10. Occurrence of depression and anxiety disorders during the pregnancy and adjacent periods (A), and during the perinatal period and adjacent periods (B)[a]

A: PREGNANCY

Parent	Disorder	Cohort	N parent	N children	Occurrence (%) before	Difference[b]	Occurrence (%) pregnancy	Difference[c]	Occurrence (%) after
Mother	Depression	Nation-wide	1,709,101	3,107,949	5,506 (0.18)	-13,5% ***	4,761 (0.15)	-30,8% ***	6,879 (0.22)
		Stockholm County	64,180	71,748	1,298 (1.81)	-12,8% ***	1,132 (1.58)	-27,2% ***	1,554 (2.17)
	Anxiety	Nation-wide	1,709,101	3,107,949	4,431 (0.14)	-1,4% ns	4,367 (0.14)	-20,6% ***	5,501 (0.18)
		Stockholm County	64,180	71,748	774 (1.08)	-18,5% ***	631 (0.88)	-19,5% ***	784 (1.09)
Father	Depression	Nation-wide	1,692,289	3,074,292	2,755 (0.09)	-9,2% ***	2,501 (0.08)	-24,3% ***	3,303 (0.11)
		Stockholm County	58,663	65,779	514 (0.78)	8,6% ns	558 (0.85)	-22,6% ***	721 (1.10)
	Anxiety	Nation-wide	1,692,289	3,074,292	2,202 (0.07)	5,3% *	2,319 (0.08)	-16,4% ***	2,775 (0.09)
		Stockholm County	58,664	65,780	352 (0.54)	17,6% **	414 (0.63)	-13,6% **	479 (0.73)

B: PERINATAL PERIOD

Parent	Disorder	Cohort	N parent	N children	Occurrence (%) before	Difference[d]	Occurrence (%) perinatal period	Difference[e]	Occurrence (%) after
Mother	Depression	Nation-wide	1,319,000	2,010,523	5,164 (0.26)	9,6% ***	5,661 (0.28)	-9,2% ***	6,237 (0.31)
		Stockholm County	28,289	28,288	759 (2.68)	12,3% **	852 (3.01)	-24,3% ***	1,125 (3.98)
	Anxiety	Nation-wide	1,319,000	2,010,523	4,059 (0.20)	21,6% ***	4,937 (0.25)	-3,6% *	5,122 (0.25)
		Stockholm County	28,289	28,288	441 (1.56)	1,4% ns	447 (1.58)	-30,0% ***	639 (2.26)
Father	Depression	Nation-wide	1,311,076	1,990,515	2,668 (0.13)	-4,0% ns	2,561 (0.13)	-38,3% ***	4,153 (0.21)
		Stockholm County	26,026	26,027	286 (1.10)	37,1% ***	392 (1.51)	-26,2% ***	531 (2.04)
	Anxiety	Nation-wide	1,311,076	1,990,515	2,021 (0.10)	12,4% ***	2,271 (0.11)	-27,0% ***	3,111 (0.16)
		Stockholm County	26,026	26,027	203 (0.78)	37,4% ***	279 (1.07)	-11,7% ns	316 (1.21)

[a] The adjacent periods are of same length as the period compared. For A, that is a period prior conception of equal length to the pregnancy, and a period after childbirth of equal length to the pregnancy. For B, that is a period prior conception of equal length to the perinatal period (pregnancy and six months postpartum), and a period after six months postpartum of equal length to the perinatal period (pregnancy and six months postpartum). For example, assuming a pregnancy of exactly nine months, A compares the nine months of pregnancy to nine months prior, and nine months after, and B compares a fifteen month perinatal period to fifteen months prior conception, and fifteen months after the perinatal period. The differences in occurrence between the studied periods were analyzed by logistic regression using robust standard errors clustered on the parent, and the resulting p-values are given with each percentual change as follows: ns (non-significant) denotes P > 0.05, * denotes P ≤ 0.05, ** denotes P ≤ 0.01, and *** denotes P ≤ 0.001. The percentual occurrences are based on the number of children (pregnancies).

[b] The percentual difference in occurrence during the pregnancy compared to the before-period. I.e. the occurrence during pregnancy divided by the occurrence during the before-period.

[c] The percentual difference in occurrence during the pregnancy compared to the after-period. I.e. the occurrence during pregnancy divided by the occurrence during the after-period.

[d] The percentual difference in occurrence during the perinatal period compared to the before-period. I.e. the occurrence during perinatal period divided by the occurrence during the before-period.

[e] The percentual difference in occurrence during the perinatal period compared to the after-period. I.e. the occurrence during perinatal period divided by the occurrence during the after-period.

5.8 STUDY IV DISCUSSION

With this study, we surveyed healthcare utilization data among 3.6 million parents of 3.5 million children in Sweden. Perinatal depression based on specialist healthcare was found uncommon, 0.56% among mothers 0.26% among fathers. However, in a sub-sample of parents living in Stockholm County during more recent years, we could also monitor primary healthcare, and estimated the occurrence of perinatal depression at 1.92% among mothers, and at 1.36% among fathers. Addition of a broad definition of anxiety disorders onto the perinatal depression further resulted in an increased estimated occurrence at 2.92% among mothers, and at 2.07% among fathers. This is still far from the estimates reported from studies using a self-report instruments,[58-60,230,235] and may indicate that anxiety disorders does not explain the discrepancy in estimated occurrence between occurrence figures based on self-report and treatment data. However, as opposed to the previous self-report estimates that survey lifetime occurrence, the Stockholm County cohort did only cover a limited number of years and it is possible that the figure would be larger if all lifetime pregnancies would be surveyed. Yet, it is unlikely that the figure would reach 10-15%. The observed occurrence is, however, in line with reports from studies using similar data from other countries, including the US and Finland,[73,80,81] showing the low occurrence of treatment for depression and anxiety disorders around the time of pregnancy is not an issue specific for Sweden.

When we compared the pregnancy with adjacent periods, the mothers displayed a pattern of reduced occurrence of both depression and anxiety disorders during pregnancy, and overall highest occurrence after pregnancy. This is in line with findings from earlier studies[73,93,236] The fathers also displayed the highest occurrence after pregnancy, but had more of a step-wise pattern with lower occurrence prior pregnancy, except for depression identified with specialist data only, that displayed a lower occurrence specifically during pregnancy. An interpretation of these patterns could be that the number of diagnosed individuals generally increases over time, which may be what is seen in the fathers. In contrast, this pattern is not seen among the mothers, where instead the occurrence is reduced during the pregnancy.

We similarly compared the whole perinatal period with adjacent periods of same length. See Figure 4.2. This meant that we now compared the occurrence during both pregnancy and a postnatal period, and this postnatal period had shown having the highest occurrence in the previous comparisons. Therefore, the observation of higher occurrence during the perinatal period compared to an equally long period before may be expected. This was consistent for both fathers and mothers, and we further observed a

higher occurrence in the period following the perinatal period. However, when using adjacent periods it is difficult to interpret if this observed stepwise increase denotes an increase in occurrence that can be attributable to the pregnancy and childbirth, or if this signifies a secular pattern of increased diagnoses over time.

The permutation approach allowed us to better understand the patterns of occurrence during the perinatal period through comparisons of periods of equal length prior or after the perinatal period within the same individual, without influence from fixed calendar time as the periods were scattered both prior and after the original perinatal period. Through being based on the perinatal periods from another individual born the same year, the permuted periods was distributed to represent the time of life when individuals born the same year would have children, thereby allowing relevant periods of life to be compared. The random distribution of the permuted periods did, however, result in some overlap between permuted periods and the individual's actual perinatal periods. This was true for about 30% of the 3.6 million perinatal periods in the nation-wide cohort, consequently causing about 30% of the permuted periods to entirely, or partially, cover a real perinatal period. This would in turn result in permuted periods that actually represent the perinatal period, and thus a conservative estimate of the difference. Nevertheless, when we applied this approach on the nation-wide cohort with specialist care data, we observed 22% lower occurrence of treatment for depressive illness among the mothers in perinatal periods, and 19% lower occurrence of anxiety disorders, compared to during the permuted periods. The fathers displayed similar although larger decreases, indicating that there indeed is a reduction in healthcare utilization during the perinatal periods, among both mothers and fathers alike. See Table 5.8.

We observed a similar pattern among the mothers when the perinatal periods in the Stockholm County cohort were permuted, but a less pronounced decrease among the fathers as opposed to using the nation-wide cohort. The Stockholm County sub-sample covered only six years, 2004-2009, consequently allowing less spread of the perinatal periods between individuals born the same year. Therefore the number of overlapping periods increased to 50%, and the time separating the permuted periods and the actual perinatal periods were reduced from around six years in the nation-wide cohort, to around two years in the Stockholm County cohort. It is possible these differences between the two cohorts may explain the difference in estimates among the fathers when using the nation-wide data compared to when using the Stockholm County data.

In additional analyses, the occurrence of healthcare utilization for *any* type of psychiatric condition was investigated between permuted and perinatal

periods and resulted in similar patterns of reduced healthcare utilization during the perinatal period.

Overall, we observed reduced healthcare utilization for mental health problems in general during the perinatal period in both parents. However, this descriptive study reports patterns of healthcare utilization, but cannot provide answers to the underlying causes of these observed patterns. Nevertheless, the reduction in healthcare utilization would have to be explained either by a reduction in the underlying disorders during this time of life, or by barriers to receiving a diagnosis. The former interpretation may be intuitive; pregnancy is a period in life where most individuals spend more time in medical facilities compared to other times of life and thus may be more likely to have a depression detected, consequently lending support to the view that fewer hospital visits likely denotes fewer sick patients. It may further feel intuitive in a biological or evolutionary perspective that this important period in life should be "protected" against depression and anxiety. However, there are several studies reporting barriers to proper healthcare for mental illness during this particular time of life,[72,87-89,91-93] despite the potentially increased proximity to healthcare, which in turn could be explained by increased focus on the child and somatic complications, or stigma surrounding mental illness among both the patients and clinicians.[72] Furthermore, it has been estimated that as many as 75% of women may experience the "baby blues" following childbirth,[237] a state of irritability, mood lability, tearfulness, generalized anxiety, and sleep and appetite disturbance, which may obscure depressive illness; even if the prevalence of perinatal depression is as high as 15%, the vast majority do not get depressed, but many do experience baby blues, making it potentially difficult for healthcare workers to distinguish the two in the postnatal period. It may further be argued that the common reaction of baby blues indicates that this is a normal reaction from a biological and evolutionary perspective. Additionally, if the period is protected against mood disorders, the observed reduction in healthcare utilization among both parents indicate that it would not be caused by the mother specific physiological changes during pregnancy and childbirth.

Moreover, an interpretation that the reduced healthcare utilization denotes a decrease in the underlying disorder is contradictory to the results of a large body of previous research that relies on screening instruments. Using the Edinburg Postnatal Depression Scale, previous research has estimated the prevalence of perinatal depression at 10-15%,[58-60,230,235] which is a high figure and far from the figure of 2% based on healthcare data observed in this study. On one hand, it could be argued that the screening tools ascertain everyone equally and does not rely on individual specific healthcare access, thereby

providing a more reliable estimate. On the other hand, it can be argued that a screening tool based on 10 items does equal a clinical examination and could potentially overestimate the prevalence.

But apart from the discrepancy in estimate size from the two methods, there is also a discrepancy in timing of symptoms. Several studies using the Edinburgh Postnatal Scale to assess depressive symptoms during both the pregnancy and the time after childbirth report markedly higher occurrence of depressive symptoms during the pregnancy,[71,238,239] which is completely opposite to what we observe using healthcare data. This further complicates the interpretation that the reduced healthcare utilization denotes reduced mental health issues. If this were the case, also these studies comparing the occurrence at different time points would have to be wrong. On the other hand, our results from the Stockholm County cohort (see Table 5.9 B) show that it is predominantly primary care visits that are reduced during the perinatal period, which may suggest that the antenatal or maternal healthcare fail to detect depressive illness that is detected by the primary are.

In the end, both the interpretation that screening instruments may overestimate the true prevalence, and the interpretation that healthcare fails to detect a subset of individuals during the perinatal period may be true. Elevated anxiety levels in anticipation of the childbirth and reduced mood following childbirth are likely natural reactions to the physiological and mental challenge that pregnancy and childbirth constitute, but may risk getting defined as pathological conditions by screening instruments. However, if these reactions are indeed common and non-pathological, but also easily miss-classified as depressive illness, it is not unlikely that individuals with depressive illness gets obscured by the large number of parents that display similar symptoms without developing a disorder, and are instead assumed to experience a state of "baby blues" and will quickly recover.

6. CONCLUSIONS

In Study I, we developed and applied a pharmacoepidemiological model that compared the risk of antidepressant induced mood elevation - or manic switch - among bipolar disorder patients, and did so within the same individual, thereby automatically adjusting for a number of factors that could otherwise not be controlled for. This includes genetics, individual specific disorder severity, and other life-events up until the study started. Using this model, we could show that there was an increased risk of antidepressant induced manic switch, but that this effect was confined to the bipolar disorder patients that were treated with an antidepressant monotherapy. In contrary, among patients that also had a mood stabilizer, we did not observe this effect. This is particularly interesting since patients with a mood stabilizer treatment in this observational setting also are patients with more mania overall - that is why they had been prescribed the mood stabilizing treatment. But even with a generally larger rate of mania, we did not observe an antidepressant-induced switch among these patients. This could indicate that mood stabilizers are effective against antidepressant induced mood elevation, a side effect that is associated with worsening of disorder symptoms. However, the observed number of individuals that experienced a manic switch in the monotherapy group was low, and even if the observed number is an underestimate, not all patients with bipolar disorder appear affected by a manic switch from antidepressant medication. This is important as adding another medication on top of the antidepressant may risk more side effects, which could create more suffering and potentially reduce the adherence to the medication. The possibility that antidepressant induced manic switch is limited to a certain subset of bipolar disorder patients offers an interesting future direction. Exploring this possibility may result in clinically relevant information that could aid in tailoring a treatment that better fits the patient and reduces the side effects.

In Study II, we utilized both a classical twin model with a validated self-rating instrument, and a sibling model using national healthcare data, to estimate the heritability of perinatal depression. We observed that the heritability of perinatal depression was higher than the corresponding figure for non-perinatal depression. We also observed a unique genetic component behind perinatal depression that was not observed in depression occurring at other times of life. This is important, as previous studies of the genetic underpinnings of depression have not found any associated loci. This has led researchers to believe that depression is a grouping of symptoms that may include several different subtypes. By separating depression depending on when during life it occurred, either during a perinatal period or at any other time of life, and analyzing the two different types of depression with a bivariate model, we demonstrated genetic differences. This in turn may indicate perinatal depression is a different type of depression. This has a

number of important implications for future research. The increased heritability of perinatal depression may make this type of depression a good candidate for genome-wide association studies, as genes play a larger role in the etiology. Furthermore, due to a different genetic profile, this type of depression may further implicate a different response to antidepressant treatment.

In Study III, we first used a Swedish population-based cohort consisting of 392,029 children and observed associations between prenatal SSRI exposure and birth size outcomes. However, using a sub-sample of 1,007 children in within-family analyses, consequently adjusting for numerous unmeasured shared confounders, only the association between SSRI exposure and reduced gestational age was observed. This association may be due to a causal effect of the medication, but could potentially be due to confounding factors that a within-family analysis cannot adjust for. These findings could indicate that many of the numerous associations between antidepressant medication during pregnancy and adverse outcome in the offspring may be due to underlying confounding factors, such as genetics or environmental exposures, and not the medication per se. This is important, as depression during pregnancy is not uncommon, and antidepressants are a central treatment option. However, this study could only focus on a finite number of outcomes, and more research is warranted to disentangle if similar results will be observed when a genetically informed design is used. Moreover, the study underlines the complex mechanisms behind medication exposures and outcomes in observational settings, and highlights potential problems with confounding both when using a within-family design and when not.

In Study IV, we approached the patterns of treatment for mental illness around the time of pregnancy on a broad scale using information from healthcare services nation-wide and over several decades. We further added information from Stockholm County specifically, to assess all types of medical care over a more recent time period. By comparing periods adjacent to the pregnancy, we observed a sudden decrease in healthcare contacts for depression and anxiety disorders among mothers. However, the fact that the chance of getting a diagnosis statistically increases with time and potentially influence the findings from our comparisons of adjacent periods, we also applied a permutation approach. This approach randomly interchanged the perinatal periods between parents of the same gender and birth year. Doing so, we were able to assess the occurrence of healthcare contacts during an individual's perinatal periods, and contrast them to the occurrence in the same individual during permuted periods that would represent a biologically possible distribution, yet cover a non-perinatal time of life. When we compared the occurrence between these periods, we observed a decrease

during the real perinatal periods, which further gave support to the observed reduction in healthcare utilization for mental health related problems during this period in life. This reduction could either denote an actual decrease in mental illness, reduced detection, or both. More studies, preferably closer to the clinics, are warranted to unravel the mechanisms behind the observed patterns in healthcare utilization.

In conclusion, the studies within this thesis demonstrate that genetically informed designs are very useful in epidemiological research. The genetically informed pharmacoepidemiological approaches, through the within-individual design in Study I, and through the within-family design in study III, may be viewed as a combination of a classic epidemiological approach and a randomized controlled trial. As such, it may provide important information that would not been possible to acquire in other ways, or may have been a lot more costly to acquire using other methods. Even with strict criteria for inclusion, Study I includes far more subjects than would have been economically and morally plausible with a randomized controlled trial. Therefore, this type of observational study of medication effects may serve as an important first step that could be followed up with randomized controlled trials.

Moreover, through the application of these designs with large-scale register data, the studies of this thesis provide enhanced understanding of mental illness in general, and bipolar disorder and perinatal depression in particular. In doing so, the work will hopefully provide information that will assist in moving away from the current stigmatized view of mental illness. To further get an idea of the potential future direction of mental illness, it can be useful to contrast mental illness to the somatic disorder of cancer, just like in the introduction of this thesis. Only a couple of decades ago, cancers were also stigmatized disorders, in which lack of understanding of the underlying complex mechanisms gave rise to ideas that cancer was in fact the result of "bad attitude".[240] This was not only wrong, but also induced a lot of stress and anxiety among the individuals suffering from cancer.[241] Today we know a lot more about cancers, and even though there is still stigma surrounding cancer, it is not as prevalent as before. In much the same ways, the lack of understanding surrounding mental illness commonly cause the suffering individuals to be blamed for their illness or outcomes as direct results of the illness.

Hopefully, the field of psychiatric research will move in the same direction as the field of cancer research, and with increased understanding of the complex mechanisms behind the disorders, better treatment and less stigma will follow.

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