Department of Psychiatry,
University of Helsinki
Helsinki, Finland

REPRODUCTIVE HEALTH AMONG FINNISH WOMEN WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

Laura Simoila

ACADEMIC DISSERTATION

To be presented with permission of the Medical Faculty of the University of Helsinki
for public examination in the Christian Sibelius Auditorium, Välskärinkatu 12, Helsinki,
on November 8, 2019, at 12 noon

Helsinki 2019

Supervised by
Professor Nina Lindberg, MD, PhD
University of Helsinki

and

Professor Erkki Isometsä, MD, PhD
University of Helsinki

Reviewed by
Adjunct Professor Erika Jääskeläinen, MD, PhD
University of Oulu

and

Adjunct Professor Max Karukivi, MD, PhD
University of Turku

Official Opponent
Professor Minna Valkonen–Korhonen, MD, PhD
University of Eastern Finland

The Faculty of Medicine uses the Urkund (plagiarism recognition) system to examine all doctoral dissertations.

Cover Photo: Luciana Ferraz from Pixabay

ISBN 978-951-51-5371-5 (paperback)
ISBN 978-951-51-5372-2 (PDF)

Unigrafia, Helsinki, 2019

Dedicated to the silent women in the registers

TABLE OF CONTENTS

ABSTRACT

This nationally representative follow-up study aimed to assess induced abortions and the pregnancy- and delivery-related health outcomes of women with schizophrenia or schizoaffective disorder. In addition, this study aimed to investigate the negative perinatal health outcomes and out-of-home placements of their offspring.

Using the Care Register for Health Care, Finnish women born between 1965 and 1980 diagnosed with schizophrenia or schizoaffective disorder were identified during the follow-up period ending 31 December 2013 (n = 5214). For each case, five age- and place-of-birth–matched controls were obtained from the population register (n = 25,999). Through the end of 2013, we identified 162 singleton pregnancies among affected women and 4683 pregnancies among unaffected controls. In this study, we used the Medical Birth Register, the Induced Abortion Register, the Register of Congenital Malformations, and the Child Welfare Register to gather information about mothers and their offspring.

We found that the incidence of induced abortions in women with schizophrenia or schizoaffective disorder is similar to that among population-level controls, but their risk per pregnancy was over two-fold.

Women with schizophrenia or schizoaffective disorder were significantly older and more often single at the beginning of a pregnancy. Furthermore, affected women's body mass index (BMI) before pregnancy was significantly higher and they smoked significantly more often both at the beginning of a pregnancy and after the first trimester.

During pregnancy, the risks of a pathological oral glucose test, the initiation of insulin, rapid fetal growth, premature contractions, and hypertension were significantly higher among affected women. Focusing on obstetric complications, the risks of labor induction, deliveray by Cesarean section, and delivery by elective Cesarean section were also significantly higher among affected women.

The risks of premature birth, a low birthweight, a low 1-min Apgar score, assisted ventilation, resuscitation, neonatal monitoring, and having a major congenital anomaly were also significantly higher among babies born to a mother with schizophrenia or schizoaffective disorder.

Children with an affected mother were placed out-of-home significantly more often than those with an unaffected mother. Among affected mothers, single motherhood and smoking at the beginning of a pregnancy, but not unwanted perinatal health outcomes in the child increased the risk of out-of-home placement.

To conclude, schizophrenia and schizoaffective disorder correlate with some risk factors related to pregnancy, as well as with some pregnancy- and delivery-related

complications. Maternal schizophrenia and schizoaffective disorder associate with some negative perinatal health outcomes, as well as with the out-of-home placement of the offspring. Family planning services, targeted health education and lifestyle interventions, and training in parenting skills should be offered to affected women who plan their pregnancies, who are mothers-to-be, and who already have children. Furthermore, intensive collaboration between healthcare professionals, gynecologists, obstetricians, and social workers are needed.

Key words: delivery, induced abortion, pregnancy, postpartum period, schizoaffective disorder, schizophrenia, out-of-home placement, women

TIIVISTELMÄ

Tämän kansallisen rekisteripohjaisen seurantatutkimuksen pyrkimyksenä oli selvittää skitsofreniaa tai skitsoaffektiivista häiriötä sairastavien naisten abortteihin, raskauksiin ja synnytyksiin liittyvä erityispiirteitä sekä tutkia heidän jälkeläistensä vastasyntyneisyyskauden mahdollisia terveysongelmia ja kodin ulkopuolelle sijoittamista.

Terveyden ja hyvinvoinnin laitoksen ylläpitämän hoitoilmoitusjärjestelmän (HILMO) avulla poimittiin ne suomalaiset naiset, jotka olivat syntyneet vuosina 1965–1980 ja joilla oli diagnosoitu skitsofrenia tai skitsoaffektiivinen häiriö seurantakauden päättymiseen 31.12.2013 mennessä (n = 5214). Kutakin skitsofreniaan/skitsoaffektiiviseen häiriöön sairastunutta naista kohti valittiin väestörekisteristä satunnaisotoksella viisi ikä- ja syntymäpaikkakaltaistettua verrokkia (n = 25999). Vuoden 2013 loppuun mennessä skitsofreniaan tai skitsoaffektiiviseen häiriöön sairastuneilla naisilla oli 1162 yksisikiöistä raskautta, kun taas vastaavasti terveillä verrokkinaisilla niitä oli 4683. Äitien ja heidän jälkeläisiään koskevat tiedot kerättiin Terveyden ja hyvinvoinnin laitoksen ylläpitämästä syntymärekisteristä, aborttirekisteristä, epämuodostumarekisteristä sekä lastensuojelurekisteristä.

Seurantajakson aikana skitsofreniaa tai skitsoaffektiivista häiriötä sairastavilla naisilla aborttien ilmaantuvuus ei eronnut tilastollisesti merkitsevästi verrokkien vastaavasta. Kun huomioitiin kaikki raskaudet, sairaiden naisten riski päätyä aborttiin oli yli kaksinkertainen.

Raskauden alkaessa skitsofreniaa tai skitsoaffektiivista häiriötä sairastavat naiset olivat tilastollisesti merkitsevästi vanhempia ja tilastollisesti merkitsevästi useammin vailla parisuhdetta. Heidän painoindeksinsä (BMI) ennen raskautta oli tilastollisesti merkitsevästi korkeampi, samoin he tupakoivat tilastollisesti merkitsevästi useammin sekä raskauden alussa että ensimmäisen raskauskolmanneksen jälkeen.

Riski raskaudenaikaiseen patologiseen sokerirasitustestiin, insuliinihoidon aloittamiseen, ennenaikaisiin supistuksiin, korkeaan verenpaineeseen sekä sikiön nopeaan kasvuun oli merkitsevästi kohonnut skitsofreniaa sairastavilla naisilla. Skitsofreniaa sairastavilla naisilla oli tilastollisesti merkitsevästi kohonnut riski synnytyksen käynnistämiseen, keisarinleikkaukseen ja suunniteltuun keisarinleikkaukseen.

Riski syntyä ennenaikaisena, alhaiseen syntymäpainoon, mataliin 1-minuutin Apgar-pisteisiin, synnytyksen jälkeisen lisähapen saantiin, seurantaan vastasyntyneiden teho-osastolla ja synnynnäisiin epämuodostumiin oli tilastollisesti merkitsevästi korkeampi vastasyntyneillä, joiden äiti sairasti skitsofreniaa tai skitsoaffektiivista häiriötä. Skitsofreniaa tai skitsoaffektiivista häiriöitä sairastavien äitien

lapset sijoitettiin kodin ulkopuolelle tilastollisesti merkitsevästi useammin kuin verrokkiäitien lapset. Tupakointi ja parisuhteen puuttuminen raskauden alussa lisäsivät skitsofreniaa tai skitsoaffektiivista häiriötä sairastavien äitien lasten kodin ulkopuolelle sijoittamisen riskiä tilastollisesti merkitsevästi, kun taas vastasyntyneen synnytyksen jälkeiset terveysongelmat eivät tätä riskiä tilastollisesti merkitsevästi nostaneet.

Yhteenvetona voidaan todeta, että skitsofreniaa tai skitsoaffektiivista häiriötä sairastavien naisten raskauksiin ja synnytyksiin liittyy tiettyjä riskitekijöitä ja erityispiirteitä. Lisäksi voidaan todeta, että äidin sairauden ja tiettyjen vastasyntyneen terveysongelmien sekä äidin sairauden ja jälkeläisen kodin ulkopuolelle sijoituksen välillä on merkittävä yhteys. Perhesuunnittelupalveluja, kohdennettuja terveyskasvatus- ja elämäntapainterventioita sekä vanhemmuustaitojen tukemista tulisi tarjota niille skitsofreniaa tai skitsoaffektiivista häiriötä sairastaville naisille, jotka suunnittelevat raskautta, ovat tulevia äitejä tai joilla on jo lapsia. Tiivistä yhteistyötä tarvitaan psykiatrian alan ammattilaisten, naistentautien ja synnytysten erikoislääkäreiden sekä sosiaalityöntekijöiden kesken.

Asiasanat: abortti, kodin ulkopuolinen sijoitus, lapsivuodeaika, naiset, raskaus, skitsoaffektiivinen häiriö, skitsofrenia, synnytys

LIST OF ABBREVIATIONS

BMI	Body mass index
95% CI	95% confidence interval
DSM-I	Diagnostic and Statistical Manual of Mental Disorders, 1st edition
DSM-II	Diagnostic and Statistical Manual of Mental Disorders, 2nd edition
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-IIIR	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECT	Electroconvulsive therapy
EUROCAT	European Surveillance of Congenital Anomalies
GEE	Generalized estimating equation
HR	Hazard ratio
ICD-8	International Classification of Diseases and Related Health Problems, 8th revision
ICD-9	International Classification of Diseases and Related Health Problems, 9th revision
ICD-10	International Classification of Diseases and Related Health Problems, 10th revision
ICD-11	International Classification of Diseases and Related Health Problems, 11th revision
IQ	Intelligence quotient
IQR	Interquartile range
IRR	Incidence rate ratio
OR	Odds ratio
PIF Study	Psychosis in Finland Study
RID	Relative infant dose
RR	Relative risk
RRadj	Adjusted relative risk
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitor
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals (studies I–IV):

I. Simoila L, Isometsä E, Gissler M, Suvisaari J, Sailas E, Halmesmäki E, Lindberg N. Schizophrenia and induced abortions: A national register-based follow-up study among Finnish women born between 1965–1980 with schizophrenia or schizoaffective disorder. *Schizophr Res* 2018; 192: 142–147.

II. Simoila L, Isometsä E, Gissler M, Suvisaari J, Halmesmäki E, Lindberg N. Schizophrenia and pregnancy: a national register-based follow-up study among Finnish women born between 1965–1980 with schizophrenia or schizoaffective disorder. *Arch Womens Ment Health* 2019;

III. Simoila L, Isometsä E, Gissler M, Suvisaari J, Halmesmäki E, Lindberg N. Obstetric and perinatal health outcomes related to schizophrenia: A national register-based follow-up study among Finnish women born between 1965 and 1980 and their offspring. *Eur Psychiatry* 2018; 52: 68–75.

IV. Simoila L, Isometsä E, Gissler M, Suvisaari J, Sailas E, Halmesmäki E, Lindberg N. Maternal schizophrenia and out-of-home placements of offspring: a national follow-up study among Finnish women born 1965–1980 and their children. *Psychiatry Res* 2019; 273: 9–14.

The publications are referred to in the text by their Roman numerals. The publications are reprinted here with the permission of their copyright holders.

1 INTRODUCTION

Throughout the nineteenth century and at the beginning of the twentieth century, the concept of eugenic ideology flourished. In 1934 in Finland, a law on forced sterilization was enacted and a government-funded sterilization program was implemented across the country. From 1935 through 1970, approximately 7500 people—primarily women—were sterilized according to that sterilization law (Hietala, 2009). In his thesis, Borgström (1958) studied sterilizations in Finland that took place between 1935 and 1955. According to him, almost half of the individuals sterilized suffered from an intellectual disability, while persons with schizophrenia and epilepsy were also sterlized. Almost 70% of the sterilizations were performed involuntarily. The Finnish sterilization law was reviewed in 1970, and the abovementioned eugenic motivations prompting sterilization were omitted from the revised law.

Until the 1980s, psychiatric treatment for persons with severe mental disorders was primarily provided in mostly closed institutions. Thus, female patients' possibilities to meet the opposite sex remained largely limited (Hemminki et al., 1997). In addition, prolactin-raising antipsychotics partly explained the diminished general fertility rate among women with schizophrenia (Howard et al., 2002). Both the ongoing de-institutialization, as well as the use of modern antipsychotic medications with fewer endocrine side effects, led to an increase in their relative fertility (Solari et al., 2008; Vigod et al., 2012).

Unfortunately, little attention has been paid in the research and service development to the fact that many women with schizophrenia are mothers or mothers-to-be (Diaz-Caneja & Johnson, 2004; Kelly & Conley, 2004). Moreover, psychiatric nursing personal has been surprisingly reluctant to discuss issues related to sexuality and parenting with their patients (Burns et al., 2001; Haboubi & Lincoln, 2003). According to Quinn et al. (2011), nurses feel ambivalent about initiating such discussions because they do not view it as part of their roles as nurses; instead, they consider their patients too ill to discuss sex and are themselves uncomfortable discussing such topics. However, according to a survey conducted among patients diagnosed with psychosis conducted by McCann (2000), patients demonstrated a willingness to talk about their intimate feelings and felt that their psychiatric symptoms are not exacerbated following such discussions. Yet, women with schizophrenia report experiencing stigma related to sexual and parenting issues (Jeffery et al., 2013). It is clear that women who are mothers or mothers-to-be and who use mental health services face specific challenges in managing the contradictions between their dual identity (Davies & Allen, 2007). Healthcare

professionals, then, must use their disciplinary power in a positive way to help women navigate this dual identity as patient and parent (Davies & Allen, 2007).

This thesis then focuses on the reproductive health of Finnish women with schizophrenia or schizoaffective disorder. To do so, I rely on high-quality Finnish health - and social-care registers to shed light on induced abortions, pregnancy, delivery, and motherhood among such women with schizophrenia or schizoaffective disorder.

2 REVIEW OF THE LITERATURE

2.1 SCHIZOPHRENIA

Schizophrenia is one of the most severe psychiatric disorders, characterized by pronounced disturbances in the fundamental processes governing human behavior (Insel, 2010). The disorder typically manifests with a marked social and occupational impairment, carrying a significant health, social, and economic burden, not only for patients, but also for families, caregivers, and the broader society (Chong et al., 2016).

The core symptoms of schizophrenia constitute positive (hallucinations and delusions), negative (a lack of drive and volition, and withdrawal from social interaction), disorganized (positive thought disorder and bizarre behaviors), and cognitive (disturbances in attention, memory, and executive functioning) symptoms. **Table 1** summarizes the diagnostic criteria of schizophrenia according to the International Classification of Diseases and Related Health problems (ICD), 10th edition (ICD-10; World Health Organization, 1992), ICD-11 (draft, available at http://gcp.network), and the Diagnostic and Statistical Manual of Mental Disorders (DSM), 5th edition (DSM-5) (American Psychiatric Association, 2013) classifications.

The prevalence of schizophrenia falls between 0.4% and 0.7%, depending on the prevalence estimate applied (Saha et al., 2005). The lifetime prevalence of schizophrenia in Finland reached 0.9% in the Psychoses in Finland (PIF) Study (Perälä et al., 2007). The PIF Study, based on a large general population health examination study—the Health 2000 Study—included a study sample representative of the Finnish population aged 30 years and older. Schizophrenia rarely onsets before the age of 13 (McClellan & Stock, 2013), since the prevalence of childhood-onset schizophrenia occurs in 1 in 10,000 children (Remschmidt & Theisen, 2005). The frequency of schizophrenia increases considerably in adolescence (Remschmidt & Theisen, 2005), reaching a peak in early adulthood, and gradually declining until the age of 60, after which incidence rates level off (van der Werf et al., 2014).

The etiology of schizophrenia is heterogeneous. The genetic risk for schizophrenia is high (around 85%), but environmental factors also influence the risk of developing the disorder (van Os et al., 2010; Sullivan et al., 2012; Hilker et al., 2018). A genetic vulnerability, pre- and perinatal hazards to the brain, and adverse life events in early childhood appear to alter neurodevelopment and sensitize the dopamine system in the brain (Howes & Murray, 2014). Adversities experienced during childhood and adolescence combined with an underlying susceptibility to an increased dopamine release are thought to cause a bias in the interpretation of experiences

during stressful situations and lead to psychotic interpretations of neutral incidents (Howes & Murray, 2014; Hietala et al., 2015).

All types of familial psychiatric disorders are associated with an increased risk of schizophrenia. Nearly 30% of schizophrenia cases in the population can be attributed to a family history of psychiatric issues in general, compared to 6% attributable to a family history of schizophrenia specifically (Mortensen et al., 2010). However, 85% of individuals with schizophrenia have no first-degree relative with this disorder (McGlashan & Johannessen, 1996). Pre- and perinatal complications, including maternal infections and hypertension (Suvisaari et al., 2013), abnormal fetal development, and obstetric complications (Cannon et al., 2002; Forsyth et al., 2013) significantly correlate with schizophrenia. In addition, mothers with schizophrenia exhibit an increased health-risk behavior during pregnancy, such as smoking and substance misuse which are related to obstetric complications (Bennedsen, 1998). Furthermore, an unwanted pregnancy (Myhrman et al., 1996) and antenatal stress (van Os & Selten, 1998; Selten et al., 1999) appear to increase the risk of schizophrenia. Still, the pathogenesis and underlying causes remain unknown (Rees et al., 2015).

Table 1. Diagnostic criteria of schizophrenia according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10), the draft of the International Classification of Diseases and Related Health Problems,11th revision (ICD-11), and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).

ICD-10: F20	Symptoms must be present for most of the time during a psychotic illness episode lasting for at least one month
	At least one of the following:
	A1. Thought echo, thought insertion or withdrawal, and thought broadcasting
	A2. Delusions of control, influence, or passivity, clearly referring to body or limb movements or specific thoughts, actions, or sensations; delusional perception
	A3. Hallucinatory voices providing a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body
	A4. Persistent delusions of other kinds considered culturally inappropriate and completely impossible
	Or at least two of the following:
	B1. Persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without a clear affective content or by persistent overvalued ideas
	B2. Neologisms, breaks, or interpolations in the train of thought resulting in incoherence or irrelevant speech
	B3. Catatonic behavior, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor
	B4. Negative symptoms, such as marked apathy, a paucity of speech, and a blunting or incongruity of emotional responses, typically resulting in social withdrawal and a diminishing social performance

ICD-11: 6A21	At least two of the following symptoms must be present most of the time for a period of one month or more. At least one of the qualifying symptoms should be from item A through D in the list below: A. Persistent delusions (e.g., grandiose delusions, delusions of reference, or persecutory delusions) B. Persistent hallucinations (typically auditory, although they may be in any sensory modality) C. Disorganized thinking (formal thought disorder; e.g., tangentiality and loose associations, irrelevant speech, or neologism). When severe, the person's speech may be so incoherent as to be incomprehensible (e.g., word salad). D. Experiences of influence, passivity, or control (e.g., the experience that one's thoughts or actions are not generated by oneself, are being placed in one's mind, or withdrawn from one's mind by others, or that one's thoughts are being broadcast to others) E. Negative symptoms such as affective flattening, alogia, or a paucity of speech, avolition, asociality, and anhedonia F. Grossly disorganized behavior noted in any form of a goal-directed activity (e.g., behavior that appears bizarre or purposeless, or unpredictable or inappropriate emotional responses that interfere with the organization of one's behavior) G. Psychomotor disturbances, such as catatonic restlessness or agitation, posturing, waxy flexibility, negativism, mutism, or stupor
DSM-5: 295.90	A. Two (or more) of the following, each present for a significant portion of time during a one-month period (or less if successfully treated). At least one of these must be 1, 2, or 3. 1. Delusions 2. Hallucinations 3. Disorganized speech 4. Disorganized or catatonic behavior 5. Negative symptoms B. For a significant portion of the time efrom the onset of the disturbance, the level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is a failure to achieve expected level of interpersonal, academic, or occupational functioning). C. Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (less if successfully treated) that meet criterion A and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance manifest as only negative symptoms or as two or more symptoms listed in criterion A in an attenuated form. D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features are ruled out. E. The disturbance is not attributable to the physiological effects of a substance or another medical condition. F. If there is a history of autism spectrum disorder or a communication disorder with a childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations in addition to other required symptoms of schizophrenia are present for at least one month (or less if successfully treated).

2.2 SCHIZOAFFECTIVE DISORDER

Schizoaffective disorder is a psychiatric disorder characterized by the same kinds of abnormal thought processes as schizophrenia, while also including dysregulated emotions (Malaspina et al., 2013). **Table 2** summarizes the diagnostic criteria of schizoaffective disorder based on the ICD-10 (World Health Organization, 1992), ICD-11 (draft; http://gcp.network), and DSM-5 (American Psychiatric Association, 2013) classifications. The onset of schizoaffective disorder typically occurs in young adulthood, with a lifetime prevalence rate of 0.3% based on the PIF Study (Perälä et al., 2007).

Schizophrenia and bipolar illness appear to lie at opposite ends of a disease continiuum, with schizoaffective disorder falling roughly in the middle (Correll, 2010). Neuropsychological studies suggest that similar patterns of cognitive impairment, general intelligence quotient (IQ) levels, and motorskill and language impairment all occur in schizophrenia, schizoaffective disorder, and psychotic bipolar disorder, although the greatest impairment appears to accompany schizophrenia (Hill et al., 2008; Barch and Keefe, 2010). Bora et al.'s (2009) review examined cognitive studies of symptomatic patients with either schizophrenia or schizoaffective disorder, as well as cognitive studies of patients whose condition stabilized. In the acute phase, few differences were found in patients' neurocognitive performance. However, when comparing stabilized patients, patients with schizoaffective disorder tended to present with milder deficits than those with schizophrenia. The levels of premorbid adjustment and psychosocial functioning appear to differ between patients with schizophrenia and schizoaffective disorder.

According to Saracco–Alvarez et al. (2009), patients with schizoaffective disorder enjoyed a significantly better premorbid adjustment than patients with schizophrenia in late adolescence. For example, scholastic performance and peer relationships were less impaired among patients with schizoaffective disorder. In a study by Norman et al. (2005), patients with schizoaffective disorder exhibited better premorbid adjustment academically than patients with schizophrenia, although no difference was observed in the social domain. Bellack et al. (1989) compared role functioning and social skills among patients with schizophrenia (with or without negative symptoms), schizoaffective disorder, and bipolar disorder, respectively. While patients with schizophrenia without negative symptoms showed similar levels of social disability compared with patients with schizoaffective disorder or bipolar disorder, those with negative symptoms were more impaired. According to Cheniaux et al.'s (2008) review, the schizophrenia group contained the highest proportion of never-married patients, followed by those with schizoaffective disorder, and then those with mood disorders. Rates of unemployment followed a similar pattern. Premorbid social adaptation was lowest in the schizophrenia group, better among

patients with schizoaffective disorder, and highest among patients with mood disorders. Cognitive deficits were greatest in the schizophrenia group, followed by those with schizoaffective disorder, and then those with mood disorders.

Table 2. Diagnostic criteria of schizoaffective disorder according to the International Classification of Diseases and Related Health Problems (ICD), 10th revision (ICD-10), the draft of ICD, 11th revision (ICD-11), and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).

ICD-10: F25	A. Psychotic symptoms of schizophrenia (except for negative and persistent hallucinatory symptoms) present for most of the time during a period of at least two weeks B. Manic or at least moderately severe depressive episode and psychotic symptoms must be present within the same episode of the disorder and simultaneously for at least a portion of it C. Disorder is not caused by substance use or organic brain disease
ICD-11: 6A21	A. All diagnostic requirements for schizophrenia are met concurrently with mood symptoms that meet the diagnostic requirements of a moderate or severe depressive episode, a manic episode, or a mixed episode B. The onset of the psychotic and mood symptoms are either simultaneous or occur within a few days of one another C. The duration of symptomatic episodes is at last one month for both psychotic and mood symptoms D. The symptoms or behaviors are not a manifestation of another medical condition and are not due to the effect of a substance or medication on the central neural system, including withdrawal effects
DSM-5: 295.70	A. An uninterrupted period of illness during which there is a major mood (depressive or manic) episode concurrent with criterion A of schizophrenia B. Delusions or hallucinations for two or more weeks in the absence of a major mood (depressive or manic) episode during the lifetime duration of the illness C. Symptoms that meet the criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of the illness D. The disturbance is not attributable to the effects of a substance or another medical condition

2.3 TREATMENT FOR SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

The goals when treating patients with schizophrenia and schizoaffective disorder include targeting symptoms, preventing relapse, and increasing adaptive functioning such that the patient can be integrated back into the community (Patel et al., 2014). The treatment of these disorders relies on a combination of pharmacotherapy and psychosocial rehabilitation (McGurk et al., 2007; Leucht et al., 2009; Dixon et al., 2010; Grant et al., 2012; Roberts et al., 2014).

Pharmacotherapy primarily relies on antipsychotic drugs as the main treatment for schizophrenia. Up to 60% of subjects with schizophrenia respond to antipsychotic medication (Sinclair & Adams, 2014), a relatively effective treatment for positive symptoms (Leucht et al., 2009). However, antipsychotic medications have proved less effective in the treatment of negative and cognitive symptoms, the two symptom dimensions demonstrating the most robust relationship to functional outcome (Karow et al., 2014; Kirkpatrick, 2014). Antipsychotics are also associated with metabolic, cognitive, sexual, and extrapyramidal side effects (de Boer et al., 2015; MacKenzie et al., 2018). When treating schizoaffective disorder, combinations of antipsychotics, mood stabilizers, and antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are typically used (Cascade et al., 2009).

In order to improve the efficacy of treatment, pharmaceuticals should be combined with psychosocial interventions (Valencia et al., 2015). Specific vocational and psychological interventions can improve the functional outcome (van Os & Kapur, 2009). According to the Finnish Current Guideline on Schizophrenia (Schizophrenia: Current Care Guidelines Abstract, 2015), psychosocial interventions, including cognitive-behavioral therapy, psychoeducation, and social skills training, as well as cognitive rehabilitation should be integrated with antipsychotic medication in individuals with schizophrenia. Persons with schizoaffective disorder generally respond best to a combination of medications, psychotherapy, and life-skills training (Schizophrenia: Current Care Guidelines Abstract, 2015). In addition, family intervention may decrease the risk of relapse, improve treatment adherence, and reduce rehospitalizations (Pharoah et al., 2010).

2.4 SEX DIFFERENCES IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

Sex differences in schizophrenia represent one of the most consistently reported aspects of schizophrenia (Abel et al., 2010). These differences are described in almost all features of the illness from incidence, prevalence, mean age at onset, clinical presentation, course of the disease, and treatment responses. Aleman et al.'s (2003) meta-analysis identified a mean ratio of male-to-female schizophrenia incidence of 1.42 [95% confidence interval (CI)1.30–1.56]. Similarly, McGrath et al. (2008) found a median ratio of 1.4 (10^{th} and 90^{th} centiles, 0.9 and 2.4). Surprisingly, this is not reflected in the prevalence of schizophrenia (Saha et al., 2005; Perälä et al., 2007). Most studies have found that women experience a later onset of schizophrenia and a better course of illness than men (Häfner et al., 1993; Abel et al., 2010; Pedersen et al., 2014; van der Werf et al., 2014). Typically, men present with a poorer premorbid adjustment and negative symptoms appear more commonly in men, whereas women experience depressive symptoms more commonly (Goldstein & Link, 1988; Morgan

et al., 2008; Abel et al., 2010). Women with schizophrenia remain in hospital for shorter durations than men and are less frequently readmitted (Grossman et al., 2008). Researchers have explored the possible biopsychosocial causes for these differences. Most findings support the "estrogen hypothesis", which emphasises the possible neuroprotective effect of estrogen in women (Falkenburg & Tracy, 2014). Differences can also be attributed to a differing psychological vulnerability between men and women as well as to various social factors.

Schizoaffective disorder is substantially more prevalent among women (Perälä et al., 2007). Specifically, a more than twofold female-to-male predominance among individuals with the depressed subtype of schizoaffective disorder and no sex difference in the bipolar subtype of schizoaffective disorder have been reported (Fochtmann et al., 2009).

2.5 PHYSICAL HEALTH OF INDIVIDUALS WITH SCHIZOPHRENIA

Individuals with schizophrenia carry a high risk for a wide range of somatic illnesses (Leucht et al., 2007; Smith et al., 2013). According to a recent study including more than 7000 Spanish individuals with schizophrenia, 55.6% exhibited one comorbid chronic physical condition and 29.3% experienced two or more comorbidities (Gabilondo et al., 2017).

In that study, hypertension, Parkinson's disease, and diabetes represented the most prevalent chronic conditions followed by hypothyroidism, dyspepsia, lung diseases (i.e., emphysema, chronic bronchitis, and chronic pulmonary disease), degenerative joint disease, and chronic liver or pancreatic disease. Overall, women exhibited a higher prevalence of comorbidities than men. In Finland, Eskelinen's (2017) thesis comprised 275 outpatients with schizophrenia, with a mean age of 45 from three different southern municipalities. All patients underwent a structured, comprehensive health examination, during which almost half of participants reported experiencing distressing somatic symptoms on a daily basis. During the health examination, 87.6% needed somatic intervention (i.e., further treatments, examinations, monitoring, and prescriptions).

Schizophrenia associates with premature mortality. Both suicide risk (Cassidy et al., 2018) and accidental deaths (Hellemose et al., 2018) appear elevated in this patient group, although somatic comorbidities play an essential role in premature mortality (Laursen et al., 2011). According to a nationwide Swedish cohort study with more than 8000 individuals with schizophrenia, on average, men with schizophrenia died 15 years earlier than men in general, and women with schizophrenia died 12 years earlier than women in the general population, an observation attributed to unnatural deaths (Crump et al., 2013). The association between schizophrenia

and mortality was stronger among women. In Finland, a follow-up study among a nationally representative sample of more than 8000 persons aged 30 or older carried out by Suvisaari et al. (2013) reported that people with schizophrenia and other nonaffective psychoses exhibited an elevated mortality risk. In individuals with a psychotic disorder, smoking and type 2 diabetes predicted mortality.

The specific reasons for the above adverse health outcomes remain unknown, although some possible explanations include unhealthy lifestyles, the side effects of psychopharmacological treatments, or selective barriers affecting access to medical treatment resulting in either underdiagnosis or undertreatment (Muck-Jorgensen et al., 2000; Druss et al., 2001; Laursen et al., 2011; Smith et al., 2013).

2.5.1 OVERWEIGHT AND OBESITY

Weight gain is linked to schizophrenia. One reason for this stems from poor dietary habits (Manu et al., 2015). A systematic review by Dipasquale et al. (2013) found that patients with schizophrenia are more likely to consume a diet poor in fiber and fruit while rich in saturated fat. Women with schizophrenia, however, tend to make healthier food choices and their diets consist of more fruits and vegetables than those among men. Other explanations for weight problems include a sedentary lifestyle and diminished physical activity (Manu et al., 2015).

Indeed, according to a recent meta-analysis by Vancampfort et al. (2017), people with severe mental illness remained more sedantary than healthy controls. Their analysis revealed that approximately half of those with severe mental illness do not meet the recommendation of at least 150 minutes of moderate or intense physical activity per week. Less physical activity levels associated with being male, single, and unemployed, as well as a longer illness duration and a schizophrenia diagnosis.

In a recent Finnish study (Sormunen et al., 2017), changes in physical activity were already observed before the onset of psychosis. In fact, a pattern of low physical activity was evident throughout childhood and adolescence among patients who later developed non-affective psychosis. Furthermore, weight gain stands as a common side effect of antipsychotics, affecting between 15% and 72% of patients (Holt, 2005). The propensity to cause weight gain differs between antipsychotics, but no agent should be considered weight-neutral (Bak et al., 2014). In fact, antipsychotics increase one's appetite and delay the satiety signalling resulting from serotonin 5-HT2C and histamine H1 receptor antagonism, leading to increased food intake (Correll et al., 2015). In addition, dopamine receptor antagonism and the effects on several neurotransmitters and gut hormones involved in appetite control participate in antipsychotic medication–induced weight gain (Manu et al., 2015; Siskind et al., 2016).

Antipsychotics may decrease resting energy expenditure (Manu et al., 2015), while some evidence exists indicating an elevated risk related to some receptor genes predisposing individuals to antipsychotic medication–induced weight gain (Shams & Muller, 2014). The risk of weight gain is particularly pronounced among patients exposed to antipsychotic medication for the first time in their lives (Tarricone et al., 2010; Keinänen et al., 2015).

2.5.2 SMOKING

According to a meta-analysis by De Leon & Diaz (2005), smoking prevalence among patients with schizophrenia is up to five times higher than other clinical and non-clinical groups. Schizophrenic patients are also more often heavy smokers with longer histories of smoking (Tidey et al., 2005; Williams et al., 2005). In Finland, Partti et al.'s (2015) population-based study reported that about 44% of individuals with schizophrenia smoked daily, whereas only approximately 23% of individuals with no psychotic disorder smoked daily. Furthermore, among individuals with schizophrenia, more than 30% smoked more than one pack per day.

Risk factors including poverty, a low education level, and environments lacking support to stay or become smoke-free may impact the initiation of smoking and endanger patients' attempts to quit (Tidey & Miller, 2015). The most popular explanation for the association between schizophrenia and smoking remains the so-called self-medication hypothesis. That is, smoking releases dopamine from the brain, and patients who use antipsychotic medications appear to alleviate their extrapyramidal side effects, as well as negative symptoms through smoking (Ruther et al., 2014). Some evidence also suggests that schizophrenia and nicotine dependency may share common genetic pathways (Loukola et al., 2014).

2.5.3 ALCOHOL AND ILLEGAL DRUGS

In a meta-analysis, Koskinen et al. (2009) found that approximately one-fifth of patients with schizophrenia had a lifetime diagnosis of an alcohol use disorder. Hunt et al. (2018), however, found a prevalence of alcohol use disorders in individuals with schizophrenia spectrum disorders of 24.3%. Some evidence suggests that a comorbid alcohol use disorder worsens clinical outcomes among patients with schizophrenia. Specifically, such patients exhibit more psychotic symptoms and more severe depressive symptoms (Potvin et al., 2006 ; Potvin et al., 2007), poorer treatment compliance, increased somatic comorbidity, a risk of violence, more negative psychosocial events, more admissions to psychiatric hospitals, and longer hospital stays (Drake & Mueser, 1996; Dixon, 1999; Gregg et al., 2007).

In Hunt et al.'s (2018) meta-analysis, the prevalence of cannabis use disorder among individuals with schizophrenia spectrum disorders reached as high as 26.2%. Cannabis use correlated with an earlier onset of psychosis, increased symptom severity, higher rates of relapse, longer hospitalization times, and overall poorer quality-of-life outcomes (Johns, 2001; van Os et al., 2002; D'Souza et al., 2005; Foti et al., 2010; Galvez-Buccollini et al., 2012; Large et al., 2011; Di Forti et al., 2014; Manrique-Garcia et al., 2014; Patel et al., 2015; Bhattacharyya; 2015). However, according to a systematic review by Iseger & Bossong (2015), cannabidiol (CBD) may carry antipsychotic properties, and thus may represent a promising new agent in the treatment of schizophrenia.

Hunt et al. (2018) also found that the prevalence of stimulant use disorders among individuals with schizophrenia spectrum disorders reached 7.3%, while opiate use disorders affected 5.1% of patients. Finally, Hunt et al. (2018) revealed that all substance use disorders occur more often in men than in women.

2.6 THE REPRODUCTIVE HEALTH OF WOMEN WITH SCHIZOPHRENIA

2.6.1 BIRTH CONTROL

According to Matevosyan (2009), the number of lifetime sexual partners was relatively high while the use of contraceptives remained low among women with schizophrenia. Thus, women with schizophrenia are at high risk of sexually transmitted infections (Seeman & Ross, 2011). This risky behavior might relate to disorder-associated issues such as an inability to plan, an inability to assess risks, communications skill deficiency, as well as a lack of information, motivation, and skills (Meade & Sikkema, 2007; Seeman, 2013).

Several clinical studies with rather small sample sizes report a higher prevalence of induced abortion among women with schizophrenia than among unaffected women. A US study by Miller and Finnerty (1996) compared sexuality, reproduction, and the childrearing characteristics of 46 women with schizophrenia or schizoaffective disorder to those among 50 control subjects without a major mental disorder. Compared to controls, women with schizophrenic disorders experienced fewer planned pregnancies, more unwanted pregnancies, and more induced abortions. Dickerson et al. (2004) interviewed a total of 100 women (36 with a diagnosis of schizophrenia and 64 with a mood disorder diagnosis) from two outpatient psychiatric centers in the Baltimore area about their sexual and reproductive behaviors. Among the 73 women who had been pregnant, 46 (63%) pregnancies ended either because of an induced abortion or a spontaneous miscarriage.

Compared with women from a national survey, women with mental disorders were more likely to have had a pregnancy that did not result in a live birth. In a

Turkish study, Özcan et al. (2014) interviewed 292 female patients treated in an acute inpatient psychiatric ward in Istanbul (55 women with schizophrenia) using a questionnaire focused on reproductive health problems. Half of the study population reported that they had experienced an unplanned pregnancy, 44.8% of whom had undergone an induced abortion, twice the rate in Turkey in general (22%; Turkey Demographic and Health Survey 2008 data). Unfortunately, no nation-based cohort studies were published on this topic.

2.6.2 PREGNANCY

Women with schizophrenia exhibit many pregnancy-related risk factors.

Mothers-to-be with schizophrenia are often single and their pregnancies are more often unplanned than those among unaffected women (Matevosyan, 2011). Furthermore, mothers-to-be with schizophrenia appear to smoke more often (Bennedsen, 1998; Judd et al., 2014) than unaffected pregnant women. Pregnancy can also worsen the mental health of some women with schizophrenia. Psychological stress often relates to the background stress of poverty and unemployment, being single and the prospect of single parenthood, as well as social exclusion (Seeman, 2013). Among mothers-to-be with schizophrenia, those who are younger and who experience more negative effects on their physical health during pregnancy are more likely to report a worse mental health status (McNeil et al., 1983).

One high-risk symptom during pregnancy consists of the psychotic denial of pregnancy (Solari, 2010). Pregnant women who maintain the delusion that they are not pregnant may refuse prenatal care. Some of these women fail to recognize the symptoms of labor, and may have precipitous, unassisted deliveries. The psychotic denial of pregnancy can be intermittent, and occurs more frequently among women who previously lost custody of a child. This led to the hypothesis that the psychotic denial of pregnancy represents a coping mechanism to deal with the anticipated loss of the infant (Miller, 1990).

In addition, the pregnancy period correlates with elevated rates of psychiatric hospital admissions, whereby a high proportion of admissions occur as early as the first trimester (Harris et al., 2018). Pregnant women with schizophrenia are more likely to use alcohol (Bennedsen, 1998) and illicit drugs (Judd et al., 2014) than unaffected pregnant women. Their psychiatric admissions often associate with substance and alcohol misuse (Harris et al., 2018).

In relation to somatic pregnancy complications, women with schizophrenia carry a higher risk of venous thromboembolism (Ellman et al., 2007), pre-eclampsia and eclampsia (Ellman et al., 2007; Nguyen et al., 2013; Judd et al., 2014; Vigod et al., 2014), and gestational diabetes (Hizkiyahu et al., 2010; Nguyen et al., 2013; Judd et al., 2014). In addition, a tendency towards higher gestational hypertension

has also been reported (Ellman et al., 2007). Some studies reported that pregnant women with schizophrenia are hospitalized in maternity hospitals substantially more often than their unaffected counterparts (Ellman et al., 2007; Vigod et al., 2014), but affected women received less prenatal care than unaffected women (Miller & Finnerty, 1996).

2.6.3 ANTIPSYCHOTIC MEDICATION DURING PREGNANCY

Mothers-to-be with schizophrenia are often advised to continue their antipsychotic medication during pregnancy (McCauley-Elsom et al., 2010) since relapse rates are high (Spielvogel & Lee, 2010) and psychosis represents a serious risk to the fetus (Einarson, 2010; Jablensky et al. 2005). According to Tosato et al. (2017), after taking into account the parents' wishes, the most reasonable and least harmful treatment option for future mothers with schizophrenia appears to be continuing the use of the safest minimum dosage. Avoiding polypharmacy and intensive monitoring are also recommended (Seeman, 2013). In fact, the guidelines from the National Institute for Health and Care Excellence (2017) highlight advising patients about the safety of medications taken during pregnancy and the risk of relapse during pregnancy and the post-partum period. This is because women with schizophrenia remain at high risk during these periods, whereby high rates of medication cessation (Petersen et al., 2014; Taylor et al., 2015) associate with illness relapse (Taylor et al., 2015). A wealth of evidence supports the risks faced by women with schizophrenia and other psychotic illnesses presenting difficulties with bonding and attachment, as well as separation from their baby if an untreated psychosis occurs in the early post-partum period (Howard, 2000).

In the presence of risk factors for gestational diabetes, olanzapine should be avoided unless the patient's history suggests switching to another medication will significantly enhance her risk of recurrence (Barnes, 2011). Concerns over a potential for relapse typically outweigh concerns related to the dysglycemic effect of clozapine use (Barnes, 2011). If a woman takes either of these two antipsychotics, the treating physician should screen for gestational diabetes (Barnes, 2011). In addition, depot medication should not be initiated during pregnancy given the lack of dosing flexibility, while Barnes (2011) recommends that if a woman successfully establishes her status on a depot, it should be continued, particularly if the risk of psychosis recurrence is high. Substantial changes in pharmacokinetics (absorption, distribution, metabolism, and excretion) occur throughout gestation potentially requiring antipsychotic dosage adjustments during each trimester of pregnancy (Tracy et al., 2005; Pavek et al., 2009).

In general, dosage for olanzapine and clozapine (primarily metabolized via CYP 1A2) should be decreased since the CYP 1A2 enzymes down-regulate as pregnancy

advances. The doses of other antipsychotic medications may require increases since the primary metabolizing enzymes up-regulate. Individual variation will occur depending on the slow or rapid metabolizer status, particularly for drugs chiefly metabolized via CYP 2D6 (Feghali & Mattison, 2011; Monostory & Dvorak, 2011). Given the extent of individual variation and the many factors that determine the dose requirements, no guidelines exist for increasing or decreasing specific antipsychotic doses during pregnancy other than the general recommendation to keep dosages as low as possible and to monitor the patient closely (Barnes, 2011). In the month prior to the delivery due date, antipsychotic doses should be kept especially low to prevent both side effects and withdrawal symptoms in the newborn (Coppola et al., 2007; Gentile, 2010). Drugs administered near term may accumulate in the fetus as well as those following delivery when their clearance relies on the immature infant kidney, possibly producing adverse effects. The toxic effects of antipsychotic drugs observed in newborns include motor restlessness, dystonia, hypertonia, and tremors (Coppola et al., 2007; Gentile, 2010).

Larsen et al. (2015) stated in their recently published Danish clinical guidelines on the use of psychotropic drugs during pregnancy that olanzapine, risperidone, quetiapine, and clozapine can be used for schizophrenia. According to Larsen et al. (2015), sertraline and citalopram represent first-line treatments among SSRIs for depression. Using lithium is recommended if an overall assessment indicates mood-stabilizing treatment during pregnancy. Lamotrigine can also be used. Valproate and carbamazepin are contraindicated because of their teratogenicity. Electroconvulsive therapy (ECT) could represent an appropriate option in pregnant women with psychosis who are acutely suicidal, in a stupor or catatonia, and who have a life-threatening physical status caused by poor oral fluid intake (Jones, et al., 2014).

Studying the effects of antipsychotic medications on mothers with schizophrenia and their offspring remains challenging, since these women and their babies are subject to a cluster of associated vulnerabilities including genetic, socioeconomic, demographic, and lifestyle-related risk factors (Breadon & Kulkarni, 2019). Yet, Petersen et al. (2016) compared outcomes among women who continued antipsychotic medications during their pregnancies (cohort A; n = 416) with those among their peers who did not (cohort B; n = 670) and with women never prescribed antipsychotics (cohort C; n = 318,434). Interestingly, their research also pointed to the importance of associated lifestyle factors, since women who continued taking antipsychotics during pregnancy were older, more likely to smoke, drink alcohol or use illicit drugs, and more often obese. These researchers also used the Townsend score to rank socioeconomic deprivation. In that study, women who took antipsychotic medication during pregnancy were similarly disadvantaged when compared with their peers who discontinued antipsychotic medication, but far more disadvantaged than the general population of women giving birth during the same time period. Furthermore, the proportion of women with gestational diabetes was

similar in cohorts A (2.6%) and B (2.7%), but lower in cohort A than in cohort B after adjustments [adjusted relative risk (RRadj): 0.43 (95% CI 0.20–0.93)]. Premature birth or low birthweight occurred more commonly in cohort A (10%) than B (4.3%) and C (3.9%), in cohort A versus B (RRadj: 2.04 (95% CI 1.13–3.67), and in cohort A versus C (RRadj: 1.43 (95% CI 0.99–2.05). Major congenital malformations were more common in cohort A (3.4%) than B (2.2%) and C (2.0%). However, no significant difference was observed in cohort A versus B (RRadj: 1.79 (95% CI 0.72–4.47) or in cohort A versus C (RRadj: 1.59; 95% CI 0.84–3.00). In general, babies exposed to antipsychotic medication during the third trimester should be delivered in a setting with access to specialized nursery care and neonatal intensive care units (Breadon & Kulkarni, 2019). Some case studies report isolated incidences of developmental delays in babies exposed to atypical antipsychotics in utero (Karakula et al., 2004; Coppola et al., 2007; Mendhekar, 2007). Peng et al. (2013) investigated the developmental effects of atypical antipsychotics on infants born to mothers taking an atypical antipsychotic throughout the pregnancy. According to that case–control study, fetal exposure to atypical antipsychotics appear to cause short-term developmental delays in cognitive, motor, social-emotional, and adaptive skills and behaviors. Shao et al. (2015) compared clozapine and other atypical antipsychotics on the infant's neurodevelopment, finding that more infants exposed to clozapine as a fetus developed adaptive-behavior delays at 2 and 6 months of age compared with those exposed to other atypical antipsychotics. Meanwhile, infants exposed to clozapine experienced more disturbed sleep and a labile state at 2 months of age. But, all these differences disappeared at 6 months of age. Overall, substantial gaps in knowledge remain in this area, requiring much more research (Breadon & Kulkarni, 2019).

2.6.4 DELIVERY

Schizophrenia correlates with some adverse delivery-related maternal health outcomes. To date, only four population-based studies focusing on this specific topic have been published. I summarize these studies and their primary findings in **Table 3** below. According to a Danish study by Bennedsen et al. (2001a), women with schizophrenia experience an increased risk of interventions such as Cesarean section, vaginal-assisted delivery, amniotomy, and the pharmacological stimulation of labor. No important differences emerged between deliveries among women with schizophrenia who gave birth before and after their first admission to a psychiatric department. In Jablensky et al.'s (2005) Australian study, women with schizophrenia showed an increased risk for placental abruption and antepartum hemorrhage. However, after adjusting for age, marital status, plurality, and being an aboriginal, the difference in antepartum hemorrhage was no longer statistically

significant. According to Hizkiyahu et al. (2010) based on their study in Israel, the need for induction and to augment delivery remained significantly increased among women with schizophrenia. In Vigod et al.'s (2014) Canadian study, women with schizophrenia required more intensive hospital resources, including operative delivery and admission to a maternal intensive care unit. Finally, schizophrenia correlated with increased risks for placental abruption, septic shock, the induction of delivery, and Cesarean section.

Table 3. Increased risk of various delivery-related health outcomes and interventions among women with schizophrenia.

Study	Health outcome / intervention
Denmark: Bennedsen et al., 2001a	Pharmacological stimulation of labor [relative risk (RR) 1.21; RRa 1.13], induction of delivery by amniotomy (RR 1.63; RRa 1.56), vaginal-assisted delivery (RR 1.12; RRa 1.16), Cesarean section (RR 1.21; RRa 1.26) a = adjusted for year of birth, sex of child, mother's age, and parity
Australia: Jablensky et al., 2005	Placenta abruption [Odds ration (OR) 2.75; OR[a] 3.17] and antepartum hemorrhage [OR 1.65; OR[a] 1.33 (no longer statistically significant)] [a] adjusted for maternal age, maternal marital status, plurality, aboriginal ethinicity, and sex
Israel: Hizkiyahu et al., 2010	Induction of delivery (OR 2.4) and augmentation of delivery (OR 1.9)
Canada: Vigod et al., 2014	Placental abruption (OR[a] 1.98), septic shock (OR[a] 2.27), induction of delivery (ORa 1.35), Cesarean section (OR[a] 1.45), and transfer to maternal intensive care unit (OR[a] 4.67) [a] adjusted for maternal age, parity, socioeconomic status, and premedical morbidity

2.6.5 POSTPARTUM

The neuroprotective estrogen hypothesis argues that higher estrogen levels during pregnancy may protect vulnerable women against psychiatric symptoms (Seeman & Lang, 1990; Grigoriadis & Seeman, 2002; Seeman, 2002). However, the sudden decrease in estrogen levels following delivery may increase a woman's vulnerability, particularly when compounded by sleep deprivation and the psychosocial stress of caring for a newborn (Wieck et al., 1991; Meakin et al., 1995; Grigoriadis & Seeman 2002). Active psychotic symptoms during the postpartum period have correlated with maternal self-harm and physical harm to the infant, as well as an inadequate maternal–infant attachment (Näslund et al., 1984; Stewart 1984; Sacker et al., 1996; Hipwell et al., 2000; Nilsson et al., 2002; Jablensky et al., 2005). In Munk-Olsen et al.'s (2009) Danish study, 15.7% of women with schizophrenia experienced a psychiatric hospitalization during the first year postpartum, with the highest risk for

hospitalization occurring within the first 60 days after delivery. A recent population-based cohort study from Ontario, Canada by Rochon-Terry et al. (2016) found that about 19% of women with schizophrenia had at least one psychiatric hospitalization in the first year postpartum. Furthermore, they found that the incidence rate of psychiatric hospitalization during pregnancy was 25 per 100 person-years and 33 per 100 person-years in the first year postpartum compared to a rate of 50 per 100 person-years in the year prior to conception. However, in the first 9 days postpartum, the incidence rate was as high as 179 per 100 person-years [incidence rate ratio (IRR) 3.59, 95% CI 2.74–4.69]. From 10 to 29 days postpartum, this decreased to 43 per 100 person-years (IRR 0.87, 95% CI 0.56–1.24), declining thereafter during the first year postpartum.

2.6.6 ANTIPSYCHOTICS AND BREAST-FEEDING

In modern mother-and-child medicine, risk assessment in connection with breastfeeding primarily relies on a quantitative estimate: How much medication is transferred to the child during breastfeeding? This quantitative estimate can be expressed as a relative infant dose (RID). However, no regulatory guidelines indicating the criteria for an acceptable exposure among nursed children exists. Internationally, no formal consensus exists either. The decision algorithm is modified in practice based on the observation of the likely side effects: drugs with undesirable properties regardless of RID (immune-modulating drugs, etc.) or drugs with a very long half-life (risk of accumulation). According to Larsen et al.'s (2015) Danish guidelines on psychotropic drugs during pregnancy and breastfeeding, olanzapine (RID < 2%, with no side effects described in nursed children), quetiapine (RID < 1%, with no side effects described in nursed children), and aripiprazole (RID < 1%, with no side effects described in nursed children) can be used. As a rule, risperidone is not recommended (RID 3–9%). Paliperidone, ziprasidone, amisulpride, and perphenazine are not recommended given the insufficient data. Clozapine's RID lies at <2%, yet is not recommended because of its side-effects profile. Haloperidol is also not recommended since its RID has been reported as high as 12%.

In focussing on SSRIs, Larsen et al. (2015) summarizes recommendations relying on sertraline and paroxetine, since these two drugs carry the fewest reported side effects and the lowest transfer rate into breast milk. Lithium carries a very high RID (12–30%), rendering its use typically not recommended. Valproate (RID 1–2%, with no side effects described among nursed children) and carbamazepine (RID 4–6%, with no side effects described among nursed children) can be used. The use of lamotrigine is possible during breastfeeding at doses of no more than 200-mg daily (with a relatively high RID at 9–18%).

2.6.7 PSYCHOSOCIAL INTERVENTIONS FOCUSING ON THE REPRODUCTIVE HEALTH OF WOMEN WITH SCHIZOPHRENIA

2.6.7.1 Family planning

Comprehensive care for women with schizophrenia means viewing each patient as a potential new mother (Seeman, 2013). Discussions about intimacy, sex, and conception should be offered to all women with schizophrenia of childbearing age (Seeman, 2013). Proactive family planning could reduce the rate of inintended pregnancies, since women with schizophrenia tend to have more limited knowledge of their family planning options (Solari et al., 2009). In fact, contraceptive counseling remains critical in women with schizophrenia (Seeman & Ross, 2011). As such, motivational interviewing can be used during this process (Petersen et al., 2005). Such counseling is a direct, client-centered style for eliciting behavior change by helping clients explore and resolve any ambivalence (Rollnick & Miller, 1995). Compared with nondirective counseling, a direct style is more focused and goal-oriented (Rollnick & Miller, 1995). Professionals should discuss the pros and cons of all family planning methods (Seeman & Ross 2011). However, contraceptives can only be prescribed once a woman understands what they are used for, how they should be used, as well as their contraindications, costs, and expected side effects (Seeman & Ross, 2011).

2.6.7.2 Pregnancy

All women of childbearing age admitted to a psychiatric ward should undergo a pregnancy test in order to initiate prenatal care as early as possible (Spielvogel & Lee 2010). If conception is accidental or unwanted, the patient may need help regarding decisions related to inducing an abortion (Seeman, 2013).

Smoking reduction or cessation remains important (Judd et al., 2014). Undoubtedly, pregnancy represents a time when all women are more motivated to quit smoking (Howard et al., 2013). Smoking cessation programs specifically geared towards pregnant women consist of advice and counseling, electronic and telephone support, cognitive-behavioral therapy, motivational interviewing, and feedback on fetal health (Petersen et al., 2010). According to a review by Coleman et al. (2011), nicotine replacement may be combined with these interventions, although its safety during pregnancy remains rather flimsy. Alcohol and other substance use screening is also important and, when necessary, motivational interviewing, psychoeducation, and cognitive-behavioral therapy should be offered (Seeman 2013). Nutritional counseling and lifestyle interventions that target diet and exercise are important towards preventing and controlling gestational diabetes (Seeman, 2013).

Psychological stress is often grafted onto the background stress of being single and the prospect of single parenthood and social exclusion (Seeman, 2013). Short-term, focused psychotherapy can prove useful in such situations for some pregnant women with schizophrenia (Solari et al., 2009). If support networks remain lacking, social services can provide interventions.

In Gentile & Fusco's (2019) recent review of managing pregnant women with schizophrenia, clinicians should consider an integrated approach that includes antipsychotic treatment, psychological treatment, optimal dietary approaches aimed at preventing excessive weight gain and gestational diabetes, meticulous gynecological and obstetric surveillance, and social and occupational support.

In 2010, an anticipatory child welfare notification was introduced to the Finnish child welfare law (www.finlex.fi). This notification can be made already during pregnancy if there is reason to suspect that the newborn and her/his family will need action from child welfare services.

2.6.7.3 Delivery and postpartum

Women with schizophrenia should be educated regarding the signs of labor and familiarized in advance with the setting in which birth will take place (Seeman, 2013). Denial of a pregnancy in the face of imminent labor represents a psychiatric emergency possibly requiring involuntary hospitalization given that an unassisted delivery poses a substantial risk to the patient (Solari, 2010).

Following delivery, women with schizophrenia should remain on the maternity hospital ward as long as necessary. This allows for the complete assessment of the overall health of both the mother (for example, evaluating possible symptoms of postpartum psychosis) and the newborn, as well as the possibility of assessing the development of the mother–child relationship (Seeman, 2013). During this period, the mother should be informed of postpartum issues and infant care (Seeman, 2013). Furthermore, providers should assess the child care competency of the mother (Seeman, 2013). Some authors (Abel et al., 2005; Robinson 2012) argue that baby–mother units that concentrate on the special treatment of women with serious mental disorders and their offspring provide encouraging care results.

On the other hand, a Cochrane review by Joy & Saylan (2007) on mother and baby units for schizophrenia found no definitive evidence of their superiority over standard in-patient treatment. Following hospital discharge, the mental health team should complete home visits (Seeman, 2013).

2.7 CHILDREN TO MOTHERS WITH SCHIZOPHRENIA

2.7.1 THE NUMBER OF CHILDREN

Multiple studies have demonstrated that individuals with schizophrenia have significantly fewer offspring than individuals in the general population (Essen-Möller, 1959; Slater et al., 1971; Haverkamp et al., 1982; Kendler & Diehl, 1993; Nanko & Moridaira, 1993; Fananas & Bertranpetit, 1995; Nimgaonkar et al., 1997; Srinivasan & Padmavati, 1997; Nimgaonkar 1998; McGrath et al., 1999). Haukka et al. (2003) in a study of all individuals born in Finland from 1950 to 1959 (n = 870,093), found that 1.3% suffered from schizophrenia. The mean number of offspring among them stood at 0.83 among women and 0.44 among men. In a Swedish population-based study by Svensson et al. (2007), female and male patients with schizophrenia had on average 0.93 and 0.56 children, respectively.

The higher fertility rates among women with schizophrenia have been partly explained by women experiencing milder symptoms than men during their reproductive years (Kohler et al., 2009). Men with schizophrenia appear to experience more negative symptoms, enjoy fewer social networks, and are more exposed to social problems and isolation (Thorup et al., 2007). Women's mental health influences their reproductive decisions (Major et al., 2008), and fertility rates may be influenced by the fact that some women with psychotic disorders may have been advised against becoming pregnant (Viguera et al., 2002). However, in a Danish population-based study by Laursen and Munk-Olsen (2010), higher abortion rates did not explain the lower fertility rates.

2.7.2 THE ADVERSE PERINATAL HEALTH OUTCOMES OF CHILDREN

Since the 1960s, mounting evidence has established an association between maternal schizophrenia and adverse perinatal health outcomes among their offspring (Sobel, 1961; Rieder et al., 1975). In what follows, I summarize the population-based studies and meta-analyses related to this topic, including only statistically significant associations.

In a meta-analysis, Sacker et al. (1996) reported that births to women with schizophrenia carry an increased risk of a low birthweight and a poor neonatal condition in the offspring. In a Danish population-based study (Bennedsen et al., 1999; Bennedsen et al., 2001a, Bennedsen et al., 2001b), the offspring of mothers with schizophrenia exhibited an increased risk of preterm delivery [relative risk (RR) 1.46], being small for gestational age (RR 1.34), having a low birthweight (RR 1.57), a 1-min Apgar score <10 (RR 1.31), having congenital malformations (RR 1.70), and post-neonatal death (RR 2.76) compared with the newborns of unaffected mothers.

In addition, a Swedish national population-based study by Nilsson et al. (2002) reported an increased risk of preterm delivery [odds ratio (OR) 1.7], low birthweight (OR 1.8), being small for gestational age (OR 1.6), stillbirth (OR 2.1), and infant death (OR 2.5) among the newborns of women with schizophrenia. These risk estimates diminished after controlling for parity, maternal smoking, mother's age and education, the mother's country of birth, pregnancy-induced hypertensive diseases, and cohabiting with the father of the child.

Moreover, an Australian population-based study (Jablensky et al., 2005) found that women with schizophrenia were significantly more likely to give birth to infants in the lowest weight or growth population decile (percentage estimated birthweight < tenth percentile; OR 1.40), as well as infants needing a narcotic antagonist (OR 1.88), and infants with congenital cardiovascular anomalies (OR 2.55) and other primarily minor physical abnormalities (OR 2.19).

In an Israeli population-based study (Hizkiyahu et al., 2010), the risk of having a congenital malformation (OR 2.1) were significantly higher among offspring with schizophrenia.

Matevosyan's (2011) meta-analysis found that neonates born to women with schizophrenia typically present with intrauterine growth retardation (OR 2.16), prematurity (OR 2.08), low Apgar scores (OR 2.22), and congenital defects (OR 2.10). However, after adjusting for maternal age, unhealthy behaviors, the duration of antipsychotic treatment, maternal–fetal attachment, and parity, maternal schizophrenia continued to predict prematurity.

Comparatively, a Canadian population-based study (Vigod et al., 2014) found that infants born to women with schizophrenia carried an increased risk of prematurity (OR 1.90), as well as being either small (OR1.56) or large for gestational age (OR1.69). These findings remained significant after controlling for maternal prepregnancy medical comorbidities, age, socioeconomic status, parity, and infant sex.

The causes of the abovementioned adverse perinatal health outcomes remain unclear. However, possible causative factors include abnormal fetal development due to a genetic predisposition, the effects of a maternal disorder and stress, concurrent problems such as a sociodemographic disadvantage, poor nutrition, and associated lifestyle factors, poor attendance at antenatal care, and the effects of medication (Judd et al., 2014).

2.7.3 THE MOTHER–INFANT RELATIONSHIP

The postpartum period represents a particularly sensitive period in terms of infant development, and the quality of care provided during this time remains critically important for a child's health outcomes later in life (Goodman & Gotlib 1999; Wan et al., 2008; Stein et al., 2009). Substantial evidence exists indicating an impairment

to the mother–infant relationship to varying degrees among mothers with severe mental health disorders. Compared with unaffected mothers and mothers with other mental health disorders, mothers with schizophrenia appear less responsive, more self-absorbed, and more withdrawn when playing with and feeding their infants (Näslund et al., 1985; McNeil et al., 1985; Persson-Blennow et al., 1986; Goodman, 1987; Riordan et al., 1999; Wan et al., 2007). According to Goodman (1987), a less severe disorder, a higher education, a higher IQ, work experience, and the presence of a spouse or other relative to help with child care all serve as protective factors. Mothers with schizophrenia tend to refrain from verbal communication with their infants (Persson-Blennow et al., 1984; Riordan et al., 1999). Compared with unaffected mothers, their speech is less infant-focused and they use significantly fewer songs and rhymes (Wan et al., 2008). A marked lack of infant-directed speech among mothers with schizophrenia reflects their low maternal sensitivity, perhaps because of a mind impairment and a blunted affect. According to Healy et al. (2016), mothers with schizophrenia consistently demonstrate impairment related to affect recognition and discrimination.

2.7.4 NEUROPSYCHOSOCIAL PROBLEMS AMONG OFFSPRING

A significant body of longitudinal research has followed the offspring of parents with schizophrenia. Hameed and Lewis (2016) reviewed 18 longitudinal studies that followed children with one or both parents meeting the diagnostic criteria for schizophrenia. Such studies suggested that these children show distinct developmental patterns characterized by higher rates of neurodevelopmental delays such as motorskills and cognitive deficits.

Recently, Ranning et al. (2018) analyzed all Danish children born and living in Denmark between 1986 and 1996 and their parents. Among children, parental schizophrenia correlated with lower grades and lower chances of graduating with a primary education. Lin et al. (2017) examined the academic performance among the 12-year-old children of mothers diagnosed with schizophrenia or other severe mental disorders using a large population-level cohort born in Western Australia. In that study, children with affected mothers carried an increased risk of subpar academic achievement, leaving such children disadvantaged in the transition to secondary school. Similarly, a Swedish population-based study (Jundong et al., 2012) found that the offspring of parents with schizophrenia performed poorer overall than the offspring of unaffected parents; genetic factors accounted for the poorer school preformance among these children.

Furthermore, early childhood behavior among high-risk offspring appears to correlate with a range of problematic behaviors, including shyness, withdrawal, anxiety, depression, aggression, and challenges in social relationships (Jablensky,

1997; Tarbox & Pogue-Geile, 2008). Hameed and Lewis (2016) through a review of 12 studies followed such offspring into adulthood and examined their psychiatric diagnoses. From 15% to 40% of children at a familial risk developed psychotic disorders in adulthood. Many of these children also received other psychiatric diagnoses such as mood and anxiety disorders. In a recent Danish population-based study (Thorup et al., 2018), the offspring of parents with severe mental disorders exhibited an increased IRR for all diagnoses of child and adolescent disorders compared to the offspring of unaffected parents. The offspring of mothers with schizophrenia exhibited an IRR of 2.60 for any psychiatric diagnosis, an IRR of 2.06 among children to fathers with schizophrenia, and an IRR of 4.57 for the offspring with two parents with schizophrenia.

2.7.5 THE OUT-OF-HOME OF OFFSPRING

A psychotic illness does not need to interfere with an individual's ability to be a good parent so long as the childcare needs are met and the home remains safe (Seeman, 2013). The difficulties mothers with schizophrenia exhibit relating to their children appear to result from multiple factors. These factors include the general illness severity, social cognitive impairments, the presence of social stressors including chronic social adversity and stigma, and a lack of protective factors including minimal social and partner support (Wan et al., 2008). Compared with mothers experiencing other psychiatric disorders, mothers with schizophrenia tend to experience more difficulties related to the practical aspects of caregiving (Abel et al., 2005). Living with a single parent with a severe mental disorder renders a child particularly vulnerable in the absence of the compensating capacities of another parent. Family cohesion appears especially difficult to maintain when parents have schizophrenia (Ranning et al., 2015).

Children themselves report experiencing child neglect and abuse as well as feeling scared or unsafe because of a parent's psychiatric symptoms and report becoming the caretakers of their parents (Duncan & Browning, 2009). Mothers with schizophrenia appear more likely to remain under social service supervision following discharge from maternity hospitals than mothers in the general population (Kumar et al., 1995; Salmon et al., 2003). In addition, mothers with schizophrenia are at a high risk of losing—either temporarily or permanently—custody of their children (Seeman, 2012).

In a population-based study by Ranning et al. (2015), a parental diagnosis of schizophrenia emerged as a prominent risk factor for children placed outside the home (children with a mother diagnosed with schizophrenia: IRR 23.75; children with a father diagnosed with schizophrenia: IRR 7.85). Risks were particularly high

during the child's first year of life, indicating a critical period particularly for the children of mothers with schizophrenia (IRR 80.19).

2.7.6 PSYCHOSOCIAL INTERVENTIONS ON PARENTING AMONG WOMEN WITH SCHIZOPHRENIA

Mental health teams can help mothers with schizophrenia by assisting them to look after their own health, to self-monitor for signs of relapse, to organize a crisis plan if their ability to care for their children becomes temporarily impaired, and to provide training on parenting skills and with practical household issues (Seeman, 2012; Seeman, 2013). A significant portion of mental health service users report experiencing mental illness–based discrimination in relation to parenthood. Mental health professionals should talk with their patients about this stigma in order to identify ways to help (Jeffery et al., 2013). A review of parenting interventions for mothers with schizophrenia found that the following proved effective: didactic parenting classes, direct parenting coaching for mothers, parent support groups in which parents help one another, and time-limited co-parenting support (Wan et al., 2008). Some findings suggest that interventions should focus on improving maternal sensitivity and maternal involvement by teaching practical techniques to increase positive maternal responsiveness, infant stimulation, and mutual enjoyment (Wan et al., 2007).

The Finnish child welfare system includes family and child protection services (the Finnish child welfare law; www.finlex.fi). Family service primarily provides assistance to families. If this is insufficient, however, the child can be placed out of the home, either voluntarily or involuntarily. Family services typically take the form of family home visits, whereby support and guidance occur closer to the family and appear more relevant to their everyday lives. During home visits, the family worker seeks to strengthen and support parenthood and family life with children through discussions, advice, and guidance as well as by doing things together. Through discussions, parents are guided to identify factors that both support and endanger their own parenting, relationships, social networks and childs' needs and balanced development. Family work is work carried out at home with the goal of not doing the work for parents, but to guide the parents' own activities through counseling and discussions and, if necessary, to provide more concrete support for their own activities (Araneva, 2016).

2.8. SUMMARY OF THE LITERATURE

Schizophrenia, a severe and often substantially disabling mental disorder with a prevalence of approximately 1%, profoundly affects the reproductive health of women with the disease. Women with schizophrenia carry a high risk for a wide range of adverse health outcomes including obesity and diabetes. While the reasons for this remain poorly understood, some possible explanations include unhealthy lifestyles, the side effects of psychopharmacological treatments, and barriers to accessing medical treatment resulting in either underdiagnosis or insufficient treatment. The prevalence of smoking and substance misuse are more prevalent among women with schizophrenia than among their unaffected counterparts.

Some evidence suggests that induced abortions are more common among women with schizophrenia than among unaffected women. Pregnant women with schizophrenia are more often single and their pregnancies are more often unplanned compared to unaffected women. The neuroprotective estrogen hypothesis suggests that higher estrogen levels during pregnancy may protect vulnerable women from psychiatric symptoms, although pregnancy can also worsen the mental health of some women with schizophrenia. Women with schizophrenia are at higher risk of somatic pregnancy complications including venous thromboembolism, pre-eclampsiaeclampsia, and gestational diabetes. Mothers-to-be with schizophrenia should continue their antipsychotic medication during pregnancy. Polypharmacy, however, must be avoided, although the lowest effective dose should be prescribed and intensive monitoring should be provided.

Women with schizophrenia exhibit an increased risk of various delivery-related health outcomes and interventions including placenta abruptia, the pharmacological stimulation of labor, induction of delivery by amniotomy, vaginal-assisted delivery, and Cesarean section. Following delivery, the sudden loss of estrogen may increase an individual's psychiatric vulnerability, particularly when compounded by sleep deprivation and the psychosocial stress of caring for a newborn. Most psychiatric hospitalizations among new mothers occur during the first two weeks post-partum.

The newborns of mothers with schizophrenia appear at higher risk of prematurity, a low birthweight, a poor neonatal condition, being either small or large for gestational age, having congenital malformations, stillbirth, and infant death. The causes of these adverse perinatal health outcomes, however, remain unclear. Possible causative factors include abnormal fetal development due to a genetic predisposition, the effects of maternal disorder and stress, concurrent problems such as a sociodemographic disadvantage, poor nutrition and associated life style factors, poor attendance at antenatal care, and the effects of medication.

Morever, mothers with schizophrenia appear more likely to remain under social service supervision following discharge from maternity hospitals than mothers in the

general population and carry an elevated risk of facing the out-of-home placement of their offspring. Children with one or both parents suffering from schizophrenia exhibit a higher prevalence of cognitive deficits and psychiatric disorders than children with unaffected parents.

Women with schizophrenia can be helped in many ways. Proactive family planning and contraceptive counseling may reduce the rate of inintended pregnancies. During pregnancy, interventions aimed at smoking cessation, substance use monitoring and treatment interventions, nutrition counseling, and lifestyle interventions remain important. Short-term, focused psychotherapy can prove useful in some women who experience psychological stress. Following delivery, women with schizophrenia should remain on the maternity hospital ward for a sufficient amount of time. This allows for the complete assessment of the overall health of both the mother and the newborn, as well as the opportunity to assess the development of the mother–child relationship. In addition, an assessment of the child care competency should be performed. The mental health team can help mothers with schizophrenia by assisting them to look after their own health, to self-monitor for signs of relapse, to organize a crisis plan if their ability to care for their child(ren) becomes temporarily impaired, and to provide training in parenting skills and related to practical household issues. Effective parenting interventions for mothers with schizophrenia exist.

To date, large-scale research remains insufficient to shed light on the relationship between schizophrenia and induced abortions, as well as on the social and medical circumstances associated with induced abortions. Induced abortion also remains a sensitive and highly culture-specific research topic influenced by religion and gender equality, as well as socioeconomic circumstances and legislation. Thus, findings related to induced abortion can be highly context-specific. Population-based studies of prenancies and deliveries among women with schizophrenia already exist, although they remain relatively scarce. Pregnancy and delivery are also influenced by cultural and socioeconomic factors, as well as by the provision and funding of healthcare services. Therefore, research findings may be context-specific, and the generalizability of findings across settings, countries, and time periods remains unclear. Schizophrenia, however, appears related to an increased risk of the out-of-home placement of the offspring, although very little is known about associations between maternal background variables, the adverse perinatal health outcomes of the offspring, and out-of-home placements.

3 AIMS OF THE STUDY

This population-wide, register-based follow-up study aimed to investigate the reproductive health of women with schizophrenia or schizoaffective disorder. To achieve this aim, this project consisted of four studies, each of which aimed:

1. To determine the number and incidence of induced abortions among women with schizophrenia or schizoaffective disorder (study I).
2. To investigate pregnancy-related health outcomes and complications among women with schizophrenia or schizoaffective disorder (study II).
3. To assess obstetric and perinatal health outcomes among women with schizophrenia or schizoaffective disorder and their offspring (study III).
4. To examine the out-of-home placements among children with a biological mother diagnosed wtih schizophrenia or schizoaffective disorder (study IV).

4 METHODOLOGY

4.1. STUDY DESIGN

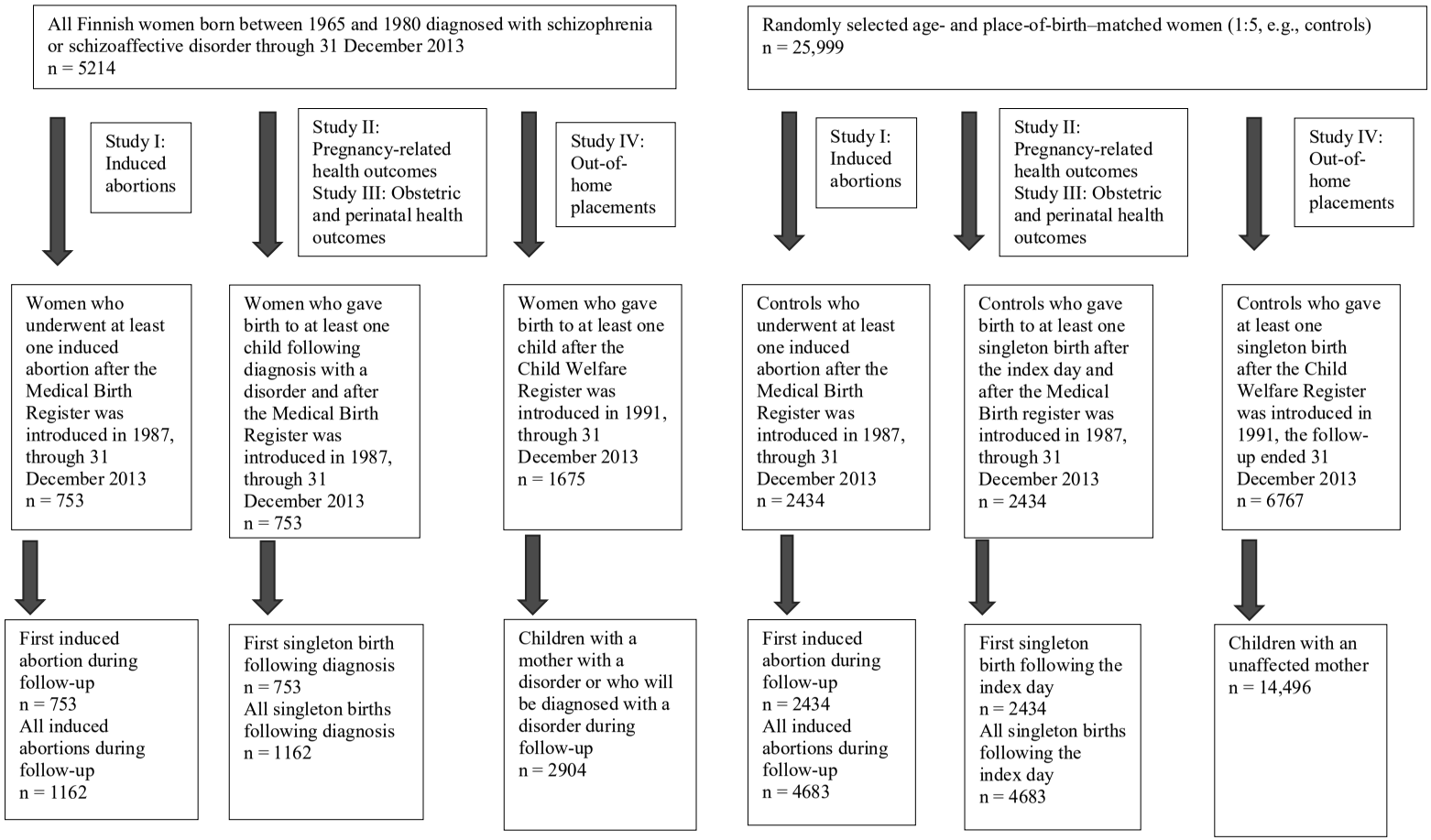
This research relied on a nationwide register-based follow-up study. **Figure 1** illustrates the sampling procedure. The Ethics Committee of Helsinki and Uusimaa Hospital District approved the study plan, and the National Institute of Health and Welfare and the Population Register Center granted permission to use register data.

4.2 PARTICIPANTS

4.2.1 WOMEN WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDIES I–IV)

Using the Care Register for Health Care of the National Institute of Health and Welfare, we selected all Finnish women born between 1965 and 1980 and diagnosed with schizophrenia or schizoaffective disorder in specialized health care through 31 December 2013 (that is, the end of the follow-up period). During the study period, diagnoses were coded using the ICD, 8th revision (ICD–8) (World Health Organization, 1965) (schizophrenia: 295.0–6, 295.8–9; schizoaffective psychosis: 295.7), ICD, 9th revision (ICD–9) (World Health Organization, 1977) (schizophrenia: 295.0–6, 295.8–9; schizoaffective psychosis: 295.7), and ICD, 10th revision (ICD–10) (World Health Organization, 1992) (schizophrenia: F20; schizoaffective psychosis: F25). In total, we identified 5214 affected women. Among these, 3444 (66.0%) were diagnosed with schizophrenia, 785 (15.1%) were diagnosed with schizoaffective disorder, and 985 (18.9%) were diagnosed with both disorders (that is, the diagnosis changed from schizophrenia to schizoaffective disorder or vice versa during the follow-up period).

Figure 1. Flowchart of study sample selection.



4.2.2 CONTROL WOMEN (STUDIES I–IV)

For each affected woman, five age- and place-of-birth–matched control women were randomly selected from the Finnish Central Population Register. Each control had not been diagnosed with schizophrenia, schizoaffective disorder, or any other psychotic disorder (F20–29) through 31 December 2013, although other mental health disorders were allowed. In total, we selected 25,999 control women since no controls were found due togiven the rigid matching criteria.

4.3 REGISTERS

4.3.1 REGISTER ON INDUCED ABORTIONS AND STERILIZATIONS: CHARACTERISTICS OF WOMEN AND OUTCOMES RELATED TO INDUCED ABORTIONS (STUDY I)

The National Institute of Health and Welfare has maintained the Register on Induced Abortions and Sterilizations since 1970 (available electronically since 1983). According to a recent data quality study by Heino et al. (2018), the validity of this register renders it a solid source for both research and health-monitoring purposes. In this study, we collected data on the following variables: maternal age, marital status, the number of previous pregnancies and deliveries, the date of an induced abortion, the gestational age at the time of an induced abortion, the legal indication for the procedure, the contraceptive method used at the time of becoming pregnant, and any immediate complications related to the procedure.

4.3.2. MEDICAL BIRTH REGISTER: CHARACTERISTICS OF WOMEN AND THEIR OFFSPRING, CONDITIONS RELATED TO OR AGGRAVATED BY PREGNANCY, AND PERINATAL HEALTH OUTCOMES OF OFFSPRING (STUDIES I–IV)

Since 1987, the National Institute of Health and Welfare has maintained the Medical Birth Register. This register covers all hospital deliveries in Finland and includes data on the live births and stillbirths of fetuses with a birthweight of at least 500 g or a gestational age of at least 22 weeks, and includes data on mothers. Individual data collection starts at the beginning of a pregnancy and ends one week following delivery. According to a study on the quality of the data carried out by Gissler et al. (1995), most of the register content corresponds well or satisfactorily with hospital records.

In this study, the following variables were collected: gestational birth age (recorded since 1987; studies II and III); the number of deliveries (recorded since 1987; studies I–IV); maternal age at birth (recorded since 1987; studies II–IV); marital status at birth (recorded since 1987; studies II and III); smoking status at

the beginning of the pregnancy (recorded since 1987; studies II–III); smoking status after the first trimester (recorded since 1991; study II); weight before pregnancy (recorded since 2004; study II); height before pregnancy (recorded since 2004; study II); pathological oral glucose tolerance test, initiation of insulin treatment, anemia, antenatal corticosteroid treatment, and other conditions related to or aggravated by the pregnancy according to ICD–10 (recorded since 2004; study II); prenatal care (recorded since 1987; study II); breech presentation (recorded since 1991; study III); induction of labor (recorded since 1991; study III), epidural anesthesia (recorded since 1991; study III); use of forceps or a vacuum (recorded since 1987; study III); asphyxia (recorded since 1991; study III); delivery via Cesarean section (recorded since 1987; study III); delivery via elective Cesarean section (recorded since 1991; study III); other delivery-related diagnoses (recorded since 2004; study III); perinatal death (recorded since 1987; study III); sex of the child (recorded since 1987; study III); premature (<37 weeks' gestation) birth (recorded since 1987; study III); very premature (<28 weeks' gestation) birth (recorded since 1987; study III); birthweight (recorded since 1987; studies III and IV); low (<2500 g) birthweight (recorded since 1987; studies III and IV); very low (<1500 g) birthweight (recorded since 1987; study III); low (0–6) 1-min postnatal Apgar score (recorded since 1987; studies III and IV); very low (0–3) 1-min postnatal Apgar score (recorded since 1987; study III); assisted ventilation (recorded since 1991; study III); resuscitation (recorded since 1991; study III); and neonatal monitoring (recorded since 1991; study III).

4.3.3 REGISTER OF CONGENITAL MALFORMATIONS: MAJOR CONGENITAL ANOMALIES AND SYNDROMES (STUDIES III AND IV)

The National Institute of Health and Welfare has maintained the Register of Congenital Malformations since 1963 (available electronically since 1986). This register contains data on congenital, chromosomal, and structural anomalies among stillborn and live born infants and fetuses, as well as pregnancy terminations due to congenital anomalies. Using the European Surveillance of Congenital Anomalies (EUROCAT) criteria (EUROCAT Central Registry, 2017), in this study we only collected data on major congenital anomalies as well as multiple anomalies and syndromes.

4.3.4 THE CHILD WELFARE REGISTER: OUT-OF-HOME PLACEMENTS

Since 1991, the National Institute of Health and Welfare has maintained the Child Welfare Register. This registry includes information on all children placed

out-of-home by municipal child welfare services. In this study, the following variables were collected: the date of the out-of-home placement and the length of the out-of-home placement.

4.4 STATISTICAL ANALYSES

In studies II and III, we focused on singleton pregnancies (to avoid multicollinearity) leading to a delivery following when the mother's schizophrenia or schizoaffective disorder was coded in a specialized healthcare setting (that is, the index day). Study IV focussed again on singletons, although children were born either before or after their mothers were diagnosed with schizophrenia or schizoaffective disorder.

In studies I, II, and III, data analysis proceded in two ways. First, only each individual's first induced abortion or pregnancy was included in the analysis. Second, all induced abortions or pregnancies were included, irrespective of the number per individual woman.

In the bivariate analyses, we used the chi-square (x^2) test (studies I, II, III, and IV), the Fisher's exact test (studies II and III), the independent samples t-test (studies I, II, III, and IV), the test of relative proportions (study I), the Wilcoxon signed-rank test (study I), and the Mann-Whitney U test (IV) where appropriate.

In study I, we used Cox's proportional hazards modeling. Risk ratios (RR), hazard risk ratios (HRs), and odds ratios (ORs) with 95% confidence intervals (CIs) are reported.

We performed both unadjusted and adjusted logistic regression analyses in studies II, III, and IV. In study II, maternal age at birth, marital status at birth (single vs. married or cohabitating), smoking status at the beginning of a pregnancy (yes vs. no), and the number of deliveries served as covariates. In study III, the abovementioned variables and the sex of the newborn served as covariates. In study IV, the abovementioned variables plus the child's birth year and a perinatal health problem (yes vs. no) served as covariates. In studies II and III, in order to take into account the clustering of pregnancies among mothers, logistic regression analysis was performed using the generalized estimating equation (GEE) method. Variables with less than 10 women (in the schizophrenia group, in the control group, or in both groups) were omitted since such models were considered too unstable. In studies II and III, we reported ORs with 95% CIs. In study IV, we reported incidence rate ratios (IRRs) with 95% CIs. Findings were considered significant with a $p < 0.05$ for the regression model . All analyses were performed using SURVO MM (version 3.41), SPSS for Windows ((version 22.0), and SAS (version 9.3).

5 RESULTS

In total, 1587 (30.4%) women with schizophrenia or schizoaffective disorder and 7765 (29.9%) controls underwent at least one induced abortion during the follow-up period. The mean age of women during their first induced abortions was 23.5 (SD) ±5.50 years] among affected women and 24.9 years (SD ±6.70 years) among controls ($p < 0.00$; study I).

Following the index day (that is, the day on which the disorder was diagnosed in a special healthcare facility), 761 women with schizophrenia and 2472 controls gave birth at least once. In total, 1184 births occurred among affected women. This study focused on singleton births and identified a total of 1162 (98.1%) singleton births. Among these, 205 women had given birth prior to a schizophrenia diagnosis, but these births ($n = 359$) were not included in further analyses. Among controls, analysis was restricted to births occurring after the index day of the case, resulting in 4848 births, of which 4683 (96.7%) were singleton births. The mean age of women at first birth following diagnosis was 30.1 years (SD ±5.20 years) among affected women and 29.2 years (SD ±4.30 years) among controls. When all births following diagnosis were taken into account, the mean age of affected women was 30.7 years (SD ±4.90 years) and 30.4 years (SD ±4.50 years; studies II and III) among unaffected women.

Between 1991 and 2013, a total of 2904 children were born to 1675 women with schizophrenia while 14,496 children were born to 6767 control women. The mean age of the women at birth was 27.2 years (SD ±5.14 years) among affected women and 29.5 years (SD ±4.82 years) among controls. From the children born to affected mothers, 335 (11.5%) had at least one adverse perinatal health outcome (that is, prematurity, low birthweight, a low 1-min Apgar score, or a major congenital anomaly). Among children born to unaffected women, 1112 (8.4%) had at least one of the abovementioned adverse perinatal health outcomes (study IV).

5.1 INDUCED ABORTIONS IN WOMEN WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY I)

Before a diagnosis was confirmed, we identified 290 (5.6%) cases with an **induced abortion** (10.4 per 1000 follow-up years) and 2136 (8.2%) controls with an induced abortion (15.6 per 1000 follow-up years; HR 0.66, 95% CI 0.58–0.75). Following confirming the diagnosis, we identified 916 (17.6%) cases with an induced abortion

(22.9 per 1000 follow-up years) and 4606 (17.7%) controls with an induced abortion (24.9 per 1000 follow-up years; HR 0.99, 95% CI 0.92–1.07).

In addition, before confirming a diagnosis, we identified 597 (11.4%) cases with a birth (18.0 per 1000 follow-up years) and 10,955 (42.1%) controls with a birth (81.3 per 1000 follow-up years; HR 0.26, 95% CI 0.18–0.35). Following the diagnosis, we identified 573 (11.0%) cases with a birth (8.2 per 1000 follow-up years) and 10,446 (40.2%) controls with a birth (29.5 per 1000 follow-up years; HR 0.29, 95% CI 0.20–0.37).

Before a diagnosis was confirmed, the proportion of induced abortions among all pregnancies was significantly higher among cases than among controls [cases: 27.7% (induced abortions, n= 455; births, n = 1642; all pregnancies n = 2097) vs. controls: 11.7% (induced abortions, n= 3230; births, n = 26,738; all pregnancies, n = 29,968); RR 2.58, 95% CI 2.18–2.37]. Following diagnosis, the proportion of induced abortions among all pregnancies was significantly higher among cases than among controls [cases: 59.1% (induced abortions, n = 1666; births, n = 2817; all pregnancies, n = 4483) vs. controls: 25.9% (induced abortions, n = 6588; births, n = 25,660; all pregnancies, n = 32,248); RR 2.28, 95% CI 2.20–2.36].

Turning our attention to all induced abortions among women with schizophrenia or schizoaffective disorder (that is, cases), the number of induced abortions ranged from one to seven: 725 (68.0%) women had one abortion, 232 (21.7%) had two, 72 (6.7%) had three, and 38 (3.6%) had four or more induced abortions. Among unaffected women (that is, controls), the number of induced abortions ranged from one to ten: 3980 individuals (72.8%) had one abortion, 1028 (18.8%) had two, 299 (5.5%) had three, and 163 (3.0%) had four or more induced abortions. Turning to induced abortions performed following diagnosis, among women with schizophrenia or schizoaffective disorder (that is, cases), 722 (67.5%) individuals had one abortion, 236 (22.1%) had two, 72 (6.7%) had three, and 39 (3.6%) had four or more induced abortions. Among unaffected women (that is, controls), 3999 (72.7%) had one abortion, 1034 (18.8) had two, 303 (5.5%) had three, and 167 (3.0%) had four or more induced abortions. The number of induced abortions did not significantly differ between groups (cases: median, 1 vs. controls: median, 1, p = NS).

Table 4 summarizes the comparisons between cases and controls in relation to their first induced abortions. Cases were significantly younger and more likely to be single compared with controls. A medical indication for an induced abortion in the pregnant woman was significantly more prevalent while a medical indication in the fetus was significantly less common among cases than among controls. Induced abortions at 12 or more gestational weeks were significantly more prevalent among cases than among controls. Yet, induced abortions at 20 or more gestational weeks were significantly more prevalent among controls than among cases. No contraceptive use was significantly more common among cases than among controls.

We found no statistically significant differences in the immediate complications associated with induced abortions.

Table 5 presents the comparisons between cases and controls related to all induced abortions. Cases were significantly younger and more often single compared with controls. Medical indications in the pregnant women were significantly more prevalent while social indications as well as medical indications related to the fetus were significantly less prevalent among cases than among controls. Induced abortions at 12 or more gestational weeks were significantly more prevalent among cases than among controls. No contraceptive use was significantly more common among cases than among controls. Controls experienced at least one complication from an induced abortion significantly more than cases.

Table 4. Comparison of women with schizophrenia or schizoaffective disorder (SZH) with their unaffected counterparts (CO) related to first induced abortions.

Variable	SZH (n = 1069)	CO (n = 5503)	p
Single, n (%)	907 (84.8)	4125 (75.0)	<0.001[a]
Married or cohabiting, n (%)	114 (10.7)	1067 (19.4)	<0.001[a]
Divorced, separated, or widowed, n (%)	46 (4.3)	294 (5.3)	NS[a]
Age, mean (SD)	23.5 (5.52)	24.9 (6.73)	<0.001[c]
Indication for an induced abortion			
Social, n (%)	1005 (94.0)	5195 (94.4)	NS[d]
Medical due to the mother, n (%)	22 (2.1)	20 (0.4)	<0.00[1]d
Medical due to the fetus, n (%)	14 (1.3)	173 (3.1)	0.001[d]
Ethical, n (%)	0 (0.0)	3 (0.1)	NS[d]
Gestational age at the time of an induced abortion			
12+ weeks, n (%)	164 (15.3)	703 (12.8)	0.02[a]
20+ weeks, n (%)	5 (0.5)	71 (1.3)	0.02[b]
Contraceptive method used at the time of conception			
None, n (%)	496 (46.4)	2010 (36.5)	<0.001[a]
Condom, n (%)	441 (41.3)	2677 (48.6)	<0.001[a]
Intra-uterine device, n (%)	16 (1.5)	84 (1.5)	NS[a]
Morning-after pill, n (%)	11 (1.0)	37 (0.7)	NS[a]
Oral contraceptive, n (%)	0 (0.0)	16 (0.3)	NS[b]
Complications			
None, n (%)	1022 (95.6)	5185 (94.2)	NS[a]
At least one complication, n (%)	17 (1.6)	133 (2.4)	NS[a]
Incomplete abortion, n (%)	13 (1.2)	84 (1.5)	NS[a]
Cervical rupture, n (%)	0 (0.0)	7 (0.1)	NS[b]
Postoperative infection, n (%)	0 (0.0)	2 (0.04)	NS[b]
Other complications, n (%)	4 (0.4)	40 (0.7)	NS[b]

Abbreviations: NS, not statistically significant; SD, standard deviation

The chi-square (x^2) test,[a] the Fisher's exact test,[b] the independent samples t-test,[c] and the test of relative proportions[d] were used in the analyses.

Table 5. Comparison of women with schizophrenia or schizoaffective disorder (SZH) with their unaffected counterparts (CO) in terms of all induced abortions.

Variable	SZH (n = 1587)	CO (n = 7765)	p
Single, n (%)	1282 (80.8)	5578 (71.8)	<0.001[a]
Married or cohabiting, n (%)	187 (11.8)	1583 (20.4)	<0.001[a]
Divorced, separated, or widowed, n (%)	114 (7.2)	575 (7.4)	NS[a]
Age, mean (SD)	24.8 (5.83)	26.2 (6.90)	<0.001[c]
Indication for an induced abortion			
Social, n (%)	1474 (92.9)	7350 (94.7)	0.005[d]
Medical due to the mother, n (%)	32 (2.0)	27 (0.3)	<0.001[d]
Medical due to the fetus, n (%)	21 (1.3)	215 (2.8)	<0.001[d]
Ethical, n (%)	1 (0.1)	4 (0.1)	NS[d]
Gestational age at the time of an induced abortion			
12+ weeks, n (%)	247 (15.6)	950 (12.3)	<0.001[a]
20+ weeks, n (%)	9 (0.6)	83 (1.1)	NS[a]
Contraceptive method used at the time of conception			
None, n (%)	734 (46.3)	2728 (35.1)	<0.001[a]
Condom, n (%)	624 (39.3)	3712 (47.8)	<0.001[a]
Intra-uterine device, n (%)	28 (1.8)	115 (1.5)	NS[a]
Morning-after pill, n (%)	13 (0.8)	88 (1.1)	NS[a]
Oral contraceptive, n (%)	33 (0.2)	35 (0.5)	NS[a]
Complications			
None, n (%)	1515 (95.5)	7278 (93.7)	0.004[a]
At least one complication, n (%)	26 (1.6)	205 (2.6)	0.04[a]
Incomplete abortion, n (%)	19 (1.2)	136 (1.8)	NS[a]
Cervical rupture, n (%)	0 (0.0)	13 (0.2)	NS[b]
Postoperative infection, n (%)	0 (0.0)	4 (0.05)	NS[b]
Other complications, n (%)	7 (0.4)	54 (0.7)	NS[a]

Abbreviations: NS, not statistically significant; SD, standard deviation.

The chi-square (x^2) test[a], the Fisher's exact test[b], the independent samples t-test,[c] and the test of relative proportions[d] were used in the analyses.

5.2 PREGNANCY IN WOMEN WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY II)

After the index day (that is, the day on which a disorder was diagnosed), 761 affected women (cases) and 2472 unaffected women (controls) gave birth at least once. In total, 1162 singleton births occurred among cases; among those, 753 represented

the first singleton birth following a diagnosis. As many as 205 women gave birth prior to a diagnosis, but these births (n = 359) were excluded from analysis. Among unaffected women (or controls), analysis was restricted to births that occurred after the index day of the matched case, resulting in 4683 singleton births. Among these births, 2434 represented women's first births.

When analyzing first pregnancies after a diagnosis, cases were significantly older, were more often single at the end of the pregnancy, had a significantly higher body mass index (BMI) before pregnancy, smoked significantly more often both at the beginning of the pregnancy and after the first trimester when compared to controls (**Table 6**). Pregnancy-related complications and disorders among cases more often involved a pathological oral glucose tolerance test, the initiation of insulin, anemia, premature contractions, rapid fetal growth, and a suspected fetal injury due to alcohol or drug misuse compared to controls. In addition, prenatal care was more intensive among cases than among controls.

Turning to the analysis of all pregnancies after a diagnosis, cases were more often single at the end of the pregnancy, presented with a significantly higher BMI before pregnancy, smoked significantly more often both at the beginning of the pregnancy and following the first trimester compared to controls (**Table 7**). Cases significantly more often experienced pregnancy-related complications and disorders, including a pathological oral glucose tolerance test, the initiation of insulin, anemia, exhaustion, and a suspected fetal injury due to alcohol or drug misuse compared to controls. Unsurprisngly, prenatal care among cases was more intensive than that among controls.

Among first pregnancies following a *diagnosis*, the risk of a pathological glucose tolerance test was twofold (OR 2.00, 95% CI 1.43–2.82), more than twofold for anemia (OR 2.23, 95% CI 1.02–4.86), and almost twofold for the risk of hospitalization (OR 1.91, 95% CI 1.58–2.30). After adjusting for maternal age at birth, marital status, smoking status, and the number of total deliveries, the risk of a pathological oral glucose tolerance test (OR 1.75, 95% CI 1.24–4.46), premature contractions (OR 2.42, 95% CI 1.31–4.49), and hospitalization (OR 2.12, 95% CI 1.73–2.58) all remained significantly higher.

Among all pregnancies following a diagnosis, the risk of a pathological glucose tolerance test (OR 1.79, 95% CI 1.40–2.28), as well as the risk of anemia (OR 1.82, 95% CI 1.08–3.09) and hospitalization (OR 1.91, 95% CI 1.65–2.22) were all significantly higher. After adjusting for maternal age at birth, marital status, smoking status, and the number of total deliveries, the risk of a pathological oral glucose tolerance test (OR 1.66, 95% CI 1.27–2.17), initiating insulin (OR 1.84, 95% CI 1.15–2.93), rapid fetal growth (OR 1.62, 95% CI 1.03–2.52), and hospitalization (OR 1.97, 95% CI 1.66–2.33) remained significantly higher.

Table 6. Health and social outcomes, risk factors, pregnancy-related complications and disorders, and prenatal care during the first pregnancy among women with schizophrenia or schizoaffective disorder (SZH) and their unaffected counterparts (CO).

Variable	SZH (n = 753)	CO (n = 2434)	p
Age at birth, mean (SD)	30.1 (5.19)	29.2 (4.28)	<0.001[c]
Cohabiting or married at the end of the pregnancy, n (%)	540 (71.7)	2138 (87.8)	<0.001[a]
Smoking at the beginning of the pregnancy, n (%)	274 (36.4)	339 (13.9)	<0.001[a]
Smoking after the first trimester of the pregnancy, n (%)	243 (33.0)	260 (10.9)	<0.001[a]
BMI before pregnancy, mean (SD)	25.8 (5.21)	24.5 (4.60)	<0.001[c]
Gestational age*, mean (SD)	10.4 (4.94)	9.3 (2.71)	<0.001[c]
Pregnancy-related complications and disorders			
Pathological oral glucose tolerance test, n (%)	75 (10.2)	115 (4.8)	<0.001[a]
Initiation of insulin, n (%)	17 (2.3)	27 (1.1)	0.02[a]
Anemia, n (%)	12 (1.6)	15 (0.6)	0.001[a]
Antenatal corticosteroid treatment, n (%)	8 (1.1)	19 (0.8)	NS[a]
Premature contractions, n (%)	17 (2.0)	30 (1.3)	0.04[a]
Hypertension, n (%)	15 (2.0)	33 (1.4)	NS[a]
Suspected fetal injury due to alcohol or drug use, n (%)	9 (2.4)	1 (0.04)	<0.001[b]
Rapid fetal growth, n (%)	8 (1.1)	8 (0.3)	0.01[a]
Slow fetal growth, n (%)	7 (0.9)	12 (0.5)	NS[a]
Fear of childbirth, n (%)	6 (0.8)	12 (0.5)	NS[b]
Pre-eclampsia, n (%)	6 (0.8)	26 (1.1)	NS[b]
Premature rupture of membrane, n (%)	4 (0.5)	21 (0.9)	NS[b]
Hepatogestosis, n (%)	3 (0.4)	8 (0.3)	NS[b]
Oligohydramnios, n (%)	2 (0.1)	12 (0.5)	NS[b]
Any vein complication, n (%)	2 (0.1)	1 (0.04)	NS[b]
Exhaustion, n (%)	2 (0.2)	2 (0.1)	NS[b]
Hyperemesis gravidarum, n (%)	1 (0.1)	2 (0.1)	NS[b]
Urogenital infection, n (%)	1 (0.1)	2 (0.1)	NS[b]
Symphyseolysis, n (%)	1 (0.1)	1 (0.04)	NS[b]
Prenatal care			
Number of visits to a maternity clinic, mean (SD)	17.4 (6.90)	16.8 (5.52)	0.005[c]
Number of outpatient hospital visits, mean (SD)	4.2 (3.12)	2.9 (2.79)	<0.001[c]
One or more hospitalizations, n (%)	235 (31.2)	464 (19.1)	<0.001[a]

Abbreviations: SD, standard deviation; BMI, body mass index; NS, not statistically significant.

*Indicates a measurement at the time of the first visit to a maternity clinic.

The chi-square (x^2) test,[a] the Fisher's exact test and the independent samples t-test[c] were used to compare groups in the analyses.

Table 7. Health and social outcomes, risk factors, pregnancy-related complications and disorders, and prenatal care during all pregnancies among women with schizophrenia or schizoaffective disorder (SZH) and their unaffected counterparts (CO).

Variable	SZH (n = 1162)	CO (n = 4683)	p
Age at birth, mean (SD)	30.7 (4.88)	30.4 (4.51)	NS[c]
Cohabiting or married at the end of the pregnancy, n (%)	895 (77.0)	4252 (90.8)	<0.001[a]
Smoking at the beginning of the pregnancy, n (%)	408 (35.1)	568 (12.1)	<0.001[a]
Smoking after the first trimester of the pregnancy, n (%)	360 (31.6)	450 (9.8)	<0.001[a]
BMI before the pregnancy, mean (SD)	26.4 (5.69)	24.8 (4.80)	<0.001[c]
Gestational age*, mean (SD)	10.2 (4.60)	9.4 (2.73)	<0.001[c]
Pregnancy-related complications and disorders			
Pathological oral glucose tolerance test, n (%)	132 (11.6)	290 (6.3)	<0.001[a]
Initiation of insulin, n (%)	35 (3.1)	69 (1.5)	<0.001[a]
Anemia, n (%)	22 (1.9)	44 (1.0)	0.006[a]
Antenatal corticosteroid treatment, n (%)	11 (1.0)	34 (0.7)	NS[a]
Premature contractions, n (%)	24 (2.1)	78 (1.7)	NS[a]
Hypertension, n (%)	18 (1.6)	57 (1.2)	NS[a]
Suspected fetal injury due to alcohol or drug use, n (%)	12 (1.1)	2 (0.04)	<0.001[a]
Rapid fetal growth, n (%)	11 (1.0)	23 (0.5)	NS[a]
Slow fetal growth, n (%)	11 (1.0)	24 (0.5)	NS[a]
Fear of childbirth, n (%)	9 (0.8)	34 (0.7)	NS[a]
Pre-eclampsia, n (%)	7 (0.6)	47 (1.0)	NS[a]
Premature rupture of the membrane, n (%)	5 (0.4)	34 (0.7)	NS[b]
Hepatogestosis, n (%)	6 (0.5)	23 (0.5)	NS[b]
Oligohydramnios, n (%)	2 (0.2)	16 (0.3)	NS[b]
Any vein complication, n (%)	3 (0.3)	5 (0.1)	NS[b]
Exhaustion, n (%)	7 (0.6)	7 (0.2)	0.005[a]
Hyperemesis gravidarum, n (%)	2 (0.2)	2 (0.04)	NS[b]
Urogenital infection, n (%)	2 (0.2)	6 (0.1)	NS[b]
Symphyseolysis, n (%)	2 (0.2)	3 (0.06)	NS[b]
Prenatal care			
Number of visits to a maternity clinic, mean (SD)	17.3 (6.79)	16.5 (5.51)	<0.001[c]
Number of hospital outpatient visits, mean (SD)	4.1 (3.19)	2.9 (2.79)	<0.001[c]
One or more hospitalizations, n (%)	332 (28.6)	809 (17.3)	<0.001[a]

Abbreviations: SD, standard deviation; BMI, body mass index; NS, not statistically significant.

*Indicates that the measurement took place at the time of the first visit to a maternity clinic.

The chi-square (x^2) the Fisher's exact test,[b] and the independent samples t-test[c] were used to compare the groups in the analyses.

5.3 OBSTETRIC COMPLICATIONS RELATED TO SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY III)

Differences emerged when comparing delivery methods. Among first deliveries, both the induction of labor and elective Cesarean section were significantly more common among cases than among controls (**Table 8**). Among all deliveries, the induction of labor, Cesarean section, and an elective Cesarean section were all significantly more common among cases than controls (**Table 9**).

We found no statistically significant differences between groups with regards to delivery-related ICD-10 diagnoses (**Tables 8 & 9**).

The details regarding the comparison of risks of obstetric complications among cases, with controls serving as the reference group, appear in original article for study III (see Table 4 specifically). Among first deliveries, the risk of inducing labor was approximately 1.3-fold (OR 1.32, 95% CI 1.07–1.63) among cases. After adjusting for maternal age, marital status, the number of births, and smoking status at the beginning of the pregnancy (that is, adjusted model 1), the risk remained 1.3-fold (OR 1.26, 95% CI 1.01–1.56). After further adjusting for the sex of the newborn (adjusted model 2), the risk again remained 1.3-fold (OR 1.26, 95% CI 1.01–1.56). Turning to all deliveries, the risk of the induction of labor (OR 1.42, 95% CI 1.21–1.67), delivery by Cesarean section (OR 1.40, 95% CI 1.07–1.84), and delivery by elective Cesarean section (OR 1.41, 95% CI 1.14–1.76) were all approximately 1.4-fold among cases. In the adjusted models, all of the abovementioned differences remained statistically significant (induction of labor: adjusted model 1, OR 1.38, 95% CI 1.16–1.65; the adjusted model 2, OR 1.38, 95% CI 1.15–1.66; Cesarean delivery: adjusted model 1, OR 1.26, 95% CI 1.04–1.53; adjusted model 2: OR 1.26, 95% CI 1.04–1.53; elective Cesarean section: adjusted model 1, OR 1.37, 95% CI 1.06–1.77; adjusted model 2, OR 1.37, 95% CI 1.06–1.77).

Table 8. Comparison of women with schizophrenia or schizoaffective disorder (SZH) with their unaffected counterparts (CO) in terms of the first deliveries.

Variable	SZH (n = 753)	CO (n = 2434)	p
Delivery by Cesarean section, n (%)	57 (7.6)	140 (5.8)	NS[a]
Asphyxia, n (%)	37 (5.2)	142 (6.1)	NS[a]
Breech presentation, n (%)	28 (3.9)	91 (3.9)	NS[a]
Induction of labor, n (%)	151 (21.2)	396 (16.9)	0.03[a]
Epidural anesthesia, n (%)	296 (41.6)	1029 (43.9)	NS[a]
Use of forceps or vacuum, n (%)	74 (2.3)	262 (8.2)	NS[a]
Delivery by elective Cesarean section, n (%)	76 (10.7)	179 (7.6)	0.02[a]
Delivery-related ICD-10 diagnoses, n (%)			
Fetal distress	32 (8.6)	97 (9.3)	NS[a]
Maternal distress	6 (1.6)	19 (1.8)	NS[b]
Rupture of perineum	0 (0.0)	3 (0.3)	NS[b]
Precipitate labor	0 (0.0)	1 (0.1)	NS[b]
Prolonged labor	17 (4.6)	32 (3.1)	NS[a]
Umbilical cord complications	0 (0.0)	0 (0.0)	NS[b]
Postpartum hemorrhage	6 (1.6)	27 (2.6)	NS[b]
Puerperal sepsis	0 (0.0)	3 (0.3)	NS[b]
Other puerperal infections	0 (0.0)	2 (0.2)	NS[b]
Puerperal venous complications	0 (0.0)	0 (0.0)	NS_b
Obstetric embolism	0 (0.0)	0 (0.0)	NS[b]
Puerperal psychosis	0 (0.0)	0 (0.0)	NS[b]
Puerperal depression	1 (0.3)	0 (0.0)	NS[b]
Perinatal health outcomes of the offspring			
Perinatal death, n (%)	3 (0.4)	10 (0.4)	NS
Gestational age, mean (SD)	39.1 (2.26)	39.4 (1.95)	0.002[c]
Premature birth, n (%)	56 (7.4)	109 (4.5)	0.003[a]
Very premature birth, n (%)	6 (0.8)	12 (0.5)	0.003[b]
Birthweight, mean (SD)	3401 (625)	3488 (561)	0.001[c]
Low birthweight, n (%)	34 (4.5)	70 (2.9)	0.05[a]
Very low birthweight, n (%)	10 (1.3)	22 (0.9)	0.05[a]
Low 1-min Apgar score, n (%)	46 (6.1)	116 (4.8)	NS[a]
Very low 1-min Apgar score, n (%)	13 (1.7)	34 (1.4)	NS[a]
Assisted ventilation, n (%)	11 (1.5)	24 (1.0)	NS[a]
Resuscitation, n (%)	14 (2.0)	17 (0.7)	0.004[a]
Neonatal monitoring, n (%)	159 (22.3)	44 (10.4)	<0.001[a]

Abbreviations: NS, not statistically significant; SD, standard deviation.

The chi-square (x^2) test,[a] the Fisher's exact test,[b] and the independent samples t-test[c] were used in the analyses.

Table 9. Comparison of women with schizophrenia or schizoaffective disorder (SZH) with their unaffected counterparts (CO) in terms of all deliveries.

Variable	SZH (n = 753)	CO (n = 2434)	p
Delivery by Cesarean section, n (%)	75 (6.5)	219 (4.7)	0.01[a]
Asphyxia, n (%)	46 (4.1)	176 (3.8)	NS[a]
Breech presentation, n (%)	35 (3.1)	132 (2.9)	NS[a]
Induction of labor, n (%)	244 (21.9)	753 (16.5)	<0.001[a]
Epidural anesthesia, n (%)	390 (34.9)	1531 (33.5)	NS[a]
Use of forceps or vacuum, n (%)	85 (8.2)	317 (7.3)	NS[a]
Delivery by elective Cesarean section[b], n (%)	121 (10.4)	355 (7.6)	0.002[a]
Delivery-related ICD-10 diagnoses, n (%)			
Fetal distress	42 (6.8)	134 (5.8)	NS[a]
Maternal distress	9 (1.4)	24 (1.0)	NS[a]
Rupture of perineum	0 (0)	10 (0.4)	NS[b]
Precipitate labor	0 (0.0)	1 (0.0)	NS[b]
Prolonged labor	18 (2.9)	45 (1.9)	NS[a]
Umbilical cord complications	0 (0.0)	0 (0.0)	NS[b]
Postpartum hemorrhage	11 (1.8)	53 (2.3)	NS[a]
Puerperal sepsis	0 (0.0)	3 (0.1)	NS[b]
Other puerperal infections	0 (0.0)	4 (0.2)	NS[b]
Puerperal venous complications	0 (0.0)	1 (0.0)	NS[b]
Obstetric embolism	0 (0.0)	0 (0.0)	NS[b]
Puerperal psychosis	1 (0.2)	0 (0.0)	NS[b]
Puerperal depression	1 (0.2)	0 (0.0)	NS[b]
Perinatal health outcomes of the offspring			
Perinatal death, n (%)	5 (0.4)	16 (0.3)	NS[b]
Gestational age, mean (SD)	39.1 (2.22)	39.4 (1.77)	<0.001[c]
Premature birth, n (%)	74 (6.4)	184 (3.9)	<0.001[a]
Very premature birth, n (%)	10 (0.9)	14 (0.3)	<0.001[a]
Birthweight, mean (SD)	3474 (646)	3560 (541)	<0.001[c]
Low birthweight, n (%)	44 (3.8)	106 (2.3)	0.001[a]
Very low birthweight, n (%)	16 (1.4)	32 (0.7)	0.001[a]
Low 1-min Apgar score, n (%)	65 (5.6)	165 (3.5)	0.001[a]
Very low 1-min Apgar score, n (%)	20 (1.7)	51 (1.1)	0.001[a]
Assisted ventilation, n (%)	18 (1.6)	36 (0.8)	0.01[a]
Resuscitation, n (%)	19 (1.7)	24 (0.5)	<0.001[a]
Neonatal monitoring, n (%)	222 (19.9)	413 (9.0)	<0.001[a]

Abbreviations: NS, not statistically significant; SD, standard deviation.

The chi-square (x2) test,a the Fisher's exact test,b and the independent samples t-testc were used in the analyses.

5.4 PERINATAL PROBLEMS AMONG CHILDREN WITH A MOTHER WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY III)

Further examining the first delivery following a diagnosis, the gestational age and birthweight of the offspring of cases were significantly lower than those of the offspring of controls (see **Table 8** above). Additionally, premature birth, very premature birth, a low birthweight, a very low birthweight, resuscitation, and neonatal monitoring were significantly more common among the offspring of cases than among the offspring of controls.

Turning to all deliveries (see **Table 9** above), we found the same statistically significant differences as first births, as well as a low (<7) and very low (<4) 1-min Apgar score, and assisted ventilation more commonly occurred among the offspring of cases than among the offspring of controls.

5.4.1 ASSOCIATIONS

The associations between maternal schizophrenia or schizoaffective disorder and negative perinatal health outcomes among their offspring appear in **Table 5** within **the original article for study III**.

Among first deliveries, the risk of premature birth (OR 1.72, 95% CI 1.25–2.37), a low birthweight (<2500g; OR 1.58, 95% CI 1.09–2.28), low 1-min Apgar score (<7; OR 1.60, 95% CI 1.07–2.41), resuscitation (OR 2.74, 95% CI 1.35–5.60), and neonatal monitoring (OR 2.47, 95% CI 1.98–3.08) were significantly higher among cases compared to controls. In the adjusted models (adjusted model 1in which maternal age, marital status, number of deliveries, smoking status at the beginning of pregnancy served as covariates; adjusted model 2 in which the sex of the newborn was added to the above variables all served as covariates), only the risk of premature birth (adjusted model 1: OR 1.54, 95% CI 1.10–2.17; adjusted model 2: OR 1.55, 95% CI 1.10–2.17) and neonatal monitoring (adjusted model 1: OR 2.03, 95% CI 1.60–2.56; adjusted model 2: OR 2.03, 95% CI 1.60–2.56) remained significantly higher for cases compared to controls.

Among all deliveries, the risk of premature birth (OR 1.77, 95% CI 1.36–2.31), low birthweight (<2500g; OR 1.79, 95% CI 1.32–2.44), very low birthweight (<1500g; OR 2.03, 95% CI 1.11–3.71), a low 1-min Apgar score (<7; OR 1.64, 95% CI 1.26–2.12), assisted ventilation (OR 2.15, 95% CI 1.23–3.76), resuscitation (OR 3.23, 95% CI 1.76–5.91), and neonatal monitoring (OR 2.44, 95% CI 1.75–2.57) were significantly higher among cases compared to controls. In the adjusted models, the risk of premature birth (adjusted model 1: OR 1.56, 95% CI 1.16–2.11; adjusted

model 2: OR 1.57, 95% CI 1.16–2.11), low birthweight (<2500g; adjusted model 1: OR 1.41, 95% CI 1.01–1.98; adjusted model 2: OR 1.41, 95% CI 1.01–1.98), low 1-min Apgar score (<7; adjusted model 1: OR 1.58, 95% CI 1.18–2.12; adjusted model 2: OR 1.60, 95% CI 1.19–2.15), resuscitation (adjusted model 1: OR 2.45, 95% CI 1.27–4.71; adjusted model 2: OR 2.45, 95% CI 1.28–4.72), and neonatal monitoring (adjusted model 1: OR 2.12, 95% CI 1.75–2.57; adjusted model 2: OR 2.13, 95% CI 1.76–2.58) remained significantly higher among cases compared to controls.

5.4.2 MAJOR CONGENITAL ANOMALIES

Among first deliveries, prevalence of major anomalies did not significantly differ between groups [offspring of cases vs. offspring of controls: 33 (4.4%) vs. 89 (3.7%), p = NS]. In terms of different types of congenital anomalies, syndromes more frequently occured among the offspring of cases than among the offspring of controls [offspring of cases vs offspring of controls: 9 (1.2%) vs. 9 (0.4%), p = 0.001], although no statistically significant group difference was observed for deliveries involving multiple anomalies [offspring of cases vs. offspring of controls: 3 (0.4%) vs. 9 (0.4%), p = NS]. We found a trend towards a higher prevalence of isolated congenital anomalies among cases, although this difference did not reach statistical significance [offspring of cases vs. offspring of controls: 21 (2.8%) vs. 71 (2.9%), p = 0.059].

Turning to all deliveries we found a trend towards a higher prevalence of major congenital anomalies among cases, although the difference did not reach statistical significance [offspring of cases vs. offspring of controls: 57 (4.9%) vs. 173 (2.9%), p = 0.057]. Both syndromes (offspring of cases vs. offspring of controls: 14 (1.2%) vs. 20 (0.4%), p = 0.001] and isolated anomalies (offspring of cases vs. offspring of controls: 37 (3.2%) vs. 137 (2.9%), p = 0.047] were significantly more frequent among the offspring of cases than among the offspring of controls. We found no statistically significant group difference related to multiple anomalies [offspring of cases vs. offspring of controls: 6 (0.5%) vs. 16 (0.3%), p = NS].

The risk of a major congenital anomaly was significantly increased (first delivery: OR 1.42, 95% CI 1.02–1.98; all deliveries: OR 1.33, 95% CI 1.04–1.70). However, in adjusted models 1 and 2 , this risk was no longer significantly increased.

5.4.3 MATERNAL SMOKING

In order to study the relationship between maternal smoking and adverse perinatal health outcomes, all women who smoked (both cases and controls) were analyzed together while non-smoking women (both cases and controls) served as the reference

group. Birth year, maternal age, marital status, and the number of births all served as covariates. Among all deliveries, smoking represented a significant risk factor for premature birth (OR 1.56, 95% CI 1.16–2.11), a low birthweight (1.41, 95% CI 1.01–1.98), a low 1-min Apgar score (<7; OR 1.58, 95% CI 1.18–2.13), and neonatal monitoring (OR 2.12, 95% CI 1.75–2.57). Next, we focussed on cases who smoked, while non-smoking cases served as the reference group. Among all deliveries, smoking represented a significant risk factor for a very low birthweight (OR 3.32, 95% CI 1.14–9.60) and neonatal monitoring (OR 1.50 95% CI 1.10–2.05).

5.5 OUT-OF-HOME PLACEMENT OF CHILDREN WITH A MOTHER WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY IV)

In total, 2904 children were born to 1675 cases and, 14,496 children were born to 6767 controls between 1991 and 2013.

5.5.1 MOTHERS

When comparing cases and controls, we found that cases were significantly younger at birth [cases vs. controls: mean 27.2 years (SD ± 5.14) vs. 29.5 years (SD ± 4.82), $p < 0.001$]. Cases were significantly more often single at the end of a pregnancy [cases vs. controls: 625 (37.3%) vs. 1404 (20.7%), $p < 0.001$] and smoked significantly more often at the beginning of a pregnancy (cases vs. controls: 944 (31.5%) vs. 1994 (13.3%), $p < 0.001$] than controls. The mean number of deliveries was significantly higher among controls than among cases [cases vs. controls: 1.8 (SD ± 1.03) vs. 2.2 (SD ± 1.14) $p < 0.001$].

5.5.2 CHILDREN

The prevalence of premature birth [children of cases vs. children of controls: 172 (5.9%) vs. 564 (3.9%), $p < 0.001$], low birthweight [children of cases vs. children of controls: 111 (3.8%) vs. 387 (2.7%), $p < 0.001$], a low 1-min Apgar score [children of cases vs. children of controls: 164 (5.6%) vs. 628 (4.3%), $p = 0.002$], and major congenital anomalies [children of cases vs. children of controls: 123 (4.2%) vs. 440 (3.4%), $p < 0.001$] were significantly higher among the children of cases than among the children of controls. The prevalence of children with at least one of the abovementioned adverse perinatal health outcomes was significantly higher among

the children of cases than among the children of controls [children of cases vs. children of controls: 335 (11.5%) vs. 1212 (8.4%), $p < 0.001$].

5.5.3 OUT-OF-HOME PLACEMENTS

As many as 684 (40.8%) cases and 322 (4.8%) controls faced an out-of-home placement of at least one child ($x^2 = 1576.45$, $p < 0.001$). Among children, 1019 (35.1%) children of cases and 469 (3.2%) children of controls were placed out of the home ($x^2 = 3219.00$, $p < 0.001$). Among the out-of-home placed children, 256 (25.1%) children of cases and 37 (7.9%) children of controls were placed out of the home during the first year of their lives ($x^2 = 60.88$, $p < 0.001$). The median number of out-of-home placements was 4 [interquartile range (IQR) 2–5] among the children of cases and 3 (IQR 1–4) among the children of controls ($U = 33{,}622$, $p = 0.001$). The number of out-of-home placements ranged from 1 to 54 among the children of cases and from 1 to 34 among the children of controls. The mean total length of an out-of-home placement was 5.1 years (SD ± 5.48) among the children of cases and 2.4 years (SD ± 3.66) among the children of controls ($t = 9.660$, $p < 0.001$).

5.5.4 PREDICTORS FOR OUT-OF-HOME PLACEMENT

After adjusting for the child's birth year, the incidence rate ratio (IRR) of out-of-home placement among the children of cases was 12.6 (95% CI 10.80–13.46) when the children of controls served as the reference. When the child's birth year and a perinatal health problem (yes vs. no) were used as the covariates, IRR was 11.9 (95% CI 10.70–13.32). When the child's birth year, maternal age, marital status, smoking status at the beginning of the pregnancy, and the number of deliveries were used as covariates, IRR fell to 9.8 (95% CI 8.71–10.92). When both the maternal and child's characteristics were used as the covariates, IRR of out-of-home placement remained 9.7 (95% CI 8.65–10.85).

Focusing on the children of cases, being a single mother at the end of a pregnancy (IRR 2.21, 95% CI 1.88–2.63) and maternal smoking at the beginning of a pregnancy (IRR 1.92, 95% CI 1.68–2.16) significantly increased the risk of out-of-home placement. Yet, maternal age at birth (IRR 1.0, 95% CI 0.97–1.00), the number of births (IRR 1.1, 95% CI 0.99–1.11), or a perinatal health problem among the child (IRR 1.2, 95% CI 0.98–1.33) did not increase this risk significantly.

Among the children of controls, maternal smoking at the beginning of pregnancy (IRR 4.00, 95% CI 3.31–4.84), being a single mother at the end of a pregnancy (IRR 2.08, 95% CI 1.67–2.59), and the mother's previous deliveries (IRR 1.25,

95% CI 1.17–1.32) significantly increased the risk of an out-of-home placement. A perinatal health problem in the child (IRR 1.3, 95% CI 0.94–1.71) did not increase that risk significantly, however. Interestingly, an advanced maternal age significantly decreased the risk of an out-of-home placement (IRR 0.90, 95% CI 0.88–0.93).

6 DISCUSSION

This register-based nationwide project focused on the reproductive health of Finnish women with schizophrenia or schizoaffective disorder. While de-institutionalization has enabled affected women to live their everyday lives more like their unaffected counterparts, schizophrenia and schizoaffective disorder as serious mental disorders remain characterized by substantial physical health problems as well as social disadvantages. This study's findings indicate that these disorders diversely impact women's reproductive, obstetric, perinatal health, and parenting outcomes as well.

The incidence of induced abortions among Finnish women with schizophrenia or schizoaffective disorder is similar to that in the general population. However, the likelihood and risk of abortion is more than twofold higher per pregnancy among affected women.

In addition, affected women less frequently used contraception compared with unaffected controls. Affected women were more often not in a permanent relationship and their pregnancies were terminated primarily due to social reasons. Focusing on pregnancies, affected women were significantly older and more often single, their pre-pregnancy BMI was significantly higher, and they smoked significantly more often both at the beginning of their pregnancies and after the first trimester than controls. Furthermore, affected women were at a significantly higher risk of a pathological oral glucose tolerance test, initiating insulin treatment, rapid fetal growth, premature contractions, hypertension, and pregnancy-related hospitalizations. Suspected fetal exposure to alcohol or drugs was significantly more common among affected women than controls.

When examining deliveries, affected women exhibited an increased risk for labor induction, delivery by Cesarean section, and delivery by elective Cesarean section. Among their offspring, the risk of premature birth, a low 1-min Apgar score (<7), requiring resuscitation, and needing neonatal monitoring were all significantly higher. Maternal schizophrenia or schizoaffective disorder served as strong risk factors for the placement of an offspring in out-of-home care. In what follows, I discuss these findings in more detail.

6.1 INDUCED ABORTIONS IN WOMEN WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY I)

6.1.1 FERTILITY AND INDUCED ABORTION RATES

Finnish women with schizophrenia or schizoaffective disorder had a lower fertility rate than controls from the general population. This finding is unsurprising, given previous reports from Finnish researchers (Haukka et al., 2003), as well as by many other researchers in Nordic and other countries (Essen-Möller, 1959; Slater et al., 1971; Haverkamp et al., 1982; Kendler & Diehl, 1993; Nanko & Moridaira, 1993; Fananas & Bertranpetit, 1995; Nimgaonkar et al., 1997; Srinivasan & Padmavati, 1997; Nimgaonkar, 1998; McGrath et al., 1999; Howard et al., 2002; Svensson et al., 2007; Laursen & Munk-Olsen, 2010).

Turning towards pregnancy terminations, the number and incidence of induced abortions among affected women did not differ from those among unaffected women. However, when all pregnancies were taken into account, pregnancies among affected women more often ended in an induced abortion. In fact, affected women exhibited a more than twofold increased risk per pregnancy of an induced abortion. Following completion of study I, Brown et al. (2018) published a population-based study from Ontario, Canada, comparing women with and without schizophrenia examining rates of induced abortions. In their study, affected women exhibited higher induced abortions rates than unaffected women in each year examined (15.5–17.5 vs. 12.8–13.6 per 1000 women; highest RR 1.33, 95% CI 1.16–1.54) and exhibited higher induced abortion ratios (592–736 vs. 321–341 per 1000 live births; highest RR 2.25, 95% CI 1.96–2.59). A younger age, multiparity, comorbidity for a non-psychotic mental illness, and substance use disorders were all associated with an increased induced abortion risk in that Canadian study.

6.1.2 CHARACTERISTICS OF INDUCED ABORTIONS

Affected women who terminated a pregnancy were significantly younger and more often single than their counterparts in the general population. The most prevalent indications for a pregnancy termination were social circumstances (almost 93%), although this was the case among unaffected women as well (almost 95%). Medical indications in the mother were, unsurprisingly, more prevalent among affected women, yet indicated in only 2% of pregnancy terminations among affected mothers. Somewhat surprisingly, since maternal schizophrenia is associated with fetal abnormalities (Jablensky et al., 2005), a fetal medical indication was significantly more common among unaffected women than among affected women. This finding

might result from the younger age at pregnancy among affected women (risk for chromosomal abnormalities increase with age). An ethical indication for a pregnancy termination remained exceptionally rare with no significant group difference. This finding is also interesting, since women with schizophrenia are often victims of sexual abuse (Solari et al., 2009).

Under Finnish legislation for induced abortions, a pregnancy must be terminated as early as possible, normally within the first 12 weeks of gestation. Since the mid-1980s, induced abortions taking place after the end of 12 weeks have remained relatively rare (5–8% of cases annually; Heino et al., 2018). In this study, induced abortions later than 12 gestational weeks were significantly more prevalent among affected women (approximately 16%). This might be explained by the fact that pregnancies among women with schizophrenia are often unplanned (Seeman & Ross, 2011), and affected women may misinterpret somatic changes related to pregnancy (Solari et al. 2009), deny their pregnancy (Miller 1990; Jenkins et al., 2011; Babbitt et al., 2014), or find it challenging to decide to terminate their pregnancy (Babbitt et al., 2014).

6.1.3. USE OF CONTRACEPTION

In the Nordic countries, especially in Finland, abortion rates remain relatively low, which, according to Knudsen et al. (2003), provide evidence of the effectiveness of preventive methods. In this study, the low use of contraceptives represented a notable challenge among women with schizophrenia or schizoaffective disorder. In fact, almost half of affected women who terminated their pregnancy reported not using a contraceptive method before becoming pregnant. This finding agrees with earlier studies (Matevosyan, 2009) and highlights the importance of integrating contraceptive counseling and family planning services with mental health services (Solari et al., 2009; Seeman & Ross, 2011).

6.1.4 IMMEDIATE COMPLICATIONS RELATED TO INDUCED ABORTIONS

The prevalence of complications related to pregnancy termination remains low in Finland (Induced abortions 2017, Statistical Report of Institute for Health and Welfare of Finland). This observation persisted in this study. Immediate complications associated with abortions remained rare in both groups, likely reflecting the relative uniformity and high quality of Finnish healthcare services. Furthermore, the majority of Finnish pregnancy terminations are medical terminations, not surgical (Induced abortion: Current Care Guidelines Abstract, 2013).

6.2 PREGNANCY AMONG WOMEN WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY II)

6.2.1 PREPREGNANCY BMI

This study demonstrated that Finnish women with schizophrenia present with a significantly higher prepregnancy BMI than women in the general population. This finding agrees with previous studies (Allison, 1999), whereby weight problems related to schizophrenia primarily result from unhealthy eating habits, a sedantary lifestyle, diminished physical activity, antipsychotic medications, and negative symptoms related to the disorder itself (Holt, 2005; Manu et al., 2015). According to an European Perinatal Health Report (www.europeristat.com), approximately 12% to 13% of all delivering women in the Nordic countries suffer from obesity. Maternal prepregnancy weight problems remain an important issue in many ways. First, maternal overweight is strongly associates with the risk of gestational diabetes (Di Cianni et al., 2003; Chu et al., 2007). Moreover, obesity increases the risk for all severe delivery-related complications (Pallasmaa et al., 2015), and maternal obesity associates with an increased risk of infant mortality (Johansson et al., 2014). Furthermore, risks for severe asphyxia-related outcomes in infants increase with maternal obesity (Persson et al., 2014). Thus, preventing obesity in women of reproductive age is important to improving perinatal health. Among individuals with schizophrenia, lifestyle interventions are effective in both treating and preventing obesity (Bruins et al., 2014).

6.2.2 SMOKING DURING PREGNANCY

While maternal smoking during pregnancy has decreased in the Nordic countries in recent decades, this trend has not characterized the situation in Finland, where the prevalence of maternal smoking remains approximately 15% (Ekblad et al., 2014). In this study, more than 30% of mothers-to-be with schizophrenia or schizoaffective disorder continued to smoke after the first trimester. Maternal smoking during pregnancy increases the risk of various pregnancy-related complications, such as miscarriage (Pineles et al., 2014), stillbirth (Marufu et al., 2015), and preterm birth (Ion & Bernal, 2015). Newborns exposed to maternal smoking tend to exhibit a lower birthweight compared to unexposed newborns (Gray et al., 2010). Furthermore, infants exposed to maternal smoking typically have a smaller head circumference at birth compared to unexposed infants, reflecting compromised fetal brain development (Ekblad et al., 2015). Very preterm infants exposed to maternal

smoking also exhibit a smaller frontal lobe and lower cerebellar volumes compared to unexposed infants (Ekblad et al., 2010 a).

Several studies identified an association between maternal smoking and psychiatric problems among offspring (Ekblad et al., 2010 b), including attention deficit hyperactivity disorder (Langley et al., 2005), behavioral problems (Tiesler & Heinrich, 2014), and schizophrenia (Niemelä et al., 2016). Söderström et al. (2013) reported that maternal smoking during pregnancy carried a 1.2-fold increased risk of psychotropic drug use among offspring. According to a recent study by Ekblad et al. (2017), maternal smoking independently associated with a higher risk of psychiatric morbidity in children, even after controlling for genetic and familial factors. In this study, maternal smoking emerged as a significant risk factor for premature birth, low birthweight, a low 1-min Apgar score, and neonatal monitoring.When comparing affected women who smoked to non-smoking affected women, smoking represented a significant risk factor for very low birthweight and neonatal monitoring.

We can argue that smoking represents one of the few preventable factors associated with pregnancy complications. A recent Cochrane review by Chamberlain et al. (2017) provided moderate- to high-quality evidence that psychosocial interventions increased both the proportion of women who ceased smoking late in their pregnancy (by 35%) and the mean infant birthweight (by 56 g), and reduced both the number of babies born with a low birthweight (by 17%) and admissions to neonatal intensive care (by 22%). According to the Finnish Current Care Guideline on Tobacco and Nicotine Dependency, Prevention, and Treatment (2018), drug treatment can be used in pregnant women if psychosocial interventions are insufficient to prevent smoking. In such cases, nicotine gum, nicotine patches, and nicotine nasal spray can be used as first-line alternatives (Dempsey & Benowitz, 2001).

6.2.3 HYPERGLYCEMIA DURING PREGNANCY

With obesity globally close to epidemic levels, the prevalence of gestational diabetes, defined as disturbed glucose metabolism first recognized during pregnancy, is increasing rapidly as well. Today in Finland, approximately 18% of mothers-to-be develop gestational diabetes (Huvinen, 2018). In line with previous studies (Nguyen et al. 2013; Judd et al., 2014), we found an approximately twofold increased risk of a pathological oral glucose test among women with schizophrenia or schizoaffective disorder. Gestational diabetes carries a huge impact on both the mother's and child's health. Among mothers, gestational diabetes serves as a risk factor for hypertension, pre-eclampsia, labor induction, Cesarean section, and post-partum hemorrhage (Suhonen & Teramo, 1993; Schmidt et al., 2001; Catalano et al., 2012). In agreement with such findings, in this study, affected women exhibited an increased risk of

pregnancy-related hypertension and specific delivery methods including labor induction and Cesarean section.

Among offspring, the primary risk is excessive fetal growth (macrosomia), which increases the risk of delivery complications such as shoulder dystosia, birth injuries, and asphyxia, as well as the risk of neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome (Jones, 2001; Crowther et al., 2005; Reece, 2010). In this study, affected women exhibited an increased risk of rapid fetal growth. Gestational diabetes also increases the risk of congenital anomalies (Feig et al., 2014). In this study, the offspring of affected women exhibited a trend for major congenital anomalies compared to the offspring of unaffected women, although the differences were not statistically significant. Women with a pathological glucose tolerance test need dietary and lifestyle counseling, while the self-monitoring of glucose concentrations represents the most effective way to monitor the glucose balance and the need for pharmacological treatment (Crowther et al., 2005).

If risk factors appear for gestational diabetes, olanzapine should be avoided unless the patient's history indicates switching to another medication significantly increases her risk of recurrence (Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology, 2011). When prescribing clozapine, concerns about the potential for relapse typically outweigh concerns about its dysglycemic effect (Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology, 2011). Polypharmacy should be avoided and the patient should be monitored closely (Seeman, 2013).

6.2.4 SUBSTANCE MISUSE DURING PREGNANCY

In this study, suspected alcohol- or drugs-related harm to the fetus rarely occured, although they were significantly more common among women with schizophrenia or schizoaffective disorder than among mothers in the general population. This presumably results from the comorbidities associated with substance misuse often related to schizophrenia (Kessler et al., 2005). According to a recently published guideline by the World Federation of Societies of Biological Psychiatry and the International Association for Women's Mental Health (2019), there is no safe level of alcohol use that can be consumed during pregnancy. Abstinence, thus, is recommended.

Ideally, women should stop alcohol use upon planning a pregnancy and, in all cases, as soon as a pregnancy is detected. Determining patterns of maternal alcohol use should be systematically carried out during the first antenatal visit and throughout pregnancy. Brief interventions are recommended in cases of low- or moderate-risk alcohol use. Low doses of benzodiazepines, for a short duration, may be used to prevent alcohol withdrawal symptoms when high and chronic alcohol

intake ceases, and hospitalization is recommended. Due to scant evidence and the low benefit–risk ratio, pharmacological treatment to maintain abstinence should not be prescribed during pregnancy. At birth, fetal alcohol spectrum disorders must be identified, and alcohol metabolites should be measured in the meconium of neonates if any doubt exists regarding fetal alcohol exposure.

6.2.5 PRENATAL CARE

Pregnancies among women with schizophrenia are challenging and require careful monitoring. In agreement with previous studies (Ellman et al., 2007; Vigod et al., 2014), Finnish women with schizophrenia or schizoaffective disorder exhibited a substantially higher number of visits to maternity clinics, as well as to the outpatient units of maternity hospitals when compared with women in the general population. In addition, the proportion of women with one or more pregnancy-related hospitalizations was significantly higher among women with schizophrenia or schizoaffective disorder. Affected women exhibited a higher prevalence of psychosocial and somatic risk factors, as well as a higher prevalence of pregnancy-related complications compared to their controls. This might also reflect that affected women were offered more intense prenatal care because of their psychiatric disorder per se. Of course, these two findings do not preclude one another. This study verifies that women with schizophrenia or schizoaffective disorder are motivated to receive prenatal care.

6.3 OBSTETRIC COMPLICATIONS RELATED TO SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY III)

In terms of delivery methods, Finnish women with schizophrenia or schizoaffective disorder were at a higher risk for labor induction, Cesarean section, and elective Cesarean section. These findings mirror earlier nationwide cohort studies (Bennedsen et al., 2001a; Hizkiyahu et al., 2010; Vigod et al., 2014). Inducing labor typically aims to decrease the risk of complications for both the mother and the newborn. Reasons indicating the induction of labor can be somatic as well as psychiatric. According to Frayne et al. (2014), some women with serious mental disorders may benefit from the planned induction of labor. Such disorders include highly anxious women or those with a low frustration tolerance who may feel more at ease knowing the date of delivery. Induction of labour may also be recommended for women on psychotropic medications such as lithium to allow for a rapid tapering or withholding of the normal dose 24 to 48 h before the planned delivery (Newport et al., 2005). Inducing labor can diminish the risk of laboring at night and, thus,

minimize sleep disruption, which may precipitate a psychotic relapse. The induction of labor or a planned Cesarean section may also benefit the coordination of staff to help manage potential difficulties arising around the time of delivery.

Delivery-related complications emerged rather rarely within our sample, and we found no significant group differences. This finding likely reflects the high quality of Finnish national healthcare services. When all deliveries were considered, the three most prevalent diagnoses both among affected and unaffected women included fetal distress, postpartum hemorrhage, and prolonged labor.

6.4 PERINATAL PROBLEMS OF CHILDREN WITH A MOTHER WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY III)

The causes of unwanted perinatal health outcomes among newborns whose mothers have schizophrenia and the possibility of preventing deleterious outcomes remain unclear. Possible causative factors include an abnormality in fetal development due to a genetic predisposition, the effects of the maternal mental illness and stress, sociodemographic disadvantages, poor nutrition and associated lifestyle factors, or the effects of prescribed drugs. It is most likely, however, that multiple factors influence the risk and mediate poor outcomes (Judd et al., 2014). According to a meta-analysis by Sacker et al. (1996) and earlier national cohort studies by Bennedsen et al. (2001b), Nilsson et al. (2002), Jablensky et al. (2005), and Vigod et al. (2014), the risk of a low birthweight (<2500g) was higher in newborns with affected mothers.

In addition, the risk of premature birth was also higher among affected women, a finding that agrees with studies by Matevosyan (2011), Bennedsen et al. (2001a), Nilsson et al. (2002), and Vigod et al. (2014). In agreement with the cohort study by Bennedsen et al. (2001b) and Matevosyan's (2011) meta-analysis, the risk of a low Apgar score was higher in newborns with affected mothers. Furthermore, the risk of neonatal monitoring was higher among newborns with affected mothers, a finding consistent with Sacker et al.'s (1996) results.

Moreover, the risk of resuscitation was higher among newborns with affected mothers. Interestingly, these risks remained significant after adjusting for maternal age and smoking status, the number of deliveries, marital status, and the sex of the newborn. The risk of a congenital anomaly was higher in newborns with affected mothers, although this finding disappeared after adjustment.

6.5 OUT-OF-HOME PLACEMENT OF CHILDREN WITH A MOTHER WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER (STUDY IV)

6.5.1 MOTHERS FACING AN OUT-OF-HOME PLACEMENT OF THEIR OFFSPRING

Among affected mothers, almost 41% faced an out-of-home placement of at least one child during the follow-up period. This finding agrees with several earlier studies reporting that approximately 50% of mothers with schizophrenia lose custody of their child or children (Seeman, 2012). Both maternal smoking at the beginning of a pregnancy and being a single parent emerged as risk factors for the out-of-home placement of a child, although this was also the case among unaffected mothers. Maternal smoking and being a single parent are not themselves grounds for the out-of-home placement of a child, but reflect a variety of problems a mother may face. Smoking, in general, as a sociodemographic pattern strongly associates with a lower socioeconomic status and a lower education (Laaksonen et al., 2002; Tidey & Miller, 2015). In addition, smoking is associated with alcohol and other substance misuse disorders (Swarbrick et al., 2017).

Turning to the offspring, exposure to a mother's smoking prenatally associates with an increased risk for various developmental disadvantages, including hyperactivity and behavioral problems (Kotimaa et al., 2003). Being a single mother often increases the risk for certain vulnerabilities in society, such as physical and mental health challenges, economic problems, and social isolation (Rousou et al., 2013). Interestingly, while perinatal health problems in a child cause stress and represent a demanding situation for the mother, particularly if she suffers from a serious mental health disorder, such problems did not increase the risk of out-of-home placement in this study.

6.5.2 CHILDREN PLACED OUT-OF-HOME

In agreement with a recent national cohort study from Denmark (Ranning et al., 2015), more than 35% of children with a mother with schizophrenia or schizoaffective disorder were placed out-of-the-home during the follow-up period. Compared to the children of unaffected mothers, the children of affected mothers faced an almost 13-fold risk of being placed out-of-the home. Similar to a Danish study (Ranning et al., 2015), a substantial proportion of out-of-home placed children were placed out-of-the-home already during his or her first year of life. Recently, in their population-wide cohort study, Côté et al. (2018) compared later psychopathology and criminality among children placed outside the home at ages 2 to 6 years old

and children who were not placed outside their home all of whom had similar sociodemographic and family characteristics. In young adulthood, those placed out-of-the-home as children were at a higher risk than their never-placed counterparts for substance-related misuse disorders (OR 2.1), psychotic or bipolar disorders (OR 4.0), depression or anxiety (OR 2.2), neurodevelopmental disorders (OR 3.59), and other psychiatric disorders (OR 2.1). Participants who were placed out-of-the-home were also more often prescribed psychotropic medications (OR 2.0) and exhibited higher rates of criminal convictions (violent offenses: OR 2.4; property offenses: OR 1.9). In the present study, children often faced several out-of-home placements; among the children of affected mothers, the median number of out-of-home placement reached 4, with a maximum of 54; among the children of unaffected mothers, the median number of placements was 3 with a maximum of 34. These figures reflect the complexity of the issue, raising a question for future studies. Specifically, the impact such placements have for the child remain unanswered.

The high prevalence of affected mothers and their children facing an out-of-home placement highlight the need for intensive treatment services, including psycho-education regarding early signs of relapse, crisis planning, training in parental skills and household issues, and the mapping of social contacts and resources within one's network (Seeman, 2012). This should result from intensive cooperation with professionals from the fields of child psychiatry, adolescent psychiatry, adult psychiatry, and social services.

6.6 MAIN CONCLUSIONS FROM THE STUDY

This nationwide register-based study aimed to understand the reproductive health of women with schizophrenia or schizoaffective disorder. In doing so, the following represent the primary conclusions:

1. The incidence of induced abortions do not substantially differ between women with schizophrenia or schizoaffective disorder and women in the general population, although the per pregnancy risk of induced abortion is more than twofold higher among affected women (study I).
2. Compared to women in the general population, women with schizophrenia are younger and more often single at the time of an induced abortion, and their pregnancies more often result from a lack of contraceptive use (study I).
3. Compared to women in the general population, women with schizophrenia or schizoaffective disorder experience a higher prevalence of psychosocial and somatic risk factors related to pregnancy, as well as a higher prevalence of pregnancy-related complications and disorders (study II).

4. Schizophrenia and schizoaffective disorder associate with specific delivery methods, but delivery-related complications and disorders remain rare, the prevalence of which does not differ from that of women in the general population (study III).
5. Maternal schizophrenia and schizoaffective disorder associate with some adverse perinatal health outcomes in the offspring (study III).
6. Maternal schizophrenia and schizoaffective disorder serve as strong risk factors for the placement of a child in out-of-home care (study IV).
7. Approximately one in four out-of-home placed children born to a mother with schizophrenia or schizoaffective disorder is already placed in out-of-home care during the first year of her/his life (study IV).

6.7 STRENGTHS AND LIMITATIONS OF THE STUDY

6.7.1 STRENGTHS OF THE STUDY

This was a nationwide follow-up study, which relied on high-quality registers. Previous studies evaluated the coverage, quality, and validity of the health registers in Finland as high (Aro et al., 1990; Gissler et al., 1995; Gissler et al., 1996; Heino et al., 2018). The coverage of the Finnish Register of Induced Abortions covers 97% of all pregnancy terminations in Finland (Heino et al., 2018). The diagnostics of psychotic disorders have all been established as high quality (Isohanni et al., 1997; Pihlajamaa et al., 2008). In addition, the large, population-based dataset proved advantageous, enabling the representative and comprehensive analysis of reproductive health among Finnish women with schizophrenia. Furthermore, the population-based sample enabled an investigation of specific health conditions, associations, lifestyle factors, hospitalizations, and sociodemographic factors related to the subgroup-specific reproductive health outcomes among these women.

The use of various registers in this study provided an opportunity to study trends over time and to design a follow-up study given the cumulative nature of the health registers in Finland. The data in the registers are reliably recorded. Since an established association exists between maternal schizophrenia and several adverse reproductive health outcomes, as reported in previous studies, the analyses in all four studies were adjusted for these confounding factors.

6.7.2 LIMITATIONS OF THE STUDY

First, several limitations relate specifically to the sample populations. Among affected women, no information was available regarding the severity of the psychotic or other neuropsychiatric and psychiatric symptoms related to schizophrenia

or schizoaffective disorder, nor was information available about the psychiatric (including substance use disorders) or somatic comorbidity, the utilization of mental health services, or medications prescribed to them. Control women were age- and place-of-birth–matched, although socioeconomic status, education, and employment status were not taken into account. Controls did not experience psychotic disorders (ICD-X codes F20–29), although other disorders were allowed. We had no information about these other psychiatric or somatic disorders or any medications prescribed for such disorders. In addition, we had no information related to the fathers or information related to the psychopathology of the offspring.

In addition, another limitation to this study stems from the definition of schizophrenia, which has changed over time. The present follow-up study covered a time period when three different versions of ICD (ICD-8, ICD-9, and ICD-10) were used in the diagnostic processes. In Finland, however, DSM-III-R was used from 1987 to 1995, and the criteria within DSM-III-R remained more or less uniformly applied to clinical practice from the beginning of the 1980s (Pihlajamaa et al., 2008). ICD-8 associates with a broad concept for schizophrenia, ICD-9 covers a rather narrow concept for schizophrenia, and ICD-10 associates with a moderately broader concept of schizophrenia (Tandon, 2012). Specifically examining the DSM system, DSM-I (American Psychiatric Association, 1952) and DSM-II (American psychiatric Association, 1968) represent an overly broad definition, resulting in a marked discrepancy between the diagnosis of schizophrenia in the United States and the rest of the world (Tandon, 2012). In response to such discrepancies, DSM-III-R (American Psychiatric Association, 1980) provides a much narrower definition of schizophrenia (Tandon, 2012). Then, moving from DSM-III to DSM-IV, a modest expansion of the boundaries of schizophrenia was introduced (Tandon, 2012).

Although the diagnostic procedures in Finland remain at a high quality, it is likely that some affected women were not included in this study because of an erroneous diagnosis. According to the Northen Finland 1966 Birth Cohort Study (Moilanen et al., 2003), clinicians do not appear to make a diagnosis of schizophrenia as often as applying the operational criteria would suggest they should. In that study, discordant cases were more likely to be older at onset, experience shorter treatment durations, and experience fewer treatment episodes. Thus, there may be differences between clinicians and local customs within hospitals in the diagnosis and the reporting of ICD-10 diagnoses related to pregnancy and childbirth.

Furthermore, it is possible that a Finnish mother-to-be does not attend maternity healthcare services, although the number of such individuals is likely extremely low. It is also possible that some measurement errors (for maternal weight, height, etc.) occurred. However, taking into consideration that this study was nationwide, their effect can be regarded as unimportant. In addition, it was impossible to take into account illegal induced abortions. However, Finnish legislation has remained rather liberal since 1970, and illegal abortions are likely very rare. All national registers

were introduced electronically in different years; thus, we had no information about induced abortions before 1983, pregnancies and deliveries before 1987, congenital malformations before 1986, and out-of-home placements before 1991. The number of cases for some variables remained rather small. Considering the high number of outcomes, we must acknowledge that some of the observed associations may have occurred due to chance. Finally, although we matched these cases and controls, the possibility of some unknown confounding factors influencing the findings remains.

6.8 IMPLICATIONS FOR FUTURE RESEARCH

This register-based study primarily focused on women with schizoprenia or schizoaffective disorder, although its importance equally applies to investigating their children. For example, a child's later morbidity, mortality, as well as criminality represent relevant themes to investigate using the high-quality Finnish registers. Register-based studies carry obvious advantages, although qualitative research might help researchers more richly understand these women's subjective feelings and experiences related to reproductive health issues. One important theme for future study lies in feelings of the stigma related to pregnancy and parenting. Future research should also focus on potential protective factors that encourage successful parenting outcomes in this vulnerable population.

6.9 CLINICAL IMPLICATIONS

Overall, better integrating reproductive healthcare services into mental healthcare settings appears important to improve outcomes. Active family planning and contraceptive counseling are needed in this patient group. The topic of a possible pregnancy should be raised when a female patient enters a psychiatric treatment unit, giving such patients an opportunity for a voluntary pregnancy test. Smoking cessation programs, nutrition counseling, and substance use screening should be actively offered to women with schizophrenia spectrum disorders who plan a pregnancy, as well as to mothers-to-be with these disorders. In addition, psychological support should be offered during pregnancy, particularly during the postpartum period. Mental health professionals can help mothers with schizophrenia or schizoaffective disorder on parenting issues by assisting them to look after their own health and with self-monitoring for signs of a relapse. Intensive collaboration between mental health professionals, social workers, and specialists in gynecology and obstetrics should become standard practice.

7 ACKNOWLEDGEMENTS

This work was carried out in the Department of Psychiatry at the Helsinki University Hospital. I am grateful to everyone who supported me throughout my research. In particular, I am enormously grateful to my main supervisors, without whose support this work would not have been possible. I have valued each and every discussion, and benefitted from each moment of their guidance throughout this journey. They are my true inspiration.

I extend my deepest gratitude to Professor Nina Lindberg for her incredible and invaluable expertise, knowledge, kindness, and patience throughout this project. In addition to her brilliant supervision, Professor Lindberg's support has allowed me as a young researcher to familiarize myself with the scientific community abroad by granting me opportunities and the possibility to network at international conferences. Without her support, this thesis would not have succeeded. I thank you for being always available to me.

I am also indebted to my other supervisor, Professor Erkki Isometsä. Both his clinical and scientific expertise in psychiatry and psychiatric research is inspirational and truly admirable. I thank you for your generous and invaluable support, as well as your insightful views throughout this study. Through your example, I have learned innumerable details related to scientific thought and writing, as well as the value of patience as a researcher.

I thank my coauthors for their essential contributions. I extend my heartfelt gratitude to my coauthor Professor Mika Gissler, who on numerous occasions provided guidance to me between his tight work schedule, particularly when helping me navigate through what felt like impossible and unsolvable methodological challenges. Without Professor Gissler's expertise and exceptionally broad knowledge of register-based research and study methodologies, and his warm attitude towards junior scholars, this work would have been infinitely more difficult to complete. I also wish to express my warmest thanks to Professor Jaana Suvisaari, whose expertise in both schizophrenia research and diagnostics has proved invaluable throughout this study. MDEila Sailas gratefully shared her expertise on the ethical considerations and challenges of treating mothers and women with schizophrenia in particular. And, Docent Erja Halmesmäki deserves my warmest thanks for providing both her scientific and clinical insights, as well as contributing her expertise as an obstetrician and gynecologist to this study.

I extend my warmest gratitude to data manager Marjut Grainger for her assistance with managing my dataset, as well as her practical support and tirelessly

sharing her knowledge of register-based studies. I have truly enjoyed our friendly atmosphere and discussions while working.

I am sincerely grateful to the official reviewers of this thesis, Docents Erika Jääskeläinen and Max Karukivi, for their invaluable insights and constructive comments, which helped improve the manuscript immeasurably. I also wish to thank Docent Matti Holi for serving as an grade assessor.

I also extend my thanks to Ms Vanessa Fuller for the final English-language and stylistic revisions, and extend my warm thanks to graphic artists Riikka Hyypiä and Mari Lindgren for their assistance in the visual design and refined work they contributed to this thesis.

I also wish to express my warmest gratitude to my colleagues and coworkers at the Helsinki University Hospital, with whom I have shared the most amazing and interesting work experiences over the years. I have always enjoyed your genuineness, great sense of humor, and our interesting and insightful discussions. Erja Tikka, my dear colleague, I thank you for your warm and unwavering support over the years. Assistant ward managers Sami Dufva and Tiina Tuuttila, have gratefully extended their friendly and supportive attitude towards managing a ward as well as showing understanding towards ward manager's numerous research leaves. It has always been easy to work with both of you, and I am grateful.

Kaisa, Raisa, Niina, Johanna, Anita, and Minna deserve a very special thanks for their lifelong friendship and support. I cherish all of our funny moments, discussions, and experiences together. My heart-felt thanks go to Ville, who during these long winter and spring months of preparing this thesis has walked with me along countless forest and national park paths in Finland and reminded me of the true beauty and empowering force of Finnish nature.

I wish to sincerely thank Hilkka and Esko Männynsalo for their friendship, support, and being the best possible grandparents to my son.

I want to thank my parents Riitta and Jukka Simoila and my brother Ilkka. All of you have served as my inspiration and provided your unconditional support to me. I could not imagine a single situation in which your encouragement and example have not carried me through in my own life.

Finally, the sun and light of my life, Akseli, I thank you for simply being lovely and the most perfect version of yourself. You give meaning to everything.

This work was financially supported by the Finnish Nurses Association and the Helsinki University Hospital.

Laura Simoila
Helsinki, September 2019

8 REFERENCES

Abel KM Webb RT, Salmon MP, Wan MW, Appleby L. Prevalenve and predicgors of parenting outcomes in a cohort of mothers with schizophrenia admitted for joint mother and baby psychiatric care in England. J Clin Psychiatry 2005; 66: 781-789.

Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. Int Rev Psychiatry 2010; 22(5): 417-428.

Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. Arch Gen Psychiatry 2003; 60(6): 565-571.

Allison DB, Newcomer JW, Dunn AL, Blumenthal JA, Fabricatore AN, Daumit GL, Cope MB, Riley WT, Vreeland B, Hibbeln JR, Alpert JE. Obesity among those with mental disorders: A national Institute of Mental Health meeting report. Am J Prev Med 2009; 36(4): 341-350.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (1st edition, Revised). American Psychiatric Press, Washington DC. 1952.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (2nd edition, Revised). American Psychiatric Press, Washington DC. 1968.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (3rd edition). American Psychiatric Press, Washington DC. 1980.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (3rd edition, Revised). American Psychiatric Press, Washington DC. 1987.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th edition). American Psychiatric Press, Washington DC. 1994.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th edition). American Psychiatric Press, Arlington, VA. 2013.

Araneva M. Lapsen suojelu. Toteuttaminen ja päätöksenteko. Talentum Media Oy 2016 : 61-62.

Aro S, Koskinen R, Keskimäki I. Reliability of Hospital Discharge data concerning diagnosis,treatments and accidents. Duodecim 1990; 106(21): 1443-1450.

Babbit KE, Bailey KJ, Coverdale JH, Chervenak FA, McCullough LB. Professionally responsible intrapartum management of patients with major mental disorders. Am J Obstet Gynecol 2014; 210(1): 27-31.

Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. PLoS One 2014; 9(4): e94112.

Barch DM,Keefe RS. Anticipating DSM-V: opportunities and challenges for cognition and psychosis. Schizophr Bull 2010; 36(1): 43-47.

Barnes TR. Schizophrenia Consensus Group of British Association for Psychopharmacology. Evidence based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2011; 25(5): 567-620.

Bellack AS, Morrison RL, Mueser KT, Wade J. Social competence in schizoaffective disorder, bipolar disorder, and negative and non-negative schizophrenia. Schizophr Res 1989; 2(4-5): 391-401.

Bennedsen BE. Adverse pregnancy outcome in schizophrenic women: occurence and risk factors. Schizophr Res 1998; 33(1-2): 1-26.

Bennedsen BE, Mortensen PB, Olesen AV. Preterm birth and intrauterine growth retardation among children of women with schizophrenia. Br J Psychiatry 1999; 175: 239–245.

Bennedsen BE, Mortensen PB, Olesen AV, Henriksen TB, Frydenberg M. Obstetric complications in women with schizophrenia. Schizophrenia Research 2001a; 47: 167-175.

Bennedsen BE, Mortensen PB, Olesen AV, Henriksen TB. Congenital malformations: stillbirths, and infant deaths among children of women with schizophrenia. Arch Gen Psychiatry 2001b; 58(7): 674–679.

Bhattacharyya S, Atakan Z, Martin-Santos R, Crippa JA, Kmbeitz J, Malhi S, Giampietro V, Williams S, Brammer M, Rubia K, Colier DA, McGuire PK. Impairment of inhibitory control processing related to acute psychotomimetic effects of cannabis. Eur Neuropsychopharmacol 2015; 25(1): 26-37.

de Boer MK, Castelein S, Wiersma D, Schoevers RA, Knegtering H. The facts about sexual (Dys)function in schizophrenia: an overview of clinically relevant findings. Schizophr Bull 2015; 41(3): 674–686.

Bora E, Yucel M, Pantelis C. Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. Br J Psychiatry 2009; 195(6): 475-482.

Borgström CA. Tillämpningen av lagen om sterilisering i Finland 13.6.1935 – 30.6.1955, kastreringarna obeaktade av Medicinalstyrelsen behandlade fall. Academic dissertation. Helsinki University. 1958.

Breadon C, Kulkarni J. An update on medication management of women with schizophrenia in pregnancy. Expert Opin Pharmacother 2019; 20(11): 1365-1376.

Brown HK, Dennis CL, Kurdyak P, Vigod SN. A population based-study of the frequency and predictors of induced abortion among women with schizophrenia. Br J Psychiatry 2018; 20: 1- 8.

Bruins J, Jörg F, Bruggeman R, Slooff C, Corpeleijn E, Pijnenborg M. The effects of lifestyle interventions on (long-term) weight management, cardiometabolic risk and depressive symptom in people with psychotic disorder: A meta-analysis. PLoS One 2014; 9(12): e112276.

Burns T, Frioritti A, Holloway F, Malm U, Rössler W. Case management and assertive community treatment in Europe. Psychiatr Serv 2001; 52(5): 631-636.

Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia.: a historical and meta-analytic review. am J Psychiatry 2002; (159): 1080-1092.

Cascade E, Kalali AH, Kennedy SH. Real-world data on SSRI antidepressant side effects. Psychiatry 2009; 6 (2): 16-18.

Cassidy RM, Yang F, Kapczinski F, Passos IC. Risk factors for suicidality in patients with schizophrenia: A systematic review, Meta-analysis and Meta-regression of 96 studies. Schizophr Bull 2018; 44(4):7 87-797.

Catalano PM, McIntyre HD, Cruickshank JK, Mccance DR, Metzger BE, Lowe LP, Trimble ER, Coustan DR, Hadden DR, Persson B, Hod M, Oats JJ; HAPO Study Cooperative Research group. The hyperglycemia and afverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care 2012; 35(4): 780-786.

Chamberlain C, O'Mara-Eves A, Porter J, Coleman T, Perlen SM, Thomas J, McKenzie JE. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev 2017; 2: CD001055.

Cheniaux E, Landeira-Fernandez J, Lessa Telles L, Lessa JLM, Dias A, Duncan T, Versiani M. Does schizoaffective disorder really exist? A systematic review of the studies compared schizoaffective disorder with schizophrenia or mood disorders. J of Affective Disorder 2008; 106 : 209 – 217.

Chong HY, Teoh SL, Wu DB, Kotirum S, Chiou CF, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. Neuropsychiatr Dis Treat 2016; 12: 357-373.

Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, Dietz PM. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care 2007; 30(8): 2070-2076.

Coleman T, Chamberlain C, Cooper S, Leonardi-Bee J. Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis. Addiction 2011; 106(1): 52-61.

Coppola D, Russo L, Kwarta RF Jr, Varughese R, Schmider J. Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. Drug Saf 2007; 30(3): 247–264.

Correll CU. Understanding schizoaffective disorder: from psychobiology to psychosocial functioning. J Clin Psychiatry 2010; 71(Suppl2): 8-13.

Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotis, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry 2015; 14(2): 119-136.

Cote SM, Orri M, Marttila M, Ristikari T. Out-of home placement in early childhood and psychiaytric diagnoses and criminal convictions in early adulthood: a population based propensity score-matched study. Lancet Child Adolesc Health 2018; 2(9): 647-653.

Coughlin CG, Blackwell KA, Bartley C, Hay M, Yonkers KA, Bloch MH. Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. Obstet Gynecol 2015; 125(5): 1224–1235.

Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Eng J Med 2005; 352(24): 2477-2486.

Crump C, Winkleby MA, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. Am J Psychiatry 2013; 170(3): 324-333.

Davies B, Allen D. Integrsting mental illness and motherhood: the positive use of surveillance of by health professionals. A qualitative study. Int J Nurs Stud 2007; 44(3): 365-376.

De Leon, J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res 2005; 76(2-3): 135-157.

Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. Drug Saf 2001; 24(4): 277-322.

Diaz-Caneja A, Johnson S. The views and experiences of severely mentally ill mothers – a qualitative study. Soc Psychiatry Psychiatr Epidemiol 2004; 39(6): 472-482.

Dickerson FB, Brown CH, Kreyenbuhl J, Goldberg RW, Fang LJ, Dixon LB. Sexual and reproductive health behaviors among persons with mental disorders. Psychiatr Serv 2004; 55: 1299-1301.

Di Cianni G, Volpe L, Lencioni C, Miccoli R, Cuccuru I, Ghio A, Chatzianagnostou K, Bottone P, Teti G, Del Prato S, Benzi L. Prevalence and risk factors for gestational diabetes assessed by universal screening. Diabetes Res Clin Pract 2003; 62(2): 131-137.

D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol Psychiatry 2005; 57(6): 594–608.

Di Forti M, Sallis H, Allegri F, Trotta A, Ferraro L, Stilo SA, Marconi A, La Cascia C, Reis Marques T, Pariante C. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr Bull 2014; 40(6): 1509-1517.

Dipasquale S,Oariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: a systematic review. J Psychiatr Res 2013: 47(2):1 97-207.

Dixon L. Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophr Res 1999; 35 (1): 93-100.

Dixon, L.B., Dickerson, F., Bellack, A.S., Bennett, M., Dickinson, D., Goldberg, R.W., Lehman, A., Tenhula, W.N., Calmes, C., Pasillas, R.M., Peer, J., Kreyenbuhl, J., Schizophrenia Patient Outcomes Research Team (PORT), 2010. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. Schizophr. Bull. 36, 48-70.

Drake RE, Mueser KT. Alcohol-use disorder and severe mental-illness. Alcohol Health Res World 1996; 20(2): 87-93.

Druss BG, Bradford WD, Rosenheck RA, Radford MJ, Krumholz HM. Quality of medical care and excess mortality in older patients with mental disorders. Arch Gen Psychiatry 2001; 58(6): 565-572.

Dudzinski DM, Burke W. Practicing moral medicine: patient care to public health. Am J Bioeth 2006; 6(2): 75-76.

Duncan G, Browning J. Adult attachment in children raised by parents with schizophrenia. J Adult Dev 2009; 16: 76-86.

Einarson A. Antipsychotic medication (safety/risk) during pregnancy and breastfeeding. Current Women's Health Reviews 2010; 6(1): 34-38.

Ekblad M, Gissler M, Lehtonen L. Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood. Arch Gen Psychiatry 2010 a; 67(8): 841-849.

Ekblad M, Korkeila J, Parkkola R, Lapinleimu H, Haataja L, Lehtonen L, PIPARI STUDY GROUP. Maternal smoking during pregnancy and regional brain volumes in preterm infants. J Pediatr 2010 b;156(2): 185-190.

Ekblad M, Gissler M, Korkeila J, Lehtonen L. Trends and risk groups for smoking during pregnancy in Finland and other Nordic countries. Eur J Public Health 2014; 24(4): 544–551.

Ekblad M, Korkeila J, Lehtonen L. Smoking during pregnancy affects foetal brain development. Acta Paediatr 2015; 104(1): 12-18.

Ekblad M, Lehtonen L, Korkeila J, Gissler M. Maternal smoking during pregnancy and the risk of psychiatric morbidity in singleton sibling pairs. Nicotine Tob Res 2017; 9(5): 597-604.

Ellman LM, Huttunen M, Lönnqvist J, Cannon TD. The effects of genetic liability for schizophrenia and maternal smoking during pregnancy on obstetric complications. Schizophr Res 2007; 93(1-3): 229-236.

Eskelinen S. Physical health of patients with schizophrenia: findings from a health examination study. Academic Dissertation. Helsinki University. 2017.

Essen-Möller E. Mating and fertility patterns in families in schizophrenia. Eugenics Quarterly 1959; 6(2):142-147.

EUROCAT Central Registry. EUROCAT Syndrome Guide: Definition and Coding of Syndromes, version July, 2017.

Falkenburg J,Tracy DK. Sex and schizophrenia: a review of gender differemces. Journal of Psychological, Social and Integrative Approaches 2014; 6: 61-69.

Fananas L, Bertranpetit J. Reproductive rates in families of schizophrenic patients in case-control study. Acta Psychiatr Scand 1995; 91(3): 202-204.

Feig DS, Shah BR, Lipscombe LL, Wu CF, Ray JG, Lowe J, Hwee J, Booth GL. Preeclampsia as a risk factor for diabetes: A population based cohort study. PLOS Med 2014; 10(4): e1001425.

Feghali MN, Mattison DR. Clinical therapeutics in pregnancy. J Biomed Biotechnol 2011; 2011: 783528, 1-13.

Fochtmann L, Mojtabai R, Bromet EJ. Other psychotic disorders. In Kaplan and Sadock's comprehensive textbook of psychiatry, 9th edition. Edited by Sadock BJ, Sadock VA, Ruiz P. Wolters Kluwer Health/Lippincott Williams & Wilkins: Philadelphia. 2009. Pages 1605-1628.

Forsyth JK, Ellman LM, Tanskanen A, Mustonen U, Huttunen MO, Suvisaari J, Cannon TD. Genetic risk for schizophrenia, obstetric complications, and adolescent school outcome: evidence for gene-environment interaction. Schizophr Bull 2013; 39(5): 1067-1076.

Foti DJ, Kotov R, Guey LT, Bromet EJ. Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. Am J Psychiatry 2010; 167: 987–993.

Frayne J, Lewis L, Allen S, Hauck Y, Nguyen T. Severe mental illness and induction of labour: outcomes for women at specialist antenatal clinic in Western Australia. Aust N Z J Obstet Gynaecol 2014; 54(2): 132-137.

Gabilondo A, Alonso-Moran E, Nuno-Solinis R, Orueta JF, Iruin A. Comorbidities with chronic physical conditions and gender profiles of illness in schizophrenia. Results from PREST, a new health dataset. J Psychosom Res 2017; 93: 102-109.

Galvez-Bucillini JA, Proal AC, Tomaselli V, Trachtenberg M, Coconcea C, Chun J, Manschreck T, Fleming J, Delisi LE. Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis. Schizophr Res 2012; 139: 157–160.

Gentile S. Antipsychotic therapy during early and late pregnancy. A systematic review. Schizophr Bull. 2010; 36(3): 518-544.

Gentile S, Fusco ML. Schizophrenia and motherhood. Psychiatry Clin Neurosci 2019; 73(7): 376-385.

Gissler M, Teperi J, Hemminki E, Meriläinen J. Data quality after restructuring a national medical registry. Scand J Soc Med 1995; 23(1): 75-80.

Gissler M, Ulander VM, Hemminki E, Rasimus A. Declining induced abortion rate in Finland: data quality of the Finnish abortion register. Int J Epidemiol 1996; 25 (2): 376-380.

Goldstein JM, Link BG. Gender and expression of schizophrenia. J Psychiatr Res 1988 ; 22(2): 141-155.

Goodman SH. Emory University project on children of disturbed parents. Schizophr Bull 1987; 13(3): 411-423.

Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. Psychol Rev 1999; 106(3): 458-490.

Grant, P.M., Huh, G.A., Perivoliotis, D., Stolar, N.M., Beck, A.T., 2012. Randomized trial to evaluate the efficacy of cognitive therapy for lowfunctioning patients with schizophrenia. Arch. Gen. Psychiatry 69, 121-127.

Gray SC, Edwards SE, Miranda ML. Assessing exposure metrics for PM and birth weight models. J Expo Sci Environ Epidemiol 2010; 20(5): 469–477.

Gregg L, Barrowclough C, Haddock G. Reasons for increased substance use in psychosis. Clin Psychol Rev 2007; 27(4): 494-510.

Grigoriadis S, Seeman MV. The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women. Can J Psychiatry 2002; 47(5): 437-442.

Grossman LS, Harrow M, Rosen C, Faull R, Strauss GP. Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery. Compr Psychiatry 2008; 49(6): 523-529.

Harris EL, Frayne J, Allen S, Renganathan K, Nguyen TN. Psychiatric admission during pregnancy in women with schizophrenia who attended a special antenatal clinic. J Psychosom Obstet Gynaecol 2018; 19: 1-6.

Haboubi NH, Lincoln N. Views of health professionals on discussing sexual issues with patients. Disabil Rehabil 2003; 25(6): 291-296.

Hameed Ma,Lewis AJ. Offspring of parents with schizophrenia: a systematic review of developmental features across childhood. Harv Rev Psychiatry 2016; 24(2): 104-117.

Haukka J, Suvisaari J, Lönnqvist J. Fertility of patients with schizophrenia, their siblings, and the general population: a cohort study from 1950 to 1959 in Finland. Am J Psychiatry 2003; 160(3): 460-463.

Haverkamp F, Propping P, Hilger T. Is there an increase of reproductive rates in schizophrenics? Arch Psychiatr Nervenkr 1982; 232(5): 439-450.

Healy SJ, Lewin J, Butler S, Vaillancourt K, Seth-Smith F. Affect recognition and the quality of mother-infant interaction: understanding parenting difficulties in mothers with schizophrenia. Arch Womens Ment Health 2016; 19(1): 113-124.

Heino A, Niinimäki M, Mentula M, Gissler M. How reliable are health registers? Registration of induced abortions and sterilizations in Finland. Inform Health Soc Care 2018; 43(3): 310-319.

Hellemose LAA, Laurse TM, Larsen JT, Toender A. Accidental deaths among persons with schizophrenia: A nationwide population based study. Schizophr Res 2018;199:149-153.

Hemminki E, Rasimus A, Forssas E. Sterilization in Finland: From eugenics to contraception. Soc Sci Med 1997; 45(12):1875-1884.

Hietala M. Eugeniikan ja rotuhygienian tausta ja seuraukset. Tieteessä tapahtuu 2009; 8: 14-19.

Hietala J, Heinimaa M, Suvisaari J. Research has changed our view about psychoses. Duodecim 2015; 131(22): 2117-2124.

Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, Werge TM, Nordentoft M, Glenthoj B. Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. Biol Psychiatry 2018; 10(5): 434-439.

Hill SK, Harris MS, Herbener ES, Pavuluri M, Sweeney JA. Neurocognitive allied phenotypes for schizophrenia and bipolar disorder. Schizophr Bull 2008; 34(4): 743-759.

Hipwell AE, Goossens FA, Melhuish EC, Kumar R. Severe maternal psychopathology and infant-mother attachment. Dev Psychopathol 2000; 12(2): 157-175.

Hizkiyahu R, Levy A, Sheiner E. Pregnancy outcome of patients with schizophrenia. Am J Pernatol 2010; 27(1):19-23.

Holt RI, Bushe C, Citrome L. Diabetes and schizophrenia in 2005: are we any closer to understanding the link? J Psychopharmacol 2005; 19(6): 56-65.

Howard L. The separation of mothers and babies in the treatment of postpartum disorders in Britain 1900–1960. Arch Womens Ment Health 2000; 3: 1-5.

Howard LM, Kumar C, Leese M, Thornicroft G. The general fertility rate in women with psychotic disorders. Am J Psychiatry 2002; 59 (6): 991–997.

Howard LM, Bekele D, Rowe M, Demilew J, Bewley S, Marteau TM. Smoking cessation in pregnant women with mental disorders: a cohort and nested qualitative study. BJOG 2013; 120: 362-370.

Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. Lancet 2014; 10(383): 1677-1687.

Hunt GE, Large MM, Leary M, Lai HMX, Saunders JB. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990-2017: systematic review and meta-analysis. Drug Alcohol Depend 2018; 91: 234-258.

Huvinen HE. The heterogeneity of gestational diabetes and long term effects of lifestyle intervention among high-risk women. Department of Obstetrics and Gynecology. Helsinki University Hospital. University of Helsinki, Finland. Academic Dissertation 2018.

Häfner H, Riecher-Rössler A, An Der Heiden W, Maurer K, Fätkenheuer B, Löffler W. Generating and testing a causal explanation of the gender difference in age at first on set of schizophrenia. Psychol Med1993; 23(4): 925-940.

Induced abortion. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Gynecology Society. The Finnish Medical Society Duodecim: Helsinki. 2013. Available online at: www.kaypahoito.fi.

Incel TR. Rethinking schizophrenia. Nature 2010; 468(7321): 187-193.

Ion R, Bernal AL. Smoking and preterm birth. Reprod Sci 2015; 22(8): 918-926.

Iseger TA, Bossong MG. A systematic review of the antipsychotic properties of cannabidiol in humans. Schizophr Res 2015; 162: 153–161.

Isohanni M, Mäkikyrö T, Moring J, Räsänen P, Hakkko H, Partanen U, Koiranen M, Jones P. A comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish nationalbirth cohort. Clinical and research diagnoses of schizophrenia. Soc Psychiatry Psychiatr Epidemiol 1997; 32(5): 303–308.

Jablensky A. The 100-year epidemiology of schizophrenia. Schizophr Res 1997; 28:111–125.

Jablensky AV, Morgan V, Zubrick SR, Bower C, Yellachich LA. Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. Am J Psychiatry 2005; 162(1): 79–91.

Jeffery D, Clement S, Corker E, Howard LM, Murray J, Thornicroft G. Discrimination in relation to parenthood reported by community psychiatric service users in the UK: a framework analysis. BMC Psychiatry 2013; 13: 120.

Jenkins A, Millar S, Robins J. Denial of pregnancy – a literature review and discussion of ethical and legal issues. J R Soc Med 2011; 104(7): 286-291.

Johansson S, Villamor E, Altman M, Bonamy AK, Granath F, Cnattingius S. Maternal overweight and obesity in early pregnancy and risk of infant mortality: a population based cohort study in Sweden. BMJ 2014; 2(349): g6572.

Johns A. Psychiatric effects of cannabis. Br J Psychiatry 2001; 178: 116–122.

Jones CW. Gestational diabetes and its impact on the neonate. Neonatal Netw 2001; 20(6): 17-23.

Jones I, Chandra PS, Dazzan P, Howard LM. Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the post-partum period. Lancet 2014; 384(9956): 1789-1799.

Joy CB, Saylan M. Mother and baby units for schizophrenia. Cochrane Database Syst Rev 2007; 1: CD006333.

Judd F, Komiti A, Sheehan P, Newman L, Cast D, Everall I. Adverse obstetrics and neonatal outcomes in women with severe mental illness: to what extend can they be prevented? Schizophr Res 2014; 157(1-3): 305-309.

Jundong J, Kuja-Halkola R, Hultman C, Långström N, D'Onofrio B, Lichtenstein P. Poor school performance in offspring of patients with schizophrenia : What are the mechanisms? Psychol Med 2012; 42(1):111-123.

Karakula H, Szajer K, Rpila B, Grzywa A, Chuchra M. Clozapine and pregnancy-a case history. Pharmacopsychiatry. 2004; 37(6): 303–304.

Karow, A., Wittmann, L., Schottle, D., Schafer, I., Lambert, M., 2014. The assessment of quality of life in clinical practice in patients with schizophrenia. Dialogues Clin. Neurosci; 16: 185-195.

Kendler KS, Diehl SR. The genetics of schizophrenia: a current, genetic-epidemiologic perspective. Schizophr Bull 1993; 19: 261–284

Keinänen J, Mantere O, Kieseppä T, Mäntylä T, Torniainen M, Lindgren M, Sundvall J, Suvisaari J. Early insulin resistance predicts weight gain and waist circumference increase in first-episode psychosis- a one year follow-up study. Schizophr Res 2015; 169(1-3): 458-463

Kelly DL, Conley RR. Sexuality and schizophrenia. Schizophr Bull 2004; 30(4): 767-779.

Kessler RC, Birnbaum H, Demler O, Falloon IR, Gagnon E, Guyer M, Howes MJ, Kendler KS, Shi L, Walters E, Wu EQ. The prevalence and correlates of nonaffective psychosis in the National Comorbidity Survey Replication (NCS-R). Biol Psychiatry 2005; 58(8): 668- 676.

Kirkpatrick, B. Progress in the study of negative symptoms. Schizophr. Bull. 2014; 40 (2) : 101-106.

Knudsen LB, Gissler M, Bender SS, Hedberg C, Ollendorff U, Sundtsröm K, Totlandsdal K, Vilhjalmsdottir S. Induced abortion in the Nordic countries: special emphasis on young women. Acta Obstet Gynecol Scand 2003; 82(3): 257-268.

Kohler S, van der Werf M, Hart B, Morrison G, McCreadie R, Kirkpatrick B, Verkaaik M, Krabbenfam L, Verhey F, van Os J, Allardyce J. Evidence that better outcome of psychosis in women is reversed with increasing age of onset: a population-based 5-year follow-up study Schizophr Res 2009; 113 : 226-232.

Koskinen J, Löhönen J, Koponen H, Isohanni M, Miettunen J. Prevalence of alcohol use disorders in schizophrenia – a systematic review and meta-analysis. Acta Psychiatr Scand 2009; 120: 85-96.

Kotimaa AJ, Moilanen I, Taanila A, Ebeling H, Smalley SL, McGough JJ, Hartikainen AL, Järvelin MR. Maternal smoking and hyperactivity in 8-year-old children. J Am acad Child Adolesc Psychiatry 2003; 42(7): 826-833.

Kumar R, Marks M, Platz C, Yoshida K. Clinical survey of psychiatric mother baby unit: characteristics of 100 consecutive admissions. J Affect Disord 1995; 33(1): 11-22.

Laaksonen M, Lahelma E, Prättälä R. Associations among health-related behaviours: sociodemographic variation in Finland. Soz Preventivmed 2002; 47(4): 225-232.

Langley K, Rice F, van den Bree MB, Thapar A. Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. Minerva Pediatr 2005; 57: 359–371.

Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen Psychiatry 2011; 68: 555–561.

Larsen ER, Damkier P, Pedersen LH, Fenger-Gron J, Mikkelsen RL, Nielsen RE, Linde VJ, Knudsen ED, Skaarup L, Videbech P; Danish Psychiatric Society; Danish Society of Obstetrics and Gynecology; Danish Paediatric Society; Danish Society of Clinical Pharmacology. Use of psychotropic drugs during pregnancy and breast-feeding. Acta Psychiatr Scand 2015; 445: 1-28.

Laursen TM, Munk-Olsen T. Reproductive patterns in psychotic patients. Schizophr Res 2010; 121(1-3): 234-240.

Laursen TM, Munk-Olsen T, Gasse C. Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. PLoS One 2011; 6(9): e24597.

Leucht S, Burkard T, Henferson MM, Sartorius N. Physical illness and schizophrenia: a review of the literature. Acta Psychiatr Scand 2007; 116(5): 317-333.

Leucht, S., Corves, C., Arbter, D., Engel, R.R., Li, C., Davis, J.M., 2009. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 373: 31-41.

Lin A, Di Prinzio P, Young D, Jacoby P, Whitehouse A, Waters F, Jablensky A, Morgan V. Academic performance in children of mothers with schizophrenia and other severe mental illness, and risk for subsequent development of psychosis: a population based study. Schizophr Bull 2017; 43(1): 205-213.

Loukola A, Wedenoja J, Keskitalo-Vuokko K, Broms U, Korhonen T, Ripatti S, Sarin AP, Pitkäniemi J, He L, Häppölä A, Heikkilä K, Chou YL, Pergadia ML, Health AC, Montgomery GW, Martin NG, Madden PA, Kaprio J. Genome-wide association study on detailed profiles of smoking behavior and nicotine dependence in a twin sample. Mol Psychiatry 2014;19(5): 615–24.

MacKenzie NE, Kowalchuk C, Agarwal SM, Costa-Doookhan KA, Caravaggio F, Gerretsen P, Chintoh A, Remington GJ, Taylor VH, Mueller DJ, Graff-Guerrero A, Hahn MK. Antipsychotics, metabolic adverse effects, and cognitive function in schizophrenia. Front Psychiatry 2018; 9: 622.

Major B, Applebaum M, Beckman L, Dutton MA, Russo NF, West C. Report of the APA task force on mental health and abortion. American Psychiatric Association. 2008.

Malaspina D, Owen MJ, Heckers S, Tandon R, Bustillo J, Schultz S, March DM, Gaebel W, Gur RE, Tsuang M, Van Os J, Carpenter W. Schizoaffective disorder in DSM-5. Schizophr Res 2013; 150(1): 21-25.

Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Prognosis of schizophrenia in persons with and without a history of cannabis use. Psychol Med 2014; 44: 2513–2521.

Manu P, Dima L, Shulman M, Vancampfort D, De Hert M, Correll CU. Weight gain and obesity in schizophrenia: Epidemiology, pathology, and management. Acta Psychiatr Scand 2015;132(2): 97-108.

Marufu TC, Ahankari A, Coleman T, Lewis S. Maternal smoking and the risk of still birth: systematic review and meta-analysis. BMC Public Health 2015;15: 239.

Matevosyan NR. Reproductive health in women with serious mental illnesses: A review. Sex Disabil 2009; 27(2): 109-118.

Matevosyan NR. Pregnancy and postpartum specifics in women with schizophrenia: a meta study. Arch Gynecol Obstet 2011; 283(2): 141-147.

McCann E. The expression of sexuality in people with psychosis: breaking the taboos. J Adv Nurs 2000; 32(1): 132-138.

McCauley-Elsom K, Gurvich C, Elsom SJ, Kulkarni J. Antipsychotics in pregnancy. J Psychiatr Ment Health Nurs 2010; 17(2): 97-104.

McGlashan TH, Johannessen JO. Early detection and intervention with schizophrenia: rationale. Schizophr Bull 1996; 22: 201-222.

McClellan J, Stock S. Practive parameter for the assessment and treatment for children and adolescents with schizophrenia. Child & Adolescent Psychiatry 2013; 52(9): 976-990.

McGrath JJ, Hearle J, Plant K, Drummond A, Barkla JM. The fertility and fecundity of patients with psychosis. Acta Psychiatr Scand 1999: 99: 441-446.

McGrath J, Saha S, Chant D, Welham J. Schizophrenia - a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008; 30: 67-76.

McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KM. A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry 2007;164(12): 1791 – 1802.

McNeil TF, Kaij L, Malmquist-Larsson A. Pregnant women with non-organic psychosis: Life situation and experience of pregnancy. Acta Psychiatr Scand 1983; 68(6): 445-457.

McNeil TF, Naslund B, Persson-Blennow I, Kaij L. Offspring of women with nonorganic psychosis: mother–infant interaction at three-and-a-half and six months of age. Acta Psychiatr Scand. 1985; 71: 551–558.

Meade CS, Sikkema KJ. Psychiatric and psychosocial correlates of sexual risk behavior among adults with severe mental illness. Commun Ment Health J 2007; 43: 153-169.

Meakin CJ, Brockington IF, Lynch S, Jones SR. Dopamine supersensitivity and hormonal status in puerperal psychosis. Br J Psychiatry 1995; 166(1): 73-79.

Mendhekar D. Possible delayed speech acquisition with clozapine therapy during pregnancy and lactation. J Neuropsychiatry Clin Neurosci. 2007; 19(2): 196–197.

Miller LJ. Psychotic denial of pregnancy: phenomenology and clinical management. Hosp Community Psychiatry 1990; 41(11): 1233-1237.

Miller LJ, Finnerty M. Sexuality, pregnancy, and child rearing among women with schizophrenia-spectrum disorders. Psychiatr Serv 1996; 47(5): 502-506.

Moilanen K, veijola J, Läksy K, Mäkikyrö T, Miettunen J, Kantojärvi L, Kokkonen P, Karvonen JT, Herva A, Joukamaa M, Järvelin MR, Moring J, Jones PB, Isohanni M. Reasons for the diagnostic discordance between clinicians and researchers in schizophrenia in the Northern Finland 1966 Birth Cohort. Soc Psychiatry psychiatry Epidemiol 2003; 38(6): 305-310.

Monostory K, Dvorak Z. Steroid regulation of drug-metbolizing cytochroimes P450. Curr Drug Metab 2011; 12(2): 154-172.

Morgan VA, Castle DJ, Jablensky AV. Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. Aust N Z J Psychiatry 2008; 42(1): 74–82.

Mortensen PB, Peedersen MG, Pedersen CB. Psychiatric family history and schizophrenia in Denmark: which mental disorders are relevant? Psychol Med 2010; 40: 201-2010.

Muck-Jorgensen P, Mors O, Mortensen PB, Ewald H. The schizophrenic patient in the somatic hospital. Acta Psychiatr Scand 2000; 407: S96-99.

Munk-Olsen T, Laursen TM, Mendelson T, Pedersen CB, Mors O, Mortensen PB. Risks and predictors of readmission for a mental disorder during the postpartum period. Arch Gen Psychiatry 2009; 66(2): 189-195.

Myhrman A, Rantakallio P, Isohanni M, Jones P, partanen U. Unwantedness of a pregnancy and schizophrenia in the child. Br J Psychiatry 1996; 169(5): 637-640.

Nanko S, Moridaira J. Reproductive rates in schizophrenic outpatients. Acta Psychiatr Scand 1993; 87: 400–404.

National Institute for Health and Welfare of Finland . Perinatal statistics - parturients, delivers and newborns 2017. First viewed 20.1.2019 : https://thl.fi/en/web/thlfi-en/statistics/statistics-by-topic/sexual-and-reproductive-health/parturients-deliveries-and-births/perinatal-statistics-parturients-delivers-and-newborns

Newport JD, Viguera AC, Beach AJ, Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. Am J Psychiatry 2005; 162: 2162-2170.

Nguyen TN, Faulkner D, Frayne JS, Allen S, Hauck YL, Rock D, Rampono J. Obstetric and neonatal outcomes of pregnant women with severe mental illness at a specialist antenatal clinic. Med J Aust 2013; 199(3 Suppl): S26–9.

National Institute for Health and Care Excellence. Antenatal and postnatal mental health. 2017. Available from: https:// www.nice.org.uk/guidance/qs115.

Niemelä S, Sourander A, Surcel HM, Hinkka-Yli-Salomäki S, McKeague IW, Cheslack-Postava K, Brown AS. Prenatal nicotine exposure and risk of schizophrenia among offspring in a national birth cohort. Am J Psychiatry 2016; 173(8): 799-806.

Nilsson E, Lichtenstein P, Cnattingius P, Murray RM, Hultman CM. Women with schizophrenia: pregnancy outcome and infant death among their offspring. Schizophr Res 2002; 58(2-3): 221-229.

Nimgaonkar VL. Reduceed fertility in schizophrenia: here to stay? Acta Psychiatr Scand 1998; 98(5): 348-353.

Nimgaonkar VL, Ward SE, Agarde H, Weston N, Ganguli R. Fertility in schizophrenia: results from a contemporary US cohort. Acta Psychiatr Scand 1997; 95(5): 364-369.

Norman RM, Malla AK, Manchanda R, Townsend L. Premorbid adjustment in first episode schizophrenia and schizoaffective disorders: a comparison of social and academic domains. Acta Psychiatr Scand 2005; 112(1): 30-39.

Näslund B, Persson-Blennow I, Kaij L, Malmquist-Larsson A. Offspring of women with nonorganic psychosis: infant attachment to the mother at one year of age. Acta Psychiatr Scand 1984; 69(3): 231-241.

Näslund B, Persson-Blennow I, Mcneil T, Kaij L. Offspring of women with nonorganic psychosis: mother–infant interaction at three and 6 weeks of age. Acta Psychiatr Scand 1985; 71: 441–450.

Pallasmaa N, Ekblad U, Gissler M, Alanen A. The impact of maternal obesity, age, pre-eclampsia and insulin debendent diabetes on severe maternal morbidity by mode of delivery – a register-based cohort study. Arch Gynecol Obstet 2015; 291(2): 311-318.

Partti K, Vasankari T, Kanervisto M, Perälä J, Saarni SI, Jousilahti P, Lönnqvist J, Suvisaari J. Lung fuction and respiratory diseases in people with psychosis: population-based study. Br J Psychiatry 2015; 207(1): 37-45.

Patel R, Cherian J, Gohil K, Atkinson D. Schizoohrenia: Overview and treatment options. P & T 2014; 39(9): 638 – 645.

Patel R, Wilson R, Jackson R, Ball M, Broadbent M, Stewart R, McGuire P, Bhattacharyya S. Cannabis use and treatment resistance in first episode psychosis: a natural language processing study. Lancet 2015; 385: S79.

Pavek P, Ceckova M, Staud F. Variation of drug kinetics in pregnancy. Curr Drug Metab 2009; 10(5): 520-529.

Pedersen CB, McGrath J, Mortensen PB, Petersen L. The importance of father's age to schizophrenia risk. Mol Psychiatry 2014;19(5):530-531.

Peng M, Gao K, Dong Y, Ou J, calabrese JR, Wu R, Zhao J. Effects of prenatal exposure to atypical antipsychotics on postnatal development and growth of infants: a case-controlled, prospective study. Psychopharmacol Ser 2013; 228(4): 577–584.

Persson M, Johansson S, Villamor E, Cnagttingius S. Maternal overweight and obesity and risks of severe birth-asphyxia complications in term infants: a population-based cohort study in Sweden. PLoS Med 2014; 11(5): e1001648.

Persson-Blennow I, Näslund B, McNeil TF, Kaij L, Malmquist-Larsson A. Offspring of women with nonorganic psychosis: mother-infant interaction at three days of age. Acta Psychiatr Scand 1984; 70(2): 149-159.

Persson-Blennow I, Näslund B, McNeil TF, Kaij L. Offspring of women with nonorganic psychosis: mother-infant interaction at one year. Acta Psychiatr Scand 1986; 73(2): 207-213.

Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kieseppä T, Härkänen T, Koskinen S, Lönnqvist J. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry 2007; 64(1): 19-28.

Petersen L, Jeppesen P, Thorup A, Abrl MB, Ohlenschlaeger J, Christensen TO, Krarup G, Jorgensen P, Nordentoft M. A randomized multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. BMJ 2005; 331(7517): 602.

Petersen Z, Steyn K, Everett-Murphy K, Emmelin M. Pregnant women's responses to a tailored smoking cessation intervention: turning hoplessness into competence. Glob Health Action 2010; 14: 3.

Petersen I, McCrea R, Osborn D, Evans S, Pinfold V, Cowen PJ, Gilbert R, Nazareth I. Discontinuation of antipsychotic medication in pregnancy: a cohort study. Schizophr Res 2014;159(1): 218–225.

Petersen I, Sammon CJ, McCrea RL, Osborn DPJ, Evans SJ, Cowen PJ, Nazareth I. Risks associated with antipsychotic treatment in pregnancy: Comparative cohort studies based on electronic health records. Schizoph Res 2016 176(2-3): 349-356.

Pharoah F, Mari JJ, Rathbone J, Wong W. Family intervention for schizophrenia. Cochrane Database Syst Rev 2010; CD00088.

Pihlajamaa J, Suvisaari J, Henriksson M, Heilä H, Karjalainen E, Koskela J, Cannon M, lönnqvist J. The validity of schizophrenia diagnosis in the Finnish Hospital Discharge Register: findings from a 10-year birth cohort sample. Nord J Psychiatry 2008; 62 (3): 198-203.

Pineles BL, Park E, Samet JM. Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. Am J Epidemiol 2014; 179(7): 807-823.

Potvin S, Sepehry AA, Stip E. A meta-analysis of negative symptoms in dual diagnosis schizophrenia. Psychol Med 2006; 36(4): 431-440.

Potvin S, Sepehry AA, Stip E. Meta-analysis of depressive symptoms in dual-diagnosis schizophrenia. Aust N Z J Psychiatry 2007; 41: 792-799.

Quinn C, Happell B, Browne G. Talking or avoiding? Mental health nurses - views about discussing sexual health with consumers. Int J Ment Health Nurs 2011; 20:21-28.

Ranning A, Munk Laursen T, Thorup A, Hjorthoj C, Nordentoft M. Serious mental illness and disrupted caregiving for children : a nationwide, register based cohort study. J Clin Psychiatry 2015; 76(8): 1006-1014.

Ranning A, Laursen T, Agerbo E, Thorup A, Hjorthoj C, Jepsen JRM, Nordentoft M. School performance from primary education in the adolescent offspring of parents with schizophrenia and bipolar disorder – a national, register-based study. Psychol Med 2018; 48(12): 1993-2000.

Reece AE. The fetal and maternal consequences of gestational diabetes mellitus. The Journal of Maternal-Fetal & Neonatal Medicine 2010; 23(3): 199-203.

Rees E, O'Donovan MC, Owen MJ. Genetics of schizophrenia 2015 J.cobeha 2015; 2: 8-14.

Remschmidt H, Theisen FM. Schizophrenia and related disorders in children and adolescents. J Neural Suupl 2005; (69): 121-141.

Rieder RO, Rosenthal D, Wender P, Blumenthal H. The offspring of schizophrenics. Fetal and neonatal detahs. Arch Gen Psychiatry 1975; 32(2): 200-211.

Riordan D, Appleby L, Faragher B. Mother-infant interaction in post-partum women with schizophrenia and affective disorders. Psychol Med 1999; 29: 991-995.

Roberts, D.L., Combs, D.R., Willoughby, M., Mintz, J., Gibson, C., Rupp, B., Penn, D.L., 2014. A randomized, controlled trial of Social Cognition and Interaction Training (SCIT) for outpatients with schizophrenia spectrum disorders. Br. J. Clin. Psychol. 53, 281-298.

Robinson GE. Treatment of schizophrenia in pregnancy and postpartum. J Popul Ther Clin Pharmacol 2012; 19(3): e380-386.

Rochon-Terry G, Gruneir MV, Seeman MV, Ray JG, Rochon P, Dennis CL, Grigoriadis S, Fung K, Kurdyak PA, Vigod SN. Hospitalizations and emergency department visits for psychiatric illness during and after pregnancy among women with schizophrenia. J Clin Psychiatry 2016; 77(4): 541-547.

Rollnick S, Miller WR. What is motivational interviewing? behave Cogn Psychother 1995; 23: 325-334.

Rousou E, Kouta C, Middleton N, Karanikola M. Single mother's assessment of health: a systematic exploration of the literature. Int Nurs Rev 2013; 60(4): 425-434.

Rüther T, Bobes J, De Hert M, Svensson TH, Mann K, Batra A, Gorwood P, Möller HJ; European Psychiatric Association. EPA guidance on tobacco dependence and strategies for smoking cessation in people with mental illness. Eur Psychiatry 2014; 29(2): 65–82.

Sacker A, Done DJ, Crow TJ. Obstetric complications in children born to parents with schizophrenia: a meta-analysis of case-control studies. Psychol Med 1996; 26(2): 279-287.

Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med 2005; 2(5): e141.

Salmon M, Abel K, Cordingley L, Friedman T, Appleby L. Clinical and parenting skills outcomes following joint mother-baby psychiatric admission. Aust N Z J Psychiatry 2003; 37(5): 556-562.

Shao P, Ou J, Peng M, Zhao J, Chen J, Wu R. Effects of clozapine and other atypical antipsychotics on infants development who were exposed to as fetus: a post-hoc analysis. Plos ONE 2015; 10(4): e0123373.

Saracco-Alvarez R, Rodriguez-Verdugo S, Garcia-Anaya M, Fresan A. Premorbid adjustment in schizophrenia and schizoaffective disorder. Psychiatry res 2009; 195(3): 234-482.

Schizophrenia. current Care Guidelines. Working group set byt The Finnish Medical Society Duodecim and the Finnish Psychiatric Association. The Finnish Medical Society Duodecim: Helsinki. 2015. Available online at: www.kaypahoito.fi.

Schmidt MI, Duncan BB, Reichelt AJ, Branchtein L, Matos MC, Costa e Fonti A, Spichler ER, Pousada JM, Teixeira MM, Yamashita T; Brazilian Gestational Diabetes Study Group. Gestational diabetes mellitus diagnosed with 2-h 75-g oral glucose tolerance test and adverse pregnancy outcomes. Diabetes Care 2001; 24(7): 1151-1155.

Seeman MV. The role of sex hormones in psychopathology: focus on schizophrenia. Prim Care 2002; 29(1): 171-182.

Seeman MV, Ross R. Prescribing contraceptives for women with schizophrenia. J Psychiatr Pract 2011; 17(4): 258-269.

Seeman MV. Intervention to prevent child custody loos in mothers with schizophrenia. Schizophr Res Treatment 2012; 2012: 796763.

Seeman MV. Clinical interventions for women with schizophrenia: pregnancy. Acta Psychiatr Scand 2013; 127: 12-22.

Selten J-P, van der Graaf Y, van Duursen R, Gispen-de Wied CC, Kahn RS. psychotic illness after prenatal exposure to the 1953 Dutch Flood Disaster. Schizophr Res 1999; 35: 243-245.

Shams TA, Muller DJ. Antipsychotic induced weight gain: genetics, epigenetics, and biomarkers reviewed. Curr Psychiatry Rep 2014; 16(10): 473.

Sinclair, D., Adams, C.E., 2014. Treatment resistant schizophrenia: a comprehensive survey of randomised controlled trials. BMC Psychiatry 14, 253.

Siskind D, McCartney L, Goldschlöager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizopjhrenia: systematic review and meta-analysis. Br J Psychiatry 2016; 209(5): 385-392.

Slater E, Hare EH, Price JS. Marriage and fertility of psychiatric patients compared with national data. Soc Biol 1971; 18: 60-73.

Smith DJ, Langan J, McLean G, Guthrie B, Mercer SW. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. BMJ Open 2013; 3(4): e002808.

Sobel DE. Children of schizophrenic patients: preliminary observations on early development. Am J Psychiatry 1961; 118: 512-517.

Solari H. Psychotic denial of pregnancy. Current Women's Health Reviews 2010; 6(1): 22-27.

Solari H, Dickson KE, Miller L. Understanding and treating women with schizophrenia during pregnancy and postpartum – Motherrisk Update 2008. Can J Clin Pharmacol 2009; 16(1): e23.32.

Sormunen E, Saarinen MM, Salokangas RKR, Telema R, Hutri-Kähönen N, Tammelin T, Viikari J, Raitakari O, Hietala J. Effects of childhood and adolescence physical activity patterns on psychosis risk – a general population cohort study. NPJ Schizophr 2017; 3: 5.

Spielvogel AM, Lee EK. Indication for psychiatric inpatient hospitalization for pregnant psychotic women. Current Women's Health Review 2010; 6(1): 44-50.

Srinivasan TN, Padmavati R. Fertility and schizophrenia: evidence for increased fertility in the relatives schizophrenic patients. Acta Psychiatr Scand 1997; 96(4): 260-264

Stein, M., Rhys, G., Hicks, L. and Gorin, S. Neglected adolescents: Literature review. Research Brief. London: Department for Children, Schools and Families. 2009. http://bit.ly/GU1uGo

Stewart D. Pregnancy and schizophrenia. Can Fam Physician 1984; 30: 1537-1542.

Suhonen L, Teramo K. Hypertension and pre-eclampsia in women with gestational glucose intolerance. Acta Obstet Gynecol Scand 1993; 72(4): 269-272.

Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: The emerging picture of its implications. Nat Rev Genet 2012; 13: 537-551.

Suvisaari J, Partti K, Perälä J, Viertiö S, Saarni SE, Lönnqvist J, Saarni SI, Härkänen T. Mortality and it's determinants in people with psychotic disorder. Psychosom Med 2013; 75(1): 60-67.

Suvisaari JM, Taxell-Lassas V, Pankakoski M, Haukka JK, Lönnqvist JK, Häkkinen LT. Obstetric complications as risk factors for schizophrenia spectrum psychoses in offspeingof mothers with psychotic disorder. schizophr Bull 2013; 39(5): 1056-1066.

Svensson AC, Lichtenstein P, Sandin S, Hultman CM. fertility of first-degree relatives of patients with schizophrenia: a three generation perspective. Schizophr Res 2007; 91(1-3): 238-245.

Swarbrick MA, Cook JA, Razzano LA, Jonikas JA, Gao N, Williams J, Yudof J. Correlates of current smoking among adults served by the public mental health system . Psychotherapy & Psychosocial issues 2017; 12 (2): 82-90.

Söderström L, Perez-Vicente R, Juarez S, Merlo J. Questioning the causal lionk between maternal smoking during pregnancy and offspring use of psychotropic medication: a sibling design analysis. PLoS One 2013; 8(5): e63420.

Tandon R. The nosology of schizophrenia. Towards DSM-5 and ICD-11. Psychiatry Clin N Am 2012; 35: 557-569.

Tarbox SI, Pogue-Geile MF. Development of social functioning in preschizophrenia children andadolescents: A systematic review. Psychol Bull 2008; 34(4): 561–583.

Tarricone I, Ferrari Gozzi B, Serretti A, Grieco D, Berardi D. Weight gain in antipsychotic-naïve patients: a review and meta-analysis. Psychol Med 2010; 40(2): 187-200.

Taylor C, Stewart R, Ogden J, Broadbent M, Pasupathy D, Howard LM. The characteristics and health needs of pregnant women with schizophrenia compared with bipolar disorder and affective psychoses. Br Med Council Psychiatry 2015;15: 88.

Thorup A, Petersen L, Jeppesen P, Ohlenschlaeger J, Christensen T, Krarup G, Jorgensen P, Nordentoft M. Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study. J Nerv Ment Dis 2007; 195(5): 396-405.

Tiesler CM, Heinrich J. Prenatal nicotine exposure and child behavioural problems. Eur Child Adolesc Psychiatry 2014; 23(10): 913-929.

Thorup AAE, Hemager N, Søndergaard A, Gregersen M, prosch ÅK, Krantz MF, Brandt JM, Carmichael L, Melau M, Ellersgaard DV, Burton BK, Greve AN, Uddin MJ, Ohland J, Nejad AB, Johnsen LK, Ver Loren van Themaat AH, Andreassen AK, Vedum L, Knudsen CB, Stadsgaard H, M Jepsen JR, Siebner HR, Ostergard L, Bliksted VF, Plessen KJ, Mor O, Nordentoft M. The Danish high risk and resilience study-VIA 11: Study Protocol for the first follow-up of the VIA 7 cohort- 522 children born to parents with schizophrenia spectrum disorders or bipolar disorder and controls being re-examined for the first time at age at 11. Front Psychiatry 2018; 12(9): 661.

Tidey JW, Miller ME. Smoking cessation and reduction in people with chronic mental illness. BMJ 2015; 351: h4065.

Tidey JW, Rohsenow DJ, Kaplan GB, Swift RM. Cigarette smoking topography in smokers with schizophrenia and matched non-psychiatric controls. Drug Alcohol Depend 2005; 80(2): 259-265.

Tosato S, Albert U, Tomassi S, Iasevoli F, Carmassi C, Ferrari S, Nanni MG, Nivoli A, Volpe U, Atti AR, Fiorillo A. A systematic review of atypical antipsychotics in pregnant women: Balancing between risks of untreated illness and risks of drug-related adverse effects. J Clin Psychiatry 2017; 78(5): 477-489.

Tracy TS, Venkataramanan R, Glover DD, Caritis SN; National Institute for Child Helath and Human Development Network of Maternal-Fetal-Medicine Units. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol 2005; 192(2): 633-639.

Valencia M., Fresan A., Barak Y., Juarez F., Escamilla R., Saracco R.. Predicting functional remission in patients with schizophrenia: a crosssectional study of symptomatic remission, psychosocial remission, functioning, and clinical outcome. Neuropsychiatr. Dis. Treat.2015; 11 : 2339-2348.

van der Werf M, Hanssen M, Köhler S, Verkaaik M, Verhey FR; RISE Investigators, van Winkel R, van Os J, Allardyce J. Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia. Psychol Med 2014; 44(1): 9-16.

van Os J, Selten JP. prenatal exposure to matrnal stress and subsequent schizophrenia. The May 1940 invasion of the Netherlands. Br j Psychiatry 1998; 172: 324-326.

van Os J, Bak M, Hanssen M, Bijl R, De Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol 2002; 156: 319–327.

van Os J, Kenis G, Rutten BPF. Schizophrenia and environment. Nature 2010; 468: 203-212.

van O J, Kapur S. Schizophrenia. Lancet 2009; 22: 374.

Vancampfort D, Rosenbaum S, Schuch F, Ward PB, Richards J, Mugisha J, Probst M, Stubbs B. Cardiorespiratory Fitness in Severe Mental Illness: A systematic review and meta-analysis. Sports Med 2017; 47(2): 343-352.

Vigod SN, Kurdyak PA, Dennis CL, Gruneir A, Newman A, Seeman MV, Rochon PA, Anderson GM, grigoriadis S, Ray JG. Maternal and newborn outcomes among women

with schizophrenia: a retrospective population-based cohort study. BJOG 2014; 121(5): 566-574.

Vigod SN, Seeman MV, Ray JG, Anderson GM, Dennis CL, Griogoriadis S, Gruneir A, Gurdyak PA, Rochon PA. Temporal trends in general and age-specific fertility rates among women with schizophrenia (1996–2009): a population-based study in Ontario, Canada. Schizophr Res 2012; 139: 169-175.

Viguera AC, Cohen LS, Bouffard S, Whitfield TH, Baldessarini RJ. Reproductive decisions by women with bipolar disorder after pregnancy psychiatric consultation. Am J Psychiatry 2002; 159(12): 2102-2104.

Wan MW, Salmon MP, Riordan DM, Appleby L. What predicts poor mother-infant interaction in schizophrenia? Psychol Med 2007; 37(4): 537-546.

Wan MW, Warren K, Salmon MP, Abel KM. Patterns of maternal responding in postpartum mothers with schizophrenia. Infant Behav Dev 2008; 31(3): 532-538.

Wieck A, Kumar R, Hirst AD, Marks MN, Cambell IC, Checkley SA. Increased sensitivity of dopamine receptors and recurrence of affective psychosis after childbirth. BMJ 1991; 14(303): 613-616.

Williams JM, Ziedonis DM, Abanyie F, Steinberg ML, Foulds J, Benowitz NL. Increased nicotine and cotinine levels in smokers with schizophrenia and schizoaffective disorder is not metabolic effect. Schizophr Res 2005; 79(2-3): 323-335.

World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, 8th revision. World Health Organization: Geneva. 1965.

World Health Organization. Manual of the iNternational Statistical Classification of Diseases, Injuries, and Causes of Death, 9th Revision. World Health Organization: Geneva. 1977.

World Health Organization. Manual of the international Statistical Classification of Diseases, Injuries, and Causes of Death, 10th Revision. World Health Organization: Geneva. 1992.

World Health Organization. International statistical classification of diseases and related health problems,11th Revision. Retrieved from https://icd.who.int/browse11/l-m/en

Özcan NK, boyacioglu NE, Enginkaya S, Dinc H, Bilgin H. Reproductive health in women with serious mental illnesses. J Clin Nurs 2014; 23: 1283-1291.