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FAMILY STUDIES OF SCHIZOPHRENIA AND PREGNANCY OUTCOMES

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Whereof one cannot speak, thereof one must be silent.

Ludwig Wittgenstein

ABSTRACT

Why do psychiatric diseases run in families? Why do some women tend to have similar obstetric complications in subsequent pregnancies? The overall aim of this thesis was to investigate how genes and environments contribute to the aggregation of schizophrenia and adverse pregnancy outcomes in some families. Further, we also studied the fertility in families of patients with schizophrenia. All papers were based on data from the population-based Multi-Generation Register, which has information on familial relationships between Swedish residents.

In Paper I, we explored the fertility of parents, siblings and offspring to patients with schizophrenia, to test the hypothesis that the decreased reproductive rate in patients with schizophrenia is compensated by an increased rate in their first-degree relatives, as suggested by previous studies. We found reduced fertility in patients with schizophrenia as well as among their offspring. In contrast to previous studies we accounted for selection bias of larger families and found that the reduced fertility was not compensated by higher parental or sibling fertility.

In Paper II, we investigated the possible moderating effect of individual characteristics (such as age at onset of disease and season of birth) and parental characteristics (such as paternal age, family history and immigrant status) on familial aggregation of schizophrenia. The familial aggregation, as measured by the sibling recurrence-risk ratios, was reduced by higher age at onset, schizophrenia in parents, advancing paternal age and immigrant status of parents. No interaction between seasonality of birth and familiality of schizophrenia was detected. There was a monotonic decrease in the sibling recurrence-risk ratio with higher age at onset of the proband. However, the familiality remained high across the different levels of the covariates, indicating a high genetic contribution during all conditions.

In Paper III and IV, we studied offspring of siblings to disentangle the genes from the mother, the genes from the child and the environmental effects on the risk of having small for gestational age (SGA) and preterm birth. In Paper IV, we also evaluated if the familial aggregation was explained by exposure to shared risk factors. Preterm birth and SGA seem to have different etiologies. Genetic factors accounted for almost half of the liability to have SGA births and these genetic effects were primarily due to fetal genes. In contrast, fetal genes explained only a small fraction of the total variation in liability to preterm birth. Our results suggest the important role of maternal genes on the risk of preterm birth and these maternal effects are independent of well known risk factors for preterm birth.

In conclusion, by using the unique possibilities in the Swedish population-based registries, we could show that genetic effects are most important for the familial aggregation for both schizophrenia and in birth complications. Nevertheless, environmental effects were also involved. Thus, the gene environment interplay should be considered when searching for the etiological factors that contribute to schizophrenia and obstetric complications.

Key words: alternating logistic regression, environment, familial aggregation, fertility, generalized estimating equations, genes, obstetric complications, preterm birth, siblings, schizophrenia, small for gestational age, variance components

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I-IV):

I. Svensson AC, Lichtenstein P, Sandin S, Hultman CM.
Fertility in first-degree relatives of patients with schizophrenia: a three generation perspective.
Schizophrenia Research. 2007; 91:238-245.

II. Svensson AC, Lichtenstein P, Sandin S, Öberg S, Sullivan PF, Hultman CM.
Familial aggregation of schizophrenia: the moderating effect of age at onset, parental characteristics and season of birth.
Manuscript submitted.

III. Svensson AC, Pawitan Y, Cnattingius S, Reilly M, Lichtenstein P.
Familial aggregation of small-for-gestational age birth: the importance of fetal genetic effects.
American Journal of Obstetrics and Gynecology. 2005; 194:474-479.

IV. Svensson AC, Sandin S, Cnattingius S, Reilly M, Pawitan Y, Hultman CM, Lichtenstein P.
Maternal effects for preterm birth: common risk factors of importance.
Manuscript submitted.

CONTENTS

LIST OF ABBREVIATIONS

The following abbreviations have been used in this thesis and in the associated four original publications:

ALR	alternating logistic regression
BMI	body mass index
C	couple effect
CI	confidence interval
E	non-shared environment
F	fetal genetic effect
GEE	generalized estimating equations
ICD	International Classification of Disease
LBW	low birth weight
M	maternal genetic effect
OR	odds ratio
Pr	probability
PTB	preterm birth
S	shared sibling environment
SGA	small for gestational age
SD	standard deviation
WHO	World Health Organization

1 INTRODUCTION

Why do psychiatric diseases run in families? What is the fertility of family members to patients with schizophrenia? Why do some women tend to have similar obstetric complications in subsequent pregnancies? Genetic epidemiology is the discipline that uses epidemiological methods as a tool to explore the role of genetic factors, and their interplay with the environment in causing a disease or a trait [1]. Genetic epidemiology also addresses more specific questions about the mode of inheritance and what genes are inherited [2]. An important first step is to investigate if there is a familial clustering of the disease. In this thesis I have been interested in the familiality of schizophrenia and pregnancy outcomes.

The life-time risk of schizophrenia is approximately ten times higher in first-degree relatives of patients with schizophrenia than in the general population [3] and twin studies indicate that the heritability is over eighty percent [4]. However, much is still to be learned about how genetic effects influence this devasting disorder. Heritability is an estimate of the relative importance of genetic factors in a given population. If genetic and/or environmental effects vary across populations, cohorts or environmental conditions, then heritability estimates might also differ [5]. For example, the familiality of schizophrenia seems to be stronger in the early-onset than in the late onset forms of the illness [6-8]. However, whether different environmental conditions are important for the familiality is still unknown. One hypothesis is that when individuals are exposed to well known environmental risk factors for schizophrenia (e.g., obstetric complications, advanced paternal age) the heritability would be lower. Nevertheless, due to lack of appropriate data, previous studies have not been able to investigate such hypotheses.

Similar to schizophrenia, members from the same family tend to have similar birth weights [9, 10]. Studies of twins have shown that this familial aggregation primarily is due to genetic effects and that genetic effects are important for birth weight as well as for the related conditions small for gestational age and preterm birth [11]. However, twin studies can not disentangle whether the genetic effects are due to genetic effects from the mother, from the father, and/or from the fetus.

Sweden has ideal conditions for studying such issues. Sweden has a long tradition of population-based registries which can be used for studying the causes of familial aggregation. Above all I have used the Swedish Multi-Generation Register, which contains information on first-degree relatives for Swedish residents born since 1932 [12]. By linking the Multi-Generation Register to other population- and disease registers, it is possible to answer questions about genetic and environmental effects for these disorders using genetic epidemiological methods.

New insights in how and why genes and environments contribute to psychiatric disease and obstetric complications will hopefully ultimately contribute to new prevention and intervention strategies.

2 BACKGROUND

2.1 SCHIZOPHRENIA

Schizophrenia is a severe and often chronic psychiatric disorder (or group of disorders). The illness is found all over the world and 0.7-0.8% of the population will be diagnosed with schizophrenia some time during their life course [13]. Schizophrenia and schizophrenia-like symptoms have consistently been described in the literature over the last two centuries [14, 15], but many believe that the disease has been present for much longer [16-18]. Over these last two centuries, society has undergone great changes with respect to industrialization, migration and urbanization, factors which possibly could affect the occurrence of schizophrenia [19, 20]. However, although changing diagnostic criteria make longitudinal comparisons difficult [18], the occurrence of schizophrenia seems be relatively stable over time [21]. Studies have indicated both an increase [22] and a decrease [23] in the incidence of schizophrenia, but there is no consensus, and even studies from the same region show conflicting results [24, 25].

2.1.1 Genetic epidemiology

It has long been recognized that there is a familial aggregation of schizophrenia [26]. The life-time risk is approximately ten times higher in first-degree relatives of patients with schizophrenia than in the general population [3] and twin studies indicate that the heritability is over eighty percent [4]. Further, the recurrence risk in extended families decreases monotonically as a function of genetic relatedness [3].

The pattern of risks in family studies implies that the mode of transmission of schizophrenia is complex and the additive effect of multiple genes and/or interaction between genes (epistasis) was suggested early [27, 28]. Despite advances in molecular biology and powerful methods for assessing genetic variation, the number and type of genetic variants, the disease risk conferred by each gene and the degree of interaction among genes is still not well understood [29, 30].

Linkage studies aim to identify chromosomal regions (rather than specific genes) linked to an illness. Families with multiple affected members are genotyped in order to determine whether some alleles are inherited together with the phenotype more often then would be expected by chance [31]. Over thirty genome-wide scans have been conducted for schizophrenia [30] and meta-analyses of these scans have located chromosomal regions linked to over 4000 genes [32-35]. This illustrates an inherent problem in linkage analysis; linkage studies are not very precise and to locate genetic regions of small effects, the number of families required rapidly becomes prohibitively large [31].

A complementary approach for connecting genes to disease is genetic association studies. Association studies offer a powerful means of evaluating the relationship between specific gene variants and the risk of developing the disease in unrelated individuals [31]. Association studies can either be based on knowledge about the disease pathogenesis (functional candidate genes), assess genetic variation throughout the genome (genome wide scans) or map a candidate region identified by linkage (positional candidate genes). If environmental exposure is collected on the genotyped subjects, patterns of risk can be evaluated for different combinations of genes and environments (gene-environment interaction) [36].

Due to well-known mechanisms of therapeutic agents targeted against the dopaminergic system, dopamine is the neurotransmitter most clearly associated with schizophrenia [37, 38]. The pathophysiology of schizophrenia is not well understood, but the widely considered neurodevelopmental hypotheses suggests that early disturbances in the development of the central nervous system lead to schizophrenia later in life [39, 40]. Altered biochemical functioning in the glutamate system has been implicated to later cause the imbalance in dopamine neurotransmission observed in schizophrenia [41-44]. Unfortunately, association studies of genes associated with dopaminergic and glutaminergic pathways have mostly led to disappointing results [29, 45, 46]. However, whereas earlier studies mainly focused on the effect of genetic variants one by one [47], new findings suggest that a network of interacting genes in the dopaminergic system increase the risk of schizophrenia [48]. Positive findings from linkage studies have identified regions of interest, which have been mapped more closely. Susceptibility genes suggested so far comprise genes encoding dysbindin (*DTNP1)*, neuregulin 1 (*NRG1*), dopamine receptors 1-4 (*DRD1-4*), disrupted in schizophrenia 1 (*DISC1*), catechol-*O*-methyl-transferase (*COMT*) and metabotropic glutamate receptor (*GRM3*) [30, 49]. Failure to replicate findings across studies means that results should be interpreted with care and the mechanisms by which altered functions of these genes lead to schizophrenia are unknown.

Recently, two independent studies reported that individuals with schizophrenia had an increased number of structural mutations (deletions and duplications), both genome-wide and at specific loci [50 51]. The International Schizophrenia Consortium estimated that cases with schizophrenia on average, had a 1.15-fold higher rate of so called 'copy number variants' than controls [51]. Although each mutation is rare, the total number of disease-causing variants in genomic regions relevant to schizophrenia may together explain a substantial number of cases.

2.1.2 Gene-environment interplay

It is becoming even more apparent that most diseases do not have a purely genetic or purely environmental origin, but depend on a complex interplay of both components [36]. Heritability averages over a lot of complexity and the causal pathways between genes and schizophrenia is probably mediated over both genetic and environmental factors. If these factors differ across populations, cohorts or environmental conditions, then heritability estimates – and even the genes contributing to the heritability – might also differ across these factors [5].

Studies of gene-environment interplay do not necessarily rely on direct molecular measure of genetic variation. Instead they can model genetic contributions using adoption, twin or family designs [52]. Finnish adoption studies have shown an increased risk of schizophrenia in the biological offspring of parents with schizophrenia versus offspring of non-schizophrenic parents, but only for those also exposed to a dysfunctional family environment[53]. Cannon *et al* [54] reported a dose-response relationship between the increased liability conferred by parental schizophrenia and degree of perinatal hypoxia in the offspring. van Os et al. [55] suggested that urban birth and family history interact synergistically, whereas season of birth does not seem to affect the sibling's risk of developing schizophrenia [56]. Other exposures for which interplay between genes and environment has been suggested include cannabis use [57], stressful life events [58], paternal age [59] and migration [19].

2.1.3 The evolutionary paradox of Schizophrenia

Many psychiatric disorders are associated with markedly decreased fertility [60]. Patients with schizophrenia have fewer offspring compared to the general population [61-66], but despite the lower rates of reproduction, the incidence of this highly heritable disorder [4] appears to be stable [21, 67]. The evolutionary origins of schizophrenia and the baffling paradox of why schizophrenia is maintained in the human genome is indeed an attractive subject for debate. This is not the least illustrated by the vivid discussions following two extensive reviews on this issue [60, 68]. However, most theories are based on theoretic reasoning and the hypotheses are hard to test empirically. Nevertheless, many of the points raised are thought-provoking and might invite to further evidence-based studies.

Hardcastle argues that schizophrenia did not affect the fertility in ancestral environments, as humans reproduced earlier than they do today and regards the reduction in fitness as a modern phenomenon caused by delayed childbearing [69]. An analogy is drawn to Huntington's Chorea, another genetic disease that has survived over evolutionary history because symptoms are not presented until after the patient has finished his or her reproductive period. It is true that we cannot draw conclusions about ancestral fertility in schizophrenia based on modern fertility, especially since schizophrenia itself only has a recorded history dating back to the 1800s [16].

In a comprehensive review by Burns [68], it is proposed that genes for schizophrenia are linked to genes offering a selective advantage. According to his theory, the human brain became more susceptible for genetic insults as it developed, and schizophrenia is the price paid in the evolution of complex social cognition. Burns´ discussion approaches the theory of *balancing selection*, according to which psychiatric disorders being dysfunctional and showing reduced fitness under some conditions, might confer advantageous qualities and increased fitness in other environments [70, 71].

It has also been suggested that schizophrenia genotypes are maintained in the population because of heterozygote advantage [71, 72]. Heterozygote advantage is a special form of balancing selection, whereby a genetic polymorphism is maintained because the heterozygote has higher fitness than the homozygote. The classic example is sickle-cell anemia, where the sickle-cell heterozygotes will suffer from malaria less often and are more likely to survive a malarial infection [73]. According to Allen et al. [71], a minor increase of 5% in reproductive rates of unaffected gene carriers would be adequate for the maintenance. The hypothesis of compensatory higher fertility in healthy relatives of patients with schizophrenia has been given support by studies of the fertility of parents of schizophrenia patients [74-78], while research on the fertility among siblings of patients with schizophrenia has failed to detect any major differences [63, 65, 79]. Little is known about how fertility is affected by having a parent with schizophrenia.

Based on observations in a North Swedish isolate, it was proposed by Böök already in 1953, that the incidence of schizophrenia was maintained at a state of equilibrium by new mutations counteracting the losses due to selection [80]. Several decades later, it was found that advancing paternal age is associated with schizophrenia in the offspring [59, 81-84]. Germ cells divide continuously in males, and because of these numerous divisions, older men have an increased risk of errors in DNA transcription [85]. Refining the theory of Böök, Malaspina et al.[82] suggested that the association between paternal age and schizophrenia might be due to de novo mutations in paternal germ cells. Estimations that 15% to 25% [59, 82]of all cases with schizophrenia are the results of paternal age

effects, could at least partly explain the continuous replenishment of schizophrenia genes.

2.2 OBSTETRIC COMPLICATIONS

Low birth weight is commonly defined as a birth weight below 2,500 gram. Birth weight is a strong predictor of infant morbidity and mortality [86] and has long-term consequences also for diseases in adulthood [87, 88]. Birth weight is a straightforward measure and has long been a focus of clinical and epidemiological studies [89, 90]. Barker and colleagues formulated the 'Fetal origins hypothesis', which states that suboptimal fetal growth permanently "programs" the physiology and metabolism of the organism, leading to hypertension, coronary heart disease and type 2 diabetes later in life [88, 91]. More recently, suboptimal conditions in utero and size at birth have also been linked to psychiatric diseases such as schizophrenia [87, 92].

Size at birth is a complex entity which results from a number of genetic and environmental factors [11, 89]. Both intergenerational studies and studies on siblings show that members from the same family tend to have similar birth weights [9, 10]. Birth weight in the offspring is more strongly associated with the birth weight of the mother than the birth weight of the father [93]. The recurrence- risk of repeated low birth weight in several pregnancies is high [10, 94].

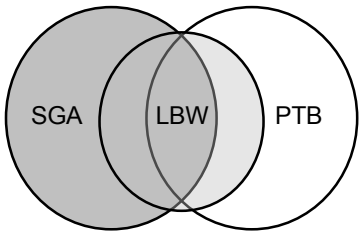


Figure 1 Low birth weight is a consequence of either preterm birth, impaired intrauterine growth, or both. SGA=small for gestational age; LBW=low birth weight; PTB=preterm birth

Low birth weight is a consequence of either preterm birth, impaired intrauterine growth, or both (Figure 1 and Table 1). Although reduced fetal growth and preterm birth represent heterogeneous pathologies, risk factors partly overlap [89, 95-97] and reduced fetal growth is in itself a risk factor for spontaneous preterm birth.

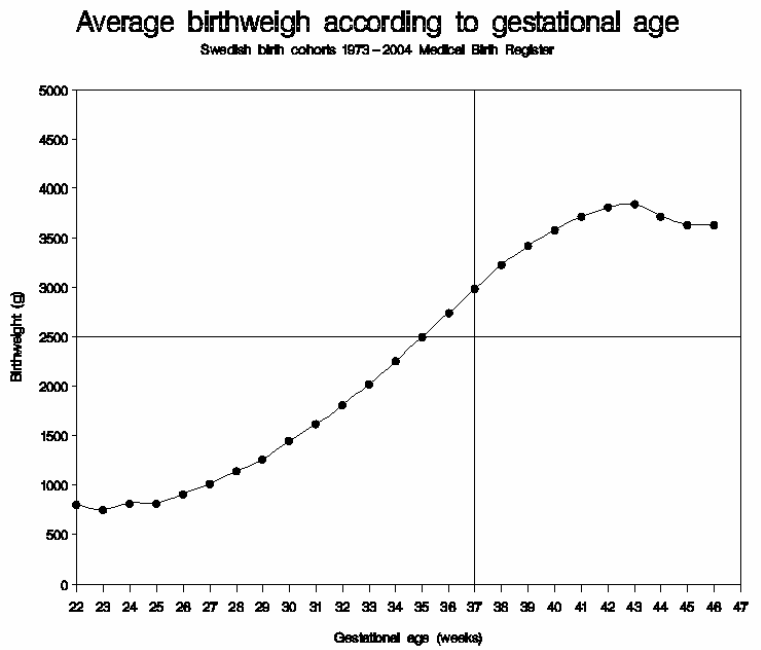


Figure 2 Mean birthweight according to gestational age for Swedish births 1973-2004. Note that curves of fetal growth cannot be inferred from birth weights, but must be based on ultrasonically estimated fetal weights.

Term births (gestational age ≥ 37 weeks)				
Preterm birth	Low birth weight	SGA	Number	Percent
0	0	0	2 869 608	92.3%
0	1	0	6 156	0.20%
0	0	1	49 290	1.6%
0	1	1	29 710	0.96%
			Total: 2 954 764	95.05%
Preterm births (gestational age < 37 weeks)				
Preterm birth	Low birth weight	SGA	Number	Percent
1	0	0	85 213	2.74%
1	1	0	52 367	1.68%
1	0	1	130	0.004%
1	1	1	16 032	0.52%
			Total: 153 742	4.95%
			Total: 3 108 506	100%

Table 1 Distribution of preterm birth, low birth weight and SGA births in Sweden 1973-2004.

2.2.1 Small for gestational age

In the Swedish Medical Birth Register, small for gestational age (SGA) is defined as having a birth weight more than 2 standard deviations below the mean for gestational age (i.e., the 2.5th percentile), according to the Swedish reference curve for estimated fetal weight [98]. This corresponds to more than 24% lower birth weight than expected or an approximately 850-g reduction in weight for a term infant. In some studies, the definition of SGA is extended to include babies with birth weights below the 10th percentile.

There is a familial aggregation of small for gestational age (SGA) births: women who were born SGA are more prone to give birth to SGA babies [99-101], a history of previous SGA births is considered to be highly predictive of a subsequent SGA birth [86, 99], and there is an increased risk of SGA births for women whose sister has had a SGA birth [99, 102]. However, it is still unknown how much of this familiality can be attributed to environmental effects and how much is due to maternal genetic effects (possibly mediated by the intrauterine environment) and fetal genetic effects (i.e. effects due to fetal genes transmitted from both the mother and father).

Risk factors for SGA include short maternal stature, low pre-pregnancy weight, preeclampsia, cigarette smoking, maternal and paternal weight at birth, preeclampsia, malnutrition, primiparity, and socioeconomic status [89]. SGA can also be caused by placental complications, infections, birth defects and multiple gestations [89]. Insuline-like growth factor (*IGF1)* affects growth in mice [103] and is a candidate gene also for reduced prenatal growth in humans [104]. Whereas some babies are SGA because of physiological reasons (e.g. their parents were small), many SGA babies are pathologically small due to fetal growth problems in utero [105]. Female fetuses are smaller than male fetuses at any given gestational age. To avoid that a female fetus of the same true age as a male fetus would be judged younger at birth than the (on average) heavier male, intrauterine growth curves are estimated separately for boys and girls [98].

2.2.2 Preterm birth

Preterm birth is defined as delivery that occurs before 37 completed weeks from the first day of the last menstrual period. Preterm birth is a major public health concern which accounts for substantial neonatal and infant morbidity and mortality. In Sweden, about 6% of all pregnancies end preterm (2003) [106], whereas the corresponding figure for the US was almost 13% (2005) [107]. Infant survival is inversely related to gestational age, with most deaths occurring in the first month of life [108]. Infants born preterm are also at greater risk for developing health problems such as cerebral palsy, chronic lung disease, gastrointestinal problems, mental retardation, vision or hearing loss [109].

Epidemiological studies have identified several environmental risk factors [95, 107], but a maternal history of preterm births remains one of the strongest indicators of preterm delivery [10, 94, 110, 111], suggesting a genetic basis or a persistent environmental component . Preterm birth in offspring is weakly associated with preterm birth in mother [10, 101, 112-114]. The relevance of genetic influences on preterm birth has been further highlighted by a study of inbreeding among Amish children in Pennsylvania, which indicated that preterm delivery was primarily associated with the maternal genotype [115]. Intrauterine infection increases the risk of preterm birth [107]and it has been

suggested that polymorphisms in the cytokines tumour necrosis factor-α (*TNF*- α) [116]or interleukin-6 (*IL-6)* [117] are related to preterm delivery.

Clausson et al. showed that monozygotic female twins had a greater similarity in having preterm offspring than dizygotic twins, and estimated that genetic effects accounted for 34% of the susceptibility to having preterm offspring [11]. This estimate is of the same order of magnitude as the heritability estimate of 27% reported by Treolar *et al*. in an Australian twin sample [118]. However, the twin design does not allow the separation of maternal from fetal genetic effects. Thus, it is still unclear whether the genetic influences also result from paternal genes transmitted to the fetus. In a Norwegian study of gestational age (rather than preterm birth), Lunde et al.[93] found that fetal genes explained 11% of the variance, whereas maternal genetic effects explained an additional 14%. Whether fetal effects are of importance for liability to preterm birth is not known.

Further, it is unclear how the familial effects for preterm birth are mediated. Early-onset preeclampsia, a common reason for induced preterm birth, is a potential genetic contributor to preterm delivery [119]. Several sociodemographic risk factors, such as ethnicity, teenage or older mothers, low socioeconomic status, cigarette smoking and not living with a partner [95, 107] have been identified, and they are all likely candidates for mediating the familial effects.

3 AIMS

The overall aim of this thesis was to investigate the genetic and environmental contributions in the development of schizophrenia and adverse pregnancy outcomes.

The specific aims were:

- To explore the fertility in parents, siblings and offspring to patients with schizophrenia, to test the hypothesis that the decreased reproductive rate in the patients is compensated by an increased rate in their first-degree relatives.

- To investigate possible moderating effects of individual characteristics (such as age at onset of disease and season of birth) and parental characteristics (such as paternal age, family history and immigrant status) on familial aggregation of schizophrenia.

- To disentangle the maternal genetic, fetal genetic and environmental effects for the risk of having small for gestational age (SGA) offspring.

- To separate the maternal genetic from the fetal genetic effects for preterm birth and to study the possibility of these effects being explained by known risk factors.

4 MATERIALS AND METHODS

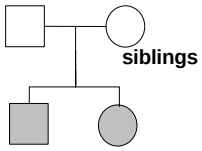
4.1 NATIONAL REGISTRATION NUMBERS

A national registration number system was introduced in Sweden in 1947, assigning a unique ten-digit personal identifier to all residents [120]. The number consists of a 6 digit date of birth and additional 4 digits. The national registration numbers are assigned immediately after birth, or at immigration. The national registration numbers are used extensively, both by official authorities and by health care providers and can be used to individually link population and health registers.

4.2 DATA SOURCES

4.2.1 The Multi-Generation Register

When introducing the national registration number system in 1947, parental information was recorded in personal files for everyone aged 15 or younger. Thus, the Multi-Generation Register provides information on first-degree relatives for Swedish residents born since 1932 [12]. To be included in the register, index persons had to be alive in 1960 or born thereafter. Paternity is assumed to be the husband of the mother at the time of birth or "by acknowledgement" for unwed mothers. Adoptions and other non-biological relations are flagged.



ID index person	ID mother	ID father
12345	00001	00002
23456	00001	00002
45678	12345	34567

Figure 3 General structure of the Multi-Generation Register. Every child (index person) exists once in the register whereas parents are included once for each offspring. The same individual can exist in the register both as a child and later as a parent. The example above illustrates two index persons with the same father and mother, i.e. full siblings. One of the siblings (i.e., individual 12345) also appears as a mother later on.

4.2.2 The Medical Birth Register

The Medical Birth Register contains information from standardized antenatal, obstetric, and neonatal records since 1973. The register contains data on pregnancy and birth for essentially all live and stillbirths in Sweden [106]. This register includes information collected prospectively, starting with the first antenatal visit through the time when mother and child are discharged from the hospital after delivery. All births and deaths reported to the Medical Birth Register are validated every year against the Register of the Total Population, by use of the mother's and the infant's unique national registration numbers. Maternal characteristics in the register include maternal age, parity, citizenship or country of birth, smoking habits, and family situation in early pregnancy. Complications during pregnancy and delivery are coded according to the International Classification of Diseases (ICD) version 8 until 1986, version 9 (ICD-9) from 1987 to 1996, and ICD-10 subsequently. Information about the infant includes if

he/she is stillborn or born alive, single or multiple birth, birth weight, birth length, head circumference, gestational age, sex, Apgar score, and infant diagnoses.

4.2.3 The Hospital Discharge Register

The Swedish Hospital Discharge Register contains details on virtually all psychiatric hospitalisations in Sweden from 1973. Dates of each hospital admission, discharge and the main discharge diagnosis assigned by the treating physician (and up to eight secondary diagnoses if occurring) are recorded according to the International Classification of Diseases (ICD), Eighth revision (ICD-8) through 1986, Ninth revision (ICD-9) between 1987 and 1996 and Tenth revision (ICD-10) from 1997 and onwards. The register has a nationwide coverage of inpatient treatment facilities and includes care in both psychiatric and somatic hospitals [121].

The standard procedure dictates that diagnosis will be given by a consultant (equivalent of an attending) psychiatrist at the time of discharge from hospital. The diagnostic assessment is then forwarded on a computer medium to the Hospital Discharge Register. These routines are standardized across Sweden and follow national guidelines.

4.2.4 The Education Register

The Education Register was established by Statistics Sweden in 1985 and includes information on highest level of formal education for all individuals living in Sweden between the ages 16 and 74. The register is updated annually [122].

5 STUDY DESIGNS

5.1 FERTILITY OF FIRST-DEGREE RELATIVES OF PATIENTS WITH SCHIZOPHRENIA: A THREE GENERATION PERSPECTIVE (PAPER I)

A population-based database was created by linking the Multi-Generation Register (where data on offspring were available through 2002) and the Hospital Discharge Register (recorded through 2001).

5.1.1 Cohorts of first-degree relatives

The fertility in three generations was analysed: parental generation ('generation I'); affected generation ('generation II'); and offspring to the affected generation ('generation III'). Because the first-degree relatives and their offspring have different likelihood of being included in our database depending on birth year (Figure 4), we created three different cohorts for the analyses. Pedigrees of the analysed cohorts are shown in Figure 5 a-c.

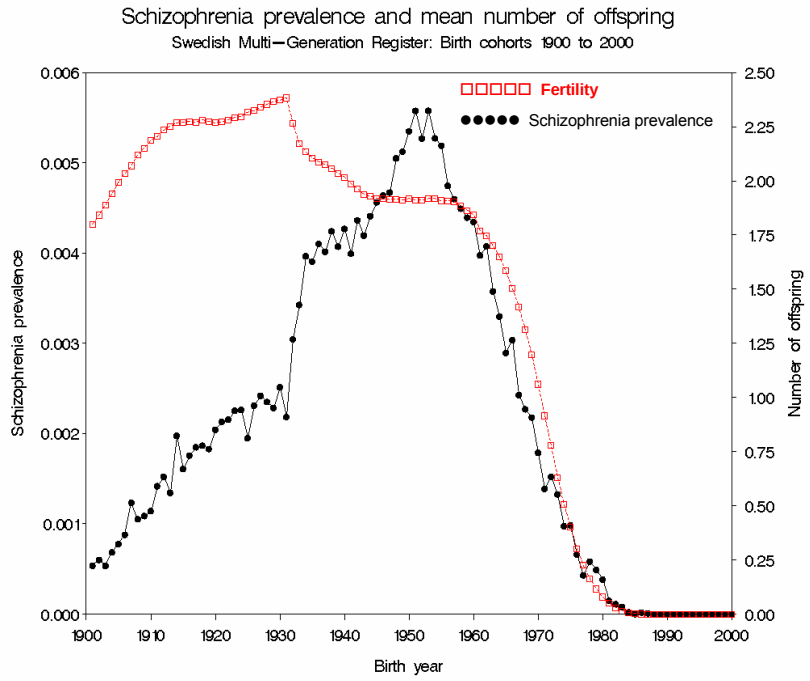
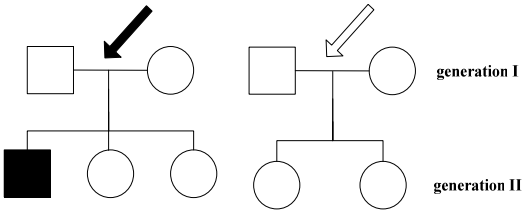


Figure 4 Schizophrenia prevalence and mean number of offspring in the Multi-Generation Register for different birth cohorts. Note that before 1932, only parents are included (average number of offspring ≥ 1).

Figure 5 General structure of the pedigrees created from the Swedish Multi-Generation Register with birth year of the different generations and reasons for cohort selection.

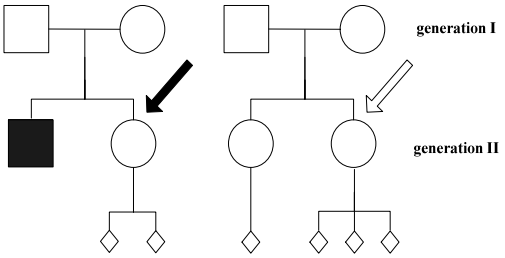
a. Parental generation



Birth year generation I: 1918-27
Birth year generation II: 1934-76

Reasons for cohort selection: Generation II has had time to develop schizophrenia and is included in the Multi-Generation Register.

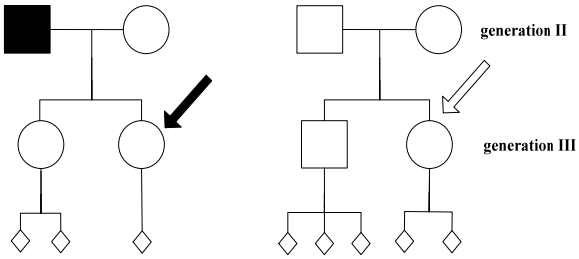
b. Affected generation



Birth year generation II: 1932-41

Reasons for cohort selection: Generation II has had time to develop schizophrenia and to have offspring.

c. Offspring to affected generation



Birth year generation II: 1911-20
Birth year generation III: 1951-60

Reasons for cohort selection: Schizophrenia diagnosis of generation II is recorded in the Hospital Discharge Register and generation III has had their offspring.

5.1.1.1 Parental generation

The cohort for the analysis of fertility among parents consisted of 274,464 couples from generation I and their offspring. The cohort was established by identifying all individuals born from 1918 through 1927, who were recorded as parents in the Multi-Generation Register (Figure 5 a, generation I). Offspring to the study subjects (Figure 5 a, generation II) were born from 1934 through 1976. There were two main reasons for the choice of cohort: Firstly, to ensure that all offspring were born after 1931 and thus included in the Multi-Generation Register. Secondly, to give the offspring enough time to develop schizophrenia, thereby minimizing misclassification of patients with late onset schizophrenia.

5.1.1.2 Affected generation

A cohort of 108,502 individuals born from 1932 through 1941 was selected (Figure 5 b, generation II). The subjects were either patients with schizophrenia, siblings of patients with schizophrenia, or neither. The cohort was selected because generation II should have had time both to develop schizophrenia and to complete their reproductive history.

5.1.1.3 Offspring to affected generation

A cohort of 103,105 individuals from generation III was selected together with their parents. This cohort comprised individuals born from 1951 through 1960 (Figure 5 c, generation III), where both parents were born between 1911 and 1920 (Fig. 5 c, generation II). Thus, follow-up time for reproductive history in both generations was set to 40 years. The purpose of this cohort selection was to ensure that generation III had completed their reproductive history and that individuals with schizophrenia in generation II were included in the Hospital Discharge Register.

5.2 FAMILIAL AGGREGATION OF SCHIZOPHRENIA: THE MODERATING EFFECT OF AGE AT ONSET, PARENTAL CHARACTERISTICS AND SEASON OF BIRTH (PAPER II)

A population-based database was created by linking the Swedish Hospital Discharge and Multi-Generation Registers. The linkage identified 5,075,998 unique individuals born between 1932 and 1990, where at least one full sibling and both the parents were identified. These individuals were followed up until 2004, resulting in 16,346 individuals who met our criteria for schizophrenia. All full siblings of cases with schizophrenia were selected and pairs consisting of these exposed individuals and the schizophrenia patient (the proband) were specified. Thus, several sibling pairs descended from one proband. In total, 35,953 pairs comprising a schizophrenia proband and his or her exposed sibling were matched to 359,102 non-exposed pairs.

5.2.1 Outcome measure (Paper I and II)

5.2.1.1 Schizophrenia

Patients with schizophrenia were defined as individuals identified in the Swedish Hospital Discharge Register having at least two inpatient hospitalisations with a discharge diagnosis of schizophrenia (ICD-8 and ICD-9 code 295 and ICD-10 codes F20, F23.1, F23.2 and F25). Latent schizophrenia (295.5, 295F and F21) was excluded. The criterion of at least two inpatient hospitalisations was chosen to increase diagnostic specificity, providing nearly identical estimates of familial risks as those from the literature [3].

5.2.2 Effect modifiers (Paper II)

Two forms of information (individual and parental) were included as interaction terms with proband schizophrenia to examine whether the risk ratio was influenced by covariates. Separate models were fitted for each covariate. Covariates were dichotomised according to predefined categories: early (< 25 years) and late age at onset (≥ 25 years), Swedish and non-Swedish place of birth, younger (< 40 years) and older paternal age (≥ 40 years) and birth in January-April and May-December. The cut-off for advancing paternal age was based on studies showing that major changes in schizophrenia risk have occurred at this age [82, 83]. Summer and winter births were defined according to Hultman et al.[123], following an extensive review by Torrey et al. [124], which concluded maximum schizophrenia birth excess in this period.

Age at onset was defined as age at first hospitalisation (as recorded in the Hospital Discharge Register) of schizophrenia of the proband. First, age at onset was dichotomised into early (< 25 years) and late age at onset (≥ 25 years). In an attempt to further investigate the effect of age at onset we grouped this variable into finer categories: < 20, 21-30, 31-40 and > 40 years, following the categorisation of age at onset in another Swedish cohort [8]. Because the Swedish Hospital Discharge Register started in1973, data on age at first hospitalisation, especially on early onset cases, can only be captured accurately in younger cohorts. Therefore, a subset of schizophrenia cases (n= 5,243) born from 1960 onwards was analysed, ensuring that cases admitted at age 13 years or older were correctly classified.

Following the same definition as for the siblings described above, family history of schizophrenia was defined as having one parent diagnosed with schizophrenia. Because research suggests that the offspring recurrence-risk ratio for schizophrenia among individuals with one affected parent differs substantially from the risk ratio among offspring to two affected parents [3], families with two affected parents (n=214) were not included in this analysis.

5.3 FAMILIAL AGGREGATION OF SMALL FOR GESTATIONAL AGE AND PRETERM BIRTHS (PAPER III AND IV)

Data for Paper III and IV was obtained by linking the Medical Birth Register and the Swedish Multi-Generation Register using the unique national registration number.

In the analysis of SGA, we extracted 2,193,142 births between 1973 and 2001 with both parents identified. In the analysis of preterm birth, 989,027 births between 1992 and 2004 were identified. The choice of birth cohort for analysis of preterm birth was decided by the availability of baseline covariates, as we wanted to explore if the familial effects could be explained by exposure to common risk factors for preterm birth.

5.3.1 Outcome measures (Paper III and IV)

5.3.1.1 Small for gestational age

Being born small for gestational age (SGA) was defined as having a birth weight more than 2 standard deviations below the mean for gestational age (i.e., the 2.5th percentile), according to the Swedish reference curve for estimated fetal weight [98]. This corresponds to more than 24% lower birth weight than expected or an approximately 850-g reduction in weight for a term infant.

5.3.1.2 Preterm birth

Preterm delivery was defined as live birth at less than 37 completed weeks of gestation. When available, ultrasound performed during the second trimester was used to estimate gestational age; otherwise gestational age was estimated from the date of the last menstrual period. Since 1990 routine ultrasound screening no later than at 18 weeks of gestation has been offered to all pregnant women in Sweden, and more than 95% accept this offer [125]. Previous investigations have demonstrated that data on gestational age is accurately recorded in the Birth Register [126].

5.3.2 Risk factors (Paper IV)

Maternal age was defined as completed years at time of delivery. At the first visit for antenatal care, the woman was classified as to whether or not she was born in a Nordic country (Sweden, Norway, Denmark, Iceland and Finland), was a daily smoker, was living with the infant's father and self-reported records were taken of height and pre-pregnancy weight. Maternal height was expressed in centimeters and body mass index (BMI) was calculated as the ratio between weight and the squared height expressed in

metres. Underweight was defined as a BMI of <18.5, normal weight as a BMI between 18.5 and 24.9, overweight as a BMI between 25 and 29.9, and obesity as a BMI ≥ 30. Information about highest achieved maternal education completed by 2004 was obtained through linkage to the Education Register and divided into four categories: attended or completed nine-year compulsory school or nine-year compulsory school, completed 2 years of upper secondary school, completed 3 years of upper secondary school, and completed university education or post-graduate education. We also retrieved information about maternal hypertension, including gestational hypertension, preeclampsia or eclampsia recorded according to the International Classification of Diseases (ICD-9 codes 642 E-G or ICD-10 codes O14-15), diagnosed by the obstetrician at the time of discharge from the hospital.

6 STATISTICAL METHODS

6.1 FERTILITY

Differences in fertility among first-degree relatives of patients with schizophrenia compared to the general population were estimated on a log scale using generalized estimating equations (GEE) [127, 128]. In comparison with for example Poisson regression, the GEE technique needs no assumption of the data following a particular distribution and takes into account the dependency between relatives within a family. We assumed independence between families, while a common correlation was assumed within a family. Results were expressed as fertility ratios, that is, ratios of estimated mean number of offspring comparing diseased and healthy study subjects. For example, a fertility ratio of 0.5 would mean that the study subjects had half as many offspring as the general population, while a fertility ratio of 2 would imply that they had twice as many offspring.

All analyses were performed separately for the different cohorts. We first performed unadjusted analyses including only the categorical covariate describing the relatives of interest, and then adjusted for birth year and parents' age at first birth as one-year categorical covariates. As fertility in schizophrenia is lower in men than in women [62, 63, 65, 66, 129, 130] and sex differences in fertility are observed in relatives of patients with schizophrenia [63, 65, 75, 129], an interaction term between schizophrenia and sex was included in the analyses of siblings and offspring to patients with schizophrenia. All data management and statistical analyses were performed using PROC GENMOD in SAS version 9.1.

6.2 FAMILIAL AGGREGATION

Family data provide an important tool for identifying whether a disease or trait clusters in families. Familial clustering can occur across generations in (e.g. parent-offspring), within a generation (e.g. between pairs of siblings) or within an individual (e.g. pregnancy outcomes within a woman). A common measure of familial aggregation is the familial risk ratio, defined as the risk among a given type of relative of an affected individual, compared with the risk among relatives of unaffected subjects. In this thesis, familial aggregation in terms of sibling recurrence-risks (Paper II) and sibling odds ratios (Paper III and IV) were estimated for schizophrenia, SGA and preterm birth. Familial clustering can be caused by common genes, shared family environment or by both. The proportion of the total variance of a trait attributable to genes is termed heritability. In Paper III and VI, a generalized linear mixed model was used to estimate the contribution of genetic and environmental effects.

It is not always that the actual size of the variance components is of interest and needs to be estimated. Sometimes the clustering can be a nuisance parameter which must be accounted for to obtain valid inferences. In these cases the correlations are simply factors to adjust for in the model. In Paper II, several sibling pairs descended from one proband, as all full siblings of cases with schizophrenia were selected. Further, all affected members of a family were used as index probands. To take into account the dependence of individuals from the same family, confidence intervals were computed

by bootstrapping. Bootstrapping was used because methods such as sandwich estimators or generalized estimating equations, which often are used to adjust for the correlations within families, were no longer sufficient.

6.2.1 Sibling recurrence-risks

6.2.1.1 Matched cohort (Paper II)

In Paper IV, a matched cohort study design was used to estimate the risk of schizophrenia among siblings of patients with schizophrenia compared with the risk among siblings of unaffected individuals [131, 132]. All full siblings of cases with schizophrenia were selected and pairs consisting of these exposed individuals and the schizophrenia patient (the proband) were specified. Thus, several sibling pairs descended from one proband. Each pair with a proband and an exposed sibling was then matched to 10 sibling pairs consisting of an unaffected individual and his or her sibling (Figure 6).

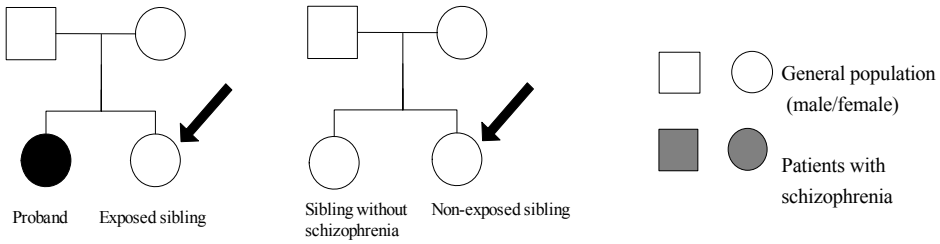


Figure 6 Sibling recurrence-risk ratio of schizophrenia was calculated comparing exposed/non-exposed siblings (indicated by black arrows). Further, we estimated risk ratios for different levels of individual and parental covariates of the exposed/non-exposed sibling and for different age at onset of the proband.

Because age, birth cohort and gender can affect the probability of a diagnosis of schizophrenia, the members of the pair were matched on these variables. The probands were matched in an attempt to reduce misclassification of exposure and the study individuals (the siblings of the proband) were matched to avoid confounding. To ensure equal follow-up time for schizophrenia, we additionally required that the proband was matched to individuals who were alive and had not been admitted to psychiatric care for schizophrenia in Sweden at the date the proband was first hospitalised. Because the magnitude of the sibling recurrence-risk ratio was not affected by gender of the patient in this population [3], brothers and sisters were analysed together.

To estimate the sibling recurrence-risk ratio of schizophrenia, the data were analyzed in a conditional logistic regression model using the PROC TPHREG procedure in SAS version 9.1. To take into account the dependence of individuals from the same cluster (family), confidence intervals were computed by bootstrapping [133]. We created 1000 bootstrap samples, each equal in size to the original sample, by randomly re-sampling with replacement from the original data. For each bootstrap sample, a matched stratum (1 exposed and 10 non-exposed study individuals) was selected at random to be included in the sample and then made available to be selected again for that same sample. Exact, asymmetric confidence intervals were calculated with PROC

UNIVARIATE using the 2.5 and 97.5 percentiles to constitute the limits of the 95% confidence interval. Statistically significant differences were declared when $p<0.05$ (two-sided).

6.2.1.2 Data related problems

Matching can be performed in both case-control and cohort studies. In an individually matched case-control (or cohort) study, the standard approach is to match each cases (or exposed study subject) to all available controls (unexposed subjects), fulfilling the matching criteria [134]. Next, an appropriate number of unexposed individuals are randomly selected for each exposed subject. In Paper II, a total number of almost forty thousand exposed pairs were extracted and each of these pairs was matched to 10 non-exposed pairs. When sampling siblings from the population-based Multi-Generation Register, the number of available non-exposed sib-pairs for each exposed pair becomes very large, often in the magnitude of several thousands of siblings per exposed sib-pair. Thus, a data set comprising all exposed subjects matched to all available unexposed grows very large. Instead an alternative selection procedure was used. Individuals displaying a similar pattern of the matching factors were grouped into larger strata and information on the number of individuals in each strata was summoned in a count variable (Figure 6). In our study, the strata variable comprised information on gender and year of birth of the individuals in a sib-pair. All individuals belonging to the same strata as the exposed sib-pair and who exited the study after the exposed individual, were available as controls. For each proband-sib unit in a stratum, a random number between 1 and the total number of available non-exposed sib-pairs was generated. This was repeated 10 times (as 1:10 matching was used). Finally the exposed sib-pairs were matched to the selected non-exposed pairs.

Exposure status	Strata_ID	Exit	N:o controls
…	…	…	…
0	132134	2004	253
0	132134	2001	254
1	132134	1999	254

Exit indicates year at schizophrenia diagnosis, migration, death or end of follow-up

One case and 254 available controls (only two controls shown)

The positions refer to:
sex sib_1, year of birth sib_1,
sex sib_2, year of birth sib_2
(i.e. two brothers born 1932 and 1934, respectively)

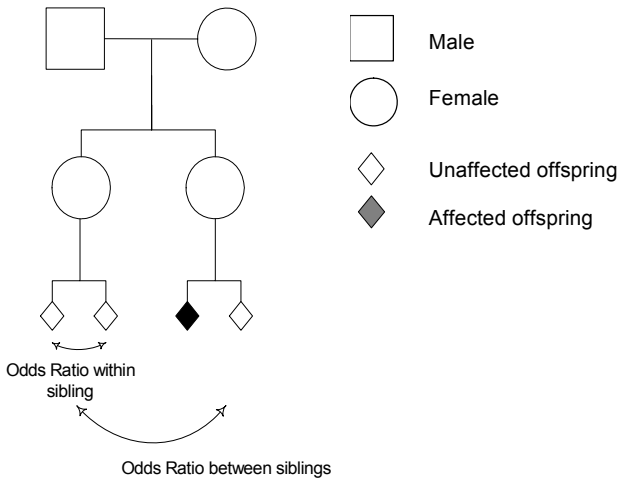
Figure 7 Illustration of the data structure facilitating selection of non-exposed sib-pairs.

6.2.1.3 Alternating logistic regression (Paper III and IV)

The familial aggregation of SGA and preterm birth were analyzed with alternating logistic regression (ALRs) procedure [135]. An ALR model consists of two parts; one model for the population mean where the effect of covariates on the outcome are estimated (corresponding to a standard logistic regression model) and one model for the clustering (i.e. the association between and within the pairs of subjects analyzed). ALR is similar to a generalized estimating equations model, but the clustering is measured

using odds ratios instead of correlations. ALRs model the clustering with pairwise odds ratios. The family data we analyze is characterized by clustered responses nested at two levels; the nesting of pregnancies within siblings (subclusters) that are nested within families (clusters). Thus, we chose a model that estimated two levels of odds ratios to describe the pattern of familial clustering: one within-siblings odds ratio (i.e., the risk for a repeated adverse pregnancy outcome, see Figure 7) and one between-sibling odds ratio (i.e., the risk for an adverse pregnancy outcome in a sibling, see Figure 8). Initially, we allowed for different odds ratios between all offspring. For example, allowing different odds ratios between the first child of the first sibling and the first child of the second sibling, and the odds ratios between the first child of the first sibling and the second child of the second sibling etc. Following a formal statistical test, we then chose to fit a model assuming equal sized odds ratios within siblings, but different odds ratios between siblings.

Figure 8 Schematic description of the three generation pedigrees created from the Swedish Multi-Generation Register.



Note: The family data is characterized by clustered responses nested at two levels; the nesting of pregnancies within siblings that are nested within families (between siblings). The odds ratios between siblings describe the correlations of SGA/preterm birth between cousins and within-sibling odds ratios describe the correlations of SGA/preterm birth between full siblings

As the outcome was measured on the offspring, the odds ratios between siblings describe the correlations of adverse pregnancy outcomes between cousins and the within-sibling odds ratios describe the correlations of adverse pregnancy outcomes between full siblings. Statistically significant differences were declared when $p<0.05$ (two-sided). The ALR was fitted by use of the SAS v9.2 PROC GENMOD procedure.

The estimated familial aggregation may be explained by exposure to shared environmental and/or genetic risk factors common to the siblings and/or their offspring. In the study of preterm birth, we included different covariates in the mean model of the ALR model described above, and tested whether the inclusion of the covariates changed the familial risks.

The ALR model is very flexible and can be extended. For example, it is possible that specific individuals or groups of individuals may be strongly affected by an exposure (i.e. interaction). Calculating odds ratios among exposed and non-exposed families, e.g. smokers versus non-smokers, offers an alternative description of the effect of a covariate. In the study of preterm birth, we fitted ALR models allowing for different magnitudes of familial clustering for different groups of individuals homogeneous with respect to some exposures. Only one covariate at a time was considered, although in theory it is possible to adjust for other baseline covariates, as well as studying change between levels of a covariate.

6.2.2 Genetic and Environmental effects

6.2.2.1 Generalized linear mixed model (Paper III and IV)

Familial clustering of a disease can be due to effects from genes, environment, or both. Our model allows the total genetic effect to be separated into maternal (M) and fetal (F) genetic effects. Mothers can influence the risk of preterm delivery by genetically influencing the intra-uterine environment, but also through genes inherited by the fetus. Fathers affect their offspring solely through their transmitted genes. Environmental effects may be decomposed into a sibling (S; contributing both to the within and the between sibling effects in Figure 8), a couple (C; corresponding to the within sibling effect) and a non-shared environment (E) component.

To separate genetic and environmental effects, the liability to preterm birth in offspring of pairs of full siblings and their partners was analysed with a generalized linear mixed model [136]. Our model specifies the probability of an adverse pregnancy outcome as the sum of the various effects according to:

Pr (pregnancy outcome) $= \beta_1 I_1 + \beta_2 I_2 + M + F + C + S,$

where β_1 and β_2 are fixed effects associated with preterm birth in primiparous and multiparous women. I_1 and I_2 are indicators of first and later pregnancies. The random effects M, F, C, and S are assumed normal with mean zero and variances σ^2_m, σ^2_f, σ^2_c and σ^2_s respectively. The unshared environmental effect E is normal with mean zero and variance $\sigma^2_e=1$. The correlations used, and the expected contributions of genetic and environmental effects for these correlations in liability are shown in Table 2.

Table 2 Expected genetic and environmental correlations in liability to small for gestational age and preterm births.

	Families joined by			
Type of effect	Sisters	Brothers	Sisters and brothers	Successive pregnancies within couples
Maternal genetic effects	0.5	0	0	1
Fetal genetic effects	0.125	0.125	0.125	0.5
Couple effect	0	0	0	1
Sibling environment	1	1	1	1
Non-shared environment	0	0	0	0

The variance accounted for by fetal genetic effects, maternal genetic effects, couple effects, sibling environment, and non-shared environmental effects were estimated using maximum likelihood and the confidence intervals were obtained using a likelihood based procedure. The parameters of the model express the degree of familial clustering of preterm births which can be expressed as a proportion of the total variance and thus the relative contribution of each factor can be assessed [136]. The generalized linear mixed model was fitted by use of the statistical software R version 1.9.1.

7 RESULTS

7.1 FERTILITY OF FIRST-DEGREE RELATIVES OF PATIENTS WITH SCHIZOPHRENIA: A THREE GENERATION PERSPECTIVE (PAPER I)

Figure 9 presents the results from the statistical analysis, adjusted for birth year and age at birth of first child and with an interaction term between schizophrenia status and sex in the analyses of siblings and offspring to patients with schizophrenia. Since there were no or only minor differences between the crude and adjusted estimates, only adjusted estimates are presented

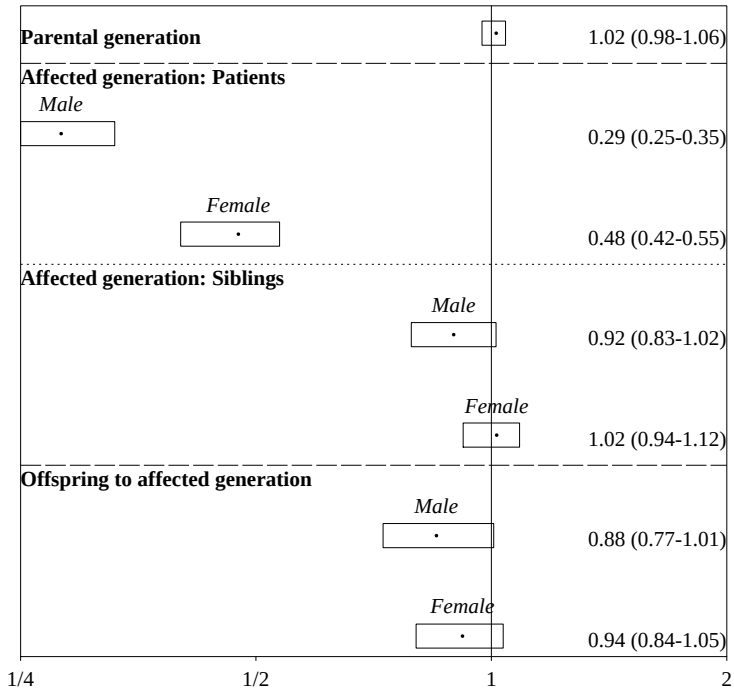


Figure 9 Estimated fertility ratios in first-degree relatives of patients with schizophrenia in three generations. The fertility ratios describe the ratios of estimated mean number of offspring between first degree relatives of patients with schizophrenia compared to the general population. Point estimates as filled circles surrounded by two-sided 95% Wald confidence intervals as boxes. Exact numbers are given to the right.

7.1.1 Parental generation

The mean number of offspring was 2.14 among parents in the general population and 2.13 among parents of patients with schizophrenia. There was no statistically significant difference in the fertility comparing parents of patients with schizophrenia and parents in the general population (fertility ratio$_{\text{parents/general population}}$=1.02, 95% CI 0.98-1.06) (Figure 9).

7.1.2 Affected generation

The mean number of offspring in the general population was 1.92 among men and 1.95 among women. The corresponding numbers for siblings of patients with schizophrenia were 1.76 (brothers) and 1.94 (sisters), whereas male and female schizophrenia patients had on average 0.56 and 0.93 offspring, respectively. As illustrated by Figure 9, there was no statistically significant difference in the fertility between sisters of schizophrenic patients and the fertility in the general population (fertility ratio$_{\text{siblings/general population}}$ =1.02, 95% CI 0.94-1.12). For brothers, a non-statistically significant negative tendency was observed (fertility ratio$_{\text{siblings/general population}}$=0.92, 95% CI 0.83-1.02). The number of offspring was lowest among men with schizophrenia; compared to the general male population, the fertility among males with schizophrenia was decreased by over seventy per cent (fertility ratio$_{\text{patients/general population}}$=0.29, 95% CI 0.25-0.35), while female patients with schizophrenia had less than half as many offspring as the general female population (fertility ratio$_{\text{patients/general population}}$ =0.48, 95% CI 0.42-0.55) (Figure 9).

7.1.3 Offspring to affected generation

Male offspring to parents with schizophrenia had somewhat lower fertility (mean number of offspring = 1.46) compared to men in the general population (1.66), whereas female offspring to parents with schizophrenia had nearly the same fertility as women in the general population. Compared to the general male population, male offspring to patients with schizophrenia had 12% fewer offspring (fertility ratio$_{\text{offspring/general population}}$=0.88, 95% CI 0.77-1.01) while this tendency was less pronounced among female offspring (fertility ratio$_{\text{offspring/general population}}$=0.94, 95% CI 0.84-1.05) (Figure 9). We performed an additional analysis, where we adjusted for schizophrenia in generation III. In this analysis, the fertility ratio for male offspring was attenuated to 0.92 (95% CI 0.81-1.05), while the fertility ratio among female offspring remained unchanged (0.94, 95% CI 0.84-1.04).

7.2 FAMILIAL AGGREGATION OF SCHIZOPHRENIA: THE MODERATING EFFECT OF AGE AT ONSET, PARENTAL CHARACTERISTICS AND SEASON OF BIRTH (PAPER II)

In total, 35 953 pairs comprising a schizophrenia proband and his or her exposed sibling were matched to 359 102 non-exposed pairs. Figure 8 illustrates the results from the statistical analyses, conditioned on the matching factors. We estimated the crude recurrence-risk ratio for schizophrenia in siblings to be 8.2 (95% CI 7.6-8.8), which is similar to previous reports [3].

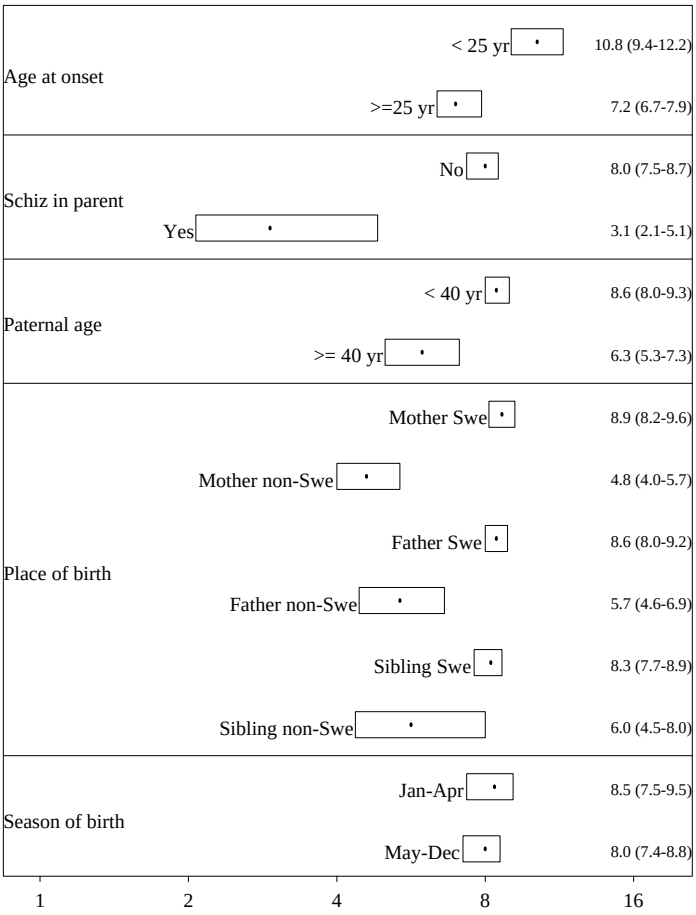


Figure 10 Sibling recurrence-risk ratio for schizophrenia from statistical modelling, conditioned on the matching factors of age, gender and year of birth. Point estimates as filled circles surrounded by two-sided 95% confidence intervals as boxes. Exact numbers are given to the right.

7.2.1 Age at onset

We found a statistically significantly higher risk ratio in siblings of earlier onset cases [10.8 (95% CI 9.4-12.2)] than of later onset cases [7.2 (95% CI 6.7-7.9)]. In an additional analysis the risk associated with sibling schizophrenia was calculated in four categories of age at onset. We found a monotonic decrease in the sibling risk ratio with higher age at onset of the proband (Figure 11).

In the later 1960 cohort there were 9 311 exposed and 92 951 non-exposed siblings. A similar effect of age at onset was found as in the full cohort though the estimates were overall higher, and because of the too short follow-up, we were not able to measure the effect in the oldest age (> 40 years) category (Figure 11).

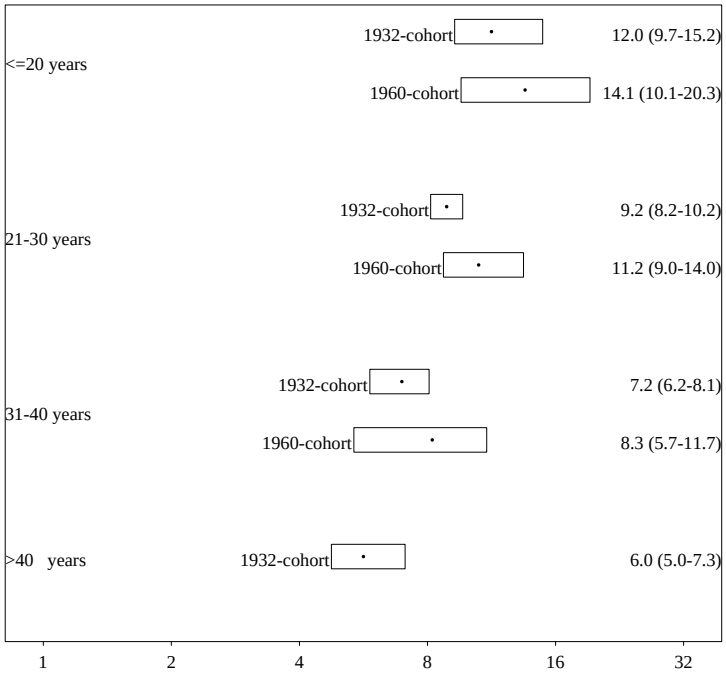


Figure 11 Sibling recurrence-risk ratio for schizophrenia according to proband age at onset in cohorts from 1932 and 1960 onwards.

7.2.2 Schizophrenia in parents

The effect of parental schizophrenia on the sibling recurrence-risk ratio was investigated in two analyses. First, the data were categorised according to parental schizophrenia and the isolated effect of sibling schizophrenia was analysed within each category. Next, the joint effect of parental and sibling schizophrenia was estimated by selecting only the fraction of the exposed siblings also having an affected mother or father (n=222) and comparing these to siblings exposed to neither parental nor sibling schizophrenia (n=2 216). In comparison with unaffected parents [8.0 (95% CI 7.5-8.7)], the recurrence-risk ratio was statistically significantly lower among siblings in which one of the parents was affected by schizophrenia [3.1 (95% CI 2.1-5.1)]. Further, it was estimated that those exposed to both sibling and parental schizophrenia had a 28.9 (95% CI 13.7-73.7) higher risk of developing schizophrenia than those with neither parents nor siblings affected.

7.2.3 Paternal age

Advancing paternal age reduced the recurrence-risk ratio in siblings: the recurrence-risk ratio in siblings was statistically significantly lower in the presence of older paternal age [6.3 (95% CI 5.3-7.3)] than in younger paternal age [8.6 (95% CI 8.0-9.3)].

7.2.4 Immigrant status

The sibling recurrence-risk ratio was statistically significantly lower among offspring to parents born outside Sweden. The recurrence-risk ratio among offspring to mothers born outside Sweden was 4.8 (95% CI 4.0-5.7) versus 8.9 (95% CI 8.2-9.6) among offspring to mothers born in Sweden. The corresponding risks based on paternal immigrant status were 5.7 (95% CI 4.6-6.9) and 8.6 (95% CI 8.0-9.2), respectively. We found no statistically significant effect of siblings' place of birth, although the point estimate for births in Sweden was lower than among births outside Sweden.

7.2.5 Season of birth

There was no statistically significant effect of seasonality of birth on the recurrence-risk ratio in siblings. The recurrence-risk ratio among siblings born in January-April [8.5 (95% CI 7.5-9.5)] was similar to the risk among siblings born in May-December [8.0 (95% CI 7.4-8.8)].

7.3 FAMILIAL AGGREGATION OF SMALL FOR GESTATIONAL AGE BIRTHS: THE IMPORTANCE OF FETAL GENETIC EFFECTS (PAPER III)

Among the 2,193,142 singleton births, the incidence of SGA births was 4.2% in the first pregnancy and 2.3% in the following pregnancies.

7.3.1 Familial aggregation

Table 3 presents the odds ratios between full- and half siblings and the recurrence risk within a nuclear family. Compared to women whose sister did not have a SGA birth, women whose sisters had a SGA birth had an 80% increased risk of giving birth to a SGA offspring (OR=1.8, 95% CI 1.7-1.9), a risk which could be due to both fetal and maternal genetic effects or environmental influences. The corresponding increase in risk for brothers and mixed sib-pairs was 30% (OR=1.3, 95% CI 1.2-1.4 and 1.3, 95% CI 1.3-1.4, respectively), suggesting fetal genetic influences on the risk of SGA births. The difference in resemblance in SGA between offspring of brothers and sisters could be used to disentangle fetal and maternal genetic effects. The higher correlation between offspring of sisters than between offspring of brothers or mixed sib-pairs indicates a maternal genetic effect.

Table 3 Odds ratios[a] with 95% confidence intervals (CI) for small for gestational age (SGA) among siblings who gave birth in Sweden 1973-2001.

	OR	95% CI
Full siblings		
Sisters	1.8	1.7-1.9
Brothers	1.3	1.2-1.4
Brothers-sisters	1.3	1.3-1.4
Half siblings		
Sisters	1.2	1.1-1.4
Brothers	1.1	0.9-1.4
Brothers-sisters	1.1	1.0-1.2
Within couples	8.5	7.5-9.7

[a]Odds ratios were calculated by alternating logistic regression, using siblings with no SGA as a reference group.

The odds ratios between half sibs were lower than the odds ratios between full sibs, corroborating the importance of genetic effects in the familial risk of SGA births (Table 3, lower panel). The odds ratio between female half sibs was statistically significantly increased by 20% (OR=1.2, 95% CI 1.1-1.4). Even though offspring of male and mixed half-sibs only share, on average, one sixteenth of their genetic material, the odds ratios were increased by 10% (OR=1.1, 95% CI 0.9-1.4 and 1.1, 95% CI 1.0-1.2, respectively). However, even in our large sample, these effects are not statistically significant.

In the analysis of successive pregnancies within couples, we found an increased risk of 8.5 (95% CI 7.5-9.7) for repeated SGA births, indicating the presence of a couple effect.

7.3.2 Genetic and environmental effects

To quantify the effects suggested by the comparisons between different types of siblings, we analyzed the oldest two full-siblings in each family using quantitative genetic methods. There was a total of 659,125 sib-pairs (167,244 sister pairs, 167,579 brother pairs and 324,302 brother-sister pairs). In this analysis, 37% (95% CI 31-44%) of the variance in liability was explained by fetal genetic effects, 9% (95% CI 8.0-10%) by maternal genetic effects, 18% (95% CI 17-18%) by couple effects and 36% (95% CI 32-42%) by non-shared environmental effects. There was no indication of a sibling environment effect. The fetal genetic effect consists of maternal and paternal genetic components. Assuming that these parts are of equal importance, the total maternal genetic contribution is 9%+18.5%=27.5%, while the paternal genetic effect is 18.5%.

In an attempt to estimate whether our results were confounded by two recognised major extrinsic risk factors for SGA, sub-groups of non-preeclampic and non-smoking women were analyzed in the same way as described above. These analyses gave similar estimates of the variance parameters as in the analysis of the full data set.

7.4 MATERNAL EFFECTS FOR PRETERM BIRTH: COMMON RISK FACTORS OF IMPORTANCE (PAPER IV)

Among the 989,027 singleton births between 1992 and 2004, the incidence of preterm births was 6.1% in the first pregnancy and 3.9% in the following pregnancies. In the multivariable model adjusting for all covariates, preterm birth was statistically significantly increased by primiparity, preeclampsia, height less than 175 centimeters, BMI below 18.5 or above 30, Nordic country of birth, smoking, age at birth younger than 30 years or older than 35 and educational level lower than university studies.

7.4.1 Familial aggregation

Table 4 presents the pairwise odds ratios for preterm birth between full siblings and the recurrence risk within a nuclear family Women whose sisters had a preterm birth had a 90% increased odds of giving birth to a preterm offspring (odds ratio [OR] =1.9, 95% confidence interval [CI]: 1.6-2.2), compared to women whose sisters who had not had a preterm birth, an increase which could be due to both fetal and maternal genetic effects or environmental influences. There was no statistically significant increased odds for brothers and mixed sib-pairs (OR=1.2, 95% CI: 1.0-1.4 and 0.9, 95% CI: 0.8-1.1), which suggests only limited influence of fetal genetic effects and shared sibling environmental influence.

As expected, there was a tendency for repeated preterm births; the unadjusted odds ratio within a nuclear family was 6.9 (95% CI: 6.5-7.3).

Table 4 Odds ratios[a] with 95% confidence intervals (CI) for preterm birth among full siblings who gave birth in Sweden 1992-2004.

	Unadjusted		Adjusted[b]	
	OR	95% CI	OR	95% CI
Sisters	1.9	1.6-2.2	1.8	1.5-2.1
Brothers	1.2	1.0-1.4	1.1	0.9-1.4
Brother-sister	0.9	0.8-1.1	0.9	0.8-1.0
Within couples[c]	6.9	5.9-7.1	6.2	5.8-6.6

[a]Odds ratios were calculated by alternating logistic regression, using siblings with no preterm birth as a reference group.

[b]Adjustments were made for maternal covariates: parity, preeclampsia, height, BMI, country of birth, cohabiting with the infant's father, smoking, age and education.

7.4.2 Explanation of the familial effects

In Table 4, last column, we present the familial risks adjusted for maternal parity, preeclampsia, height, BMI, country of birth, cohabiting with the infant's father, smoking, age and education. Compared to the non-adjusted model, the fully adjusted model only marginally changed the odds ratios between siblings (e.g., the crude OR for sisters was 1.9 and the adjusted OR was 1.8). The odds ratio of recurrent preterm birth within a family was only slightly attenuated (from 6.9 to 6.2).

7.4.3 Genetic and environmental effects

A generalized linear mixed model was used to quantify the familial effects suggested by the comparisons between different pairs of siblings. We estimated that 25% (95% CI: 23-27%) of the variance in liability to preterm birth was explained by maternal genetic effects, 5% (95% CI: 0-23%) by fetal genetic effects, 18% (95% CI: 16-20%) by the environment created by the couple and 52% (95% CI: 41-58%) by unshared environmental effects. There was no indication of sibling environmental effects.

7.4.4 Interaction between familial effects and maternal covariates

We also tested whether there was an interaction between the risk factors and the familial risk. Because the univariate analyses suggested that only the maternal and couple effects were important for the familial aggregation of preterm birth, the appendices only test for interaction within siblings and between sisters (but not between brothers). There was no consistent pattern of interactions between the risk factors and the familial risk of preterm birth, except for smoking status. Smoking status had a statistically significant impact on the risk between sisters: in families where both sisters smoked, the odds ratio was 0.6 (95% CI: 0.2-1.5), while the corresponding odds ratio between non-smoking sisters was 1.9 (95% CI: 1.6-2.3; *p*-value for difference 0.025). We therefore also tested whether there was an interaction effect between smoking status and the within-family effect. In a nuclear family where the mother smoked, the odds ratio was 4.0 (95% CI 3.1-5.3), whereas offspring from non-smoking mothers had an odds ratio of 6.6 (95% CI: 6.1-7.1; *p*-value for difference < 0.001).

8 DISCUSSION

8.1 METHODOLOGICAL CONSIDERATIONS

8.1.1 Cohort studies (Paper I-IV)

The term *cohort study* is used to describe an epidemiological investigation that follows a group of subjects who share a common experience or condition [137]. For example, a birth cohort consists of individuals who were born during a particular period, a cohort of workers at an industry shares the same occupational exposure, and a cohort of snuff users has the experience of snuff use in common. Sweden has a long history of nationwide population and disease registers [138], offering the opportunity to design population-based cohort studies.

Cohort studies can be either prospective or retrospective. In prospective cohort studies, exposure information is collected before start of follow-up. This means that the temporal relationship between the exposure and the outcome can be safely inferred, and reverse causation is avoided. It is possible to study rare exposures by assembling cohorts of individuals sharing the exposure of interest (e.g. occupational groups). The quality of exposure is not affected by the outcome (e.g. recall bias), and once exposure information is collected, multiple outcomes can be studied. Cohort studies may suffer from low response rates, but this does not cause selection bias, as the tendency to respond is not related to disease.

However, cohort studies can be expensive and time consuming and have several disadvantages. Cohort studies are inefficient for studying rare diseases, as only a minority of those followed will develop the disease. Prospective cohort studies are inefficient for diseases with long latent periods. These limitations do not apply to the register-based cohort studies in the present thesis. The main drawback using a retrospective cohort design, is that the studies are restricted to information on exposures, confounders and effect modifiers already recorded.

8.1.2 Internal validity

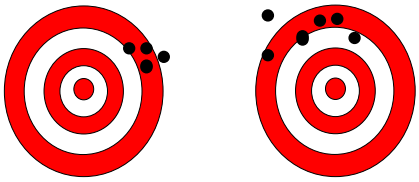
Internal validity of a study is defined as the absence of bias, confounding and chance. Systematic errors, which on average lead to the wrong conclusion, can be due to bias or confounding. Random errors (chance) affect the precision, but on average the results are correct (Figure 12) [139].

8.1.3 Bias

Bias is any source of error in the determination of the association between the disease and the exposure. Bias can be the result of a systematic error in the design of the study. It can be caused by the way study subjects are brought into the study (selection bias) or from how the participants provide information (observation/information bias). This type of bias cannot be controlled for in the analysis. Bias can also occur when the true effect of exposure is mixed with the effect of another determinant, i.e. a confounder. Bias due to confounding can be avoided if the confounders are measured and controlled for in the analysis.

Figure 12 Illustration of how random and systematic errors affect precision and accuracy.

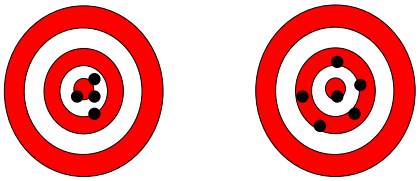
a. Systematic error – bias



High precision
Low accuracy

Low precision
Low accuracy

b. No systematic error



High precision
High accuracy

Low precision
High accuracy

8.1.3.1 Selection bias

In case control studies, selection bias occurs when the selection of cases and/or controls is related to the exposure. In cohort studies, selection bias occurs when the selection of exposed and/or unexposed is related to their outcome status. Selection bias is generally less common in cohort studies. Even when differential response rates lead to disproportionate sampling of exposed and non-exposed, this will not be related to the outcome and measures of association will be unaffected. However, cohort studies are susceptible to selection bias due to losses to follow-up. Loss to follow-up can be non-differential. That is, when losses are related to only one axis, outcome or exposure. The relative measure of association will be the same, but absolute measures will be biased towards the null. If losses are related to both outcome and exposure, the loss to follow-up is differential. In general, loss to follow-up can bias the results in either direction.

In Paper I, one has to consider selection bias in the analysis of parental fertility. Families of different sizes are affected with different probabilities and cases are more likely to be found in larger families [140, 141]. In a family without offspring, the probability of a schizophrenia diagnosis in generation II is null, and the more offspring, the higher the probability of a schizophrenia diagnosis. Thus, the selection of offspring with schizophrenia (the exposure) depends on the number of offspring (the outcome). Since family size was our outcome, it was not possible to control for number of offspring in the analysis. To avoid artificial over-representation of larger families, we only considered affection status of the first born child. We compared the fertility of the parents of all first-born children with and without schizophrenia. This comparison is valid, assuming that if parental fertility is affected by schizophrenia in the offspring, then this effect is the same independently of the birth-order of the offspring.

In paper II, we analyzed a cohort of siblings to patients with schizophrenia and compared these to siblings of non-affected individuals. The diagnoses were extracted from the nation-wide Hospital Discharge Register. In paper III and IV, the cohorts were based on the Medical Birth Register which includes essentially all live and stillbirths in Sweden [106]. Thus, there is no reason to believe that loss to follow-up would result in selection bias in neither of these studies.

8.1.3.2 Observation bias

Observation bias occurs when there is lack of comparability between the accuracy of information in the study groups. Non-differential (random) misclassification leads to noisy measurements and generally dilutes the measurement of association towards the null. If the degree of misclassification varies according to the disease- or exposure status, the measure of association is biased upwards or downwards.

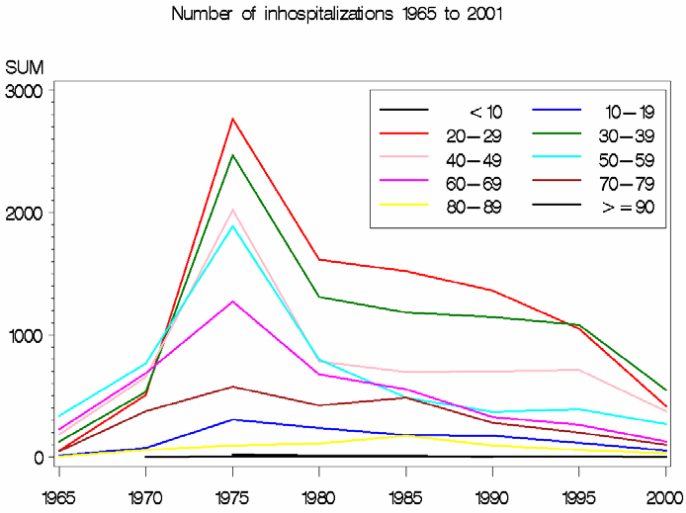


Figure 13. Number of hospitalizations of schizophrenia according to age groups in Sweden 1965-2001.

In Paper I and II, information on schizophrenia was collected from The Hospital Discharge Register, including all inpatient care in Sweden. The Swedish diagnostic practices of schizophrenic psychoses are considered to reflect diagnostic caution rather than over inclusiveness, and few false cases are reported [142]. However, the number of hospitalizations for schizophrenia has decreased since the mid 1990s (Figure 13).

This is not because of a lower incidence of schizophrenia, but to a restructuring of the psychiatric care in Sweden when the mental health care reform was introduced in 1995 [143]. Patients with schizophrenia, especially younger patients, are to a greater extent treated in outpatient facilities than earlier. This has increased the probability that patients not treated in the inpatient care have been misclassified as non-schizophrenic. We cannot rule out that some of the relatives of patients with schizophrenia might be misclassified as relatives of unaffected subjects. This would underestimate the

differences in fertility (Paper I) or bias the sibling recurrence risk ratios towards the null (Paper II).

In Paper I, the fertility among patients with schizophrenia and their first-degree relatives was estimated based on cohorts from the Multi-Generation Register. The information about paternity was based on recordings of "stated biological father" in the Multi-Generation Register. Pregnancies which do not have information about the father are overrepresented among mothers with schizophrenia. Further, it is known that individuals with schizophrenia are more likely to mate with another schizophrenia patient [3]. This could mean that the fertility among men with schizophrenia was underestimated. However, the main focus of interest was not the fertility among the patients themselves, but among their relatives.

In Paper II, we investigated how the risk ratio for schizophrenia in siblings was influenced by age at onset, approximating age at onset as age at first hospitalization of schizophrenia of the proband. However, as age at onset often precedes hospitalization by many months [144], age at first hospitalization is only a crude proxy for true age at onset. If age at onset is misclassified, patients with dissimilar age at onset could end up in the same category, masking the true effect of this variable.

In Paper III and IV, information on outcome status was collected from the Swedish Medical Birth Register. Gestational age and birth weight is recorded for all births and it is unlikely that systematic over-reporting of short gestational age and/or low birth weight in families who previous experienced a similar outcome would lead to exaggeration of familiality of SGA or preterm birth.

8.1.3.3 Left truncation

Left truncation arises when individuals come under observation after the natural time origin of the phenomenon under study. For example, spontaneous abortion studies that recruit pregnant women are left truncated because an unknown proportion of the source population experiences losses prior to enrolment [145]. In our studies, left-truncation due to start-up of the Hospital Discharge Register means that the probability of detecting a patient with schizophrenia is birth-cohort dependent. This is illustrated by Figure 4, where the prevalence of schizophrenia is lower in earlier birth cohorts (the shape of the curve is a result of several effects; before 1932, only parents are included in the Multi-Generation Register. As patients with schizophrenia have a reduced fertility, we would expect lower schizophrenia prevalence in a cohort of parents).

Using breast cancer as an example, Leu et al. have investigated bias from start-up of disease registration and missing links in the Multi-Generation Register [146]. They conclude that bias due to left truncation of disease registration is worse for early onset-diseases, for diseases with higher familial risks and when the background incidence rate is high. The biased familial risks were underestimated, as diseased individuals were incorrectly classified as healthy. In Paper I and II, we use registers to study schizophrenia, a disease with generally young age at onset and high familial risks, making the studies susceptible to bias. However, when comparing the magnitude of bias in sibling relative-risks with that in for example maternal relative-risks, Leu et

al. [146] conclude that the bias was smaller for sibling relative-risks. Siblings belong to the same generation, whereas mothers might be diagnosed in the distant past, resulting in differential loss of disease history. Bearing this in mind, the familial risk of schizophrenia in Paper II was measured in terms of sibling recurrence-risks.

There are several alternatives of how to deal with left truncation. Leu et al suggest a bias-correction method [147] using the software package "Population Lab" [148] to create a virtual population of related individuals where family history of disease is complete. In Paper I, we try to account for left truncation by careful cohort-selection (Figure 5 a-c and section 5.1.1.1-5.1.1.3). For example, parents of patients with schizophrenia were selected in order to assure that their offspring were included in the Multi-Generation Register and offspring of patients with schizophrenia were selected to have their parents recorded in the Hospital Discharge Register. In Paper II, the probands were matched in an attempt to reduce misclassification of exposure. However, matching does not overcome the issue of left-truncation bias. This is clearly shown when comparing sibling recurrence-risk from different birth cohorts. The risks are overall somewhat lower in our main cohort (comprising all cases of schizophrenia born since 1932), than among the cohort of cases born since 1960. In Paper II, we analyzed the effect of age at onset on the sibling recurrence risk. The Swedish Hospital Discharge Register started in 1973 and data on age at first hospitalization, especially on early onset cases, can only be captured accurately in younger cohorts. To avoid left-truncation bias, a subset of schizophrenia cases born from 1960 onwards was analyzed, ensuring that cases admitted at age 13 or older were correctly classified (Figure 11).

Left truncation is not a major issue of Paper III and IV. The outcome is registered at birth and only parents to offspring born after 1973 (or 1992) are included in the studies. Thus, information on outcome status is independent of birth cohort and we have very good access to parental links in the Multi-Generation Register.

8.1.3.4 Right censoring

Patients who do not reach a disease endpoint during their period of follow-up are referred to as censored observations. Right-censoring occurs when the true unobserved event is to the right of our censoring time; i.e., all we know is that the event has not yet happened at the end of follow-up. However, if the subject had been able to stay in the study, then it would have been possible to observe the time of the event eventually. Survival analysis (or time to event analysis) is a common approach to account for time under observation [149].

The younger cohorts of Figure 4 show effects of censoring both for schizophrenia and fertility; i.e. they are too young to have completed their fertile period and to have a schizophrenia diagnosis. In Paper I, we try to minimize right censoring while at the same time accounting for left truncation by means of cohort-selection, and the cohorts analyzed represent a compromise between these issues. In all analyses, we want to maximize follow-up time for both fertility and schizophrenia and avoid left truncation of too old cohorts.

In studies of perinatal morbidity, follow-up time is generally very short and right censoring is seldom a big problem [150]. However, in Paper IV, we analyze a birth cohort from 1992 to 2004. This means that many families who had their first child in the later part of the follow-up time, have not yet had their second offspring. Families with fewer than two offspring are less informative, as they provide no information about the couple effect within a family. Thus, the fetal effect can not be distinguished from the couple effect. To encounter this issue, a cohort of parents of at least two offspring was analyzed. In Paper III, families with short follow-up time only comprised a small proportion of the total number of families and they did not affect the estimates.

8.1.4 Confounding

Confounding may be considered a mixing of effects. The apparent effect of the exposure on the outcome is distorted because the effect of an extraneous factor is mistaken for, or mixed with the actual exposure effect. Rothman [139] defines a confounder according to three criteria. A confounding factor should: 1. be associated with the exposure in the population, 2. be associated with the outcome conditional on the exposure (e.g., among the unexposed) and 3. must not be affected by the exposure or the disease. In particular, it cannot be a in the causal pathway from exposure to outcome.

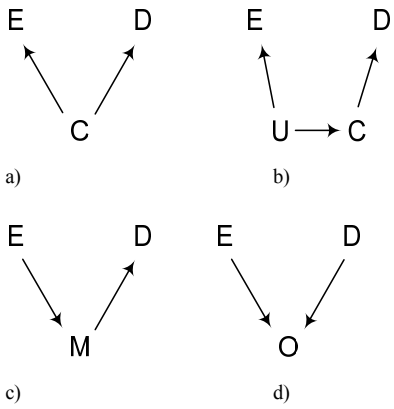


Figure 14
a) C causes both E and D and is therefore a *confounder*.

b) U causes both E and C, and C causes D. The unmeasured factor U is the confounder, but C can be adjusted for as the surrogate confounder.

c) E causes M, which in turn causes D. Hence, M is a *mediator* in the pathway between E and D and not a confounder.

d) O is caused by both E and D, E and D are not associated. O is a *collider* and conditioning on O creates a spurious association between E and D.

Statistical association between two factors occurs when one is the cause of the other, when they share a common cause, or both [151]. Thus, the criteria that the confounder cannot be in the causal pathway between the exposure and the outcome (i.e. the exposure that causes the confounder), implies that the confounder must cause the exposure or that they have a common cause (which would then in turn be the confounder). The criteria can therefore be redefined as a single criterion: Confounding is the presence of common causes to the exposure and the outcome [152 151]. The confounder does not necessarily have to be a direct common cause of the exposure and outcome (Figure 14 a), but can also be a common cause indirectly (Figure 14 c).

There are several ways to control for confounding: *randomization* of exposure controls for both known and unknown confounders, *restriction* of study subjects to individuals who fall within a specified category of the confounder, *matching* study subjects so that

the potential confounders are distributed in an identical manner among the exposed and unexposed groups (cohort study) or among the cases and controls (case control study), *stratify* and evaluate the association within homogeneous categories (strata) of the confounding variable, *multivariable analysis* where the confounder is adjusted for in a statistical model.

In paper I, we used multivariable analyses and adjusted for birth year and parents' age at first birth. Birth cohort is clearly a confounder in the analyses of all generations, as the fertility varies in different birth cohorts and the probability of a schizophrenia diagnosis also varies across cohorts (Figure 4). Age at first birth affects fertility, but the association with schizophrenia varies in different generations. In the analyses of fertility in the parental generation, age at birth is probably a true confounder, as advancing paternal age is associated with an increased likelihood of schizophrenia in the offspring [59] and older age at first birth leads to decreased fertility (Figure 15 a). In the analysis of the patients with schizophrenia, age at first birth might rather be a mediator than a confounder. If women with schizophrenia had their offspring later [153], this would cause an overall decrease in fertility (Figure 15 b).

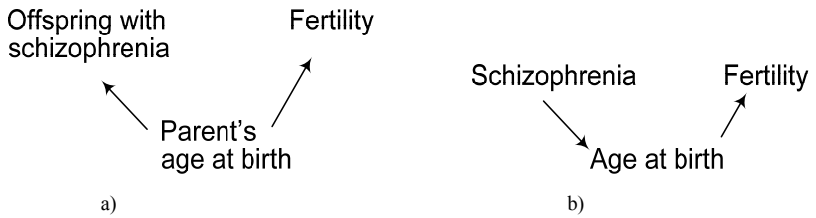


Figure 15 Illustration of how the variable age at birth affect fertility in parents of patients with schizophrenia (a) and in patients with schizophrenia (b).

To investigate if the reduced fertility among the offspring to patients with schizophrenia was mediated by schizophrenia in the offspring themselves, an additional analysis was performed where we adjusted for schizophrenia in the offspring generation. In this analysis, the reduction in fertility among male offspring to parents with schizophrenia was attenuated, indicating that the reduced fertility among male offspring is partly explained by schizophrenia among these individuals.

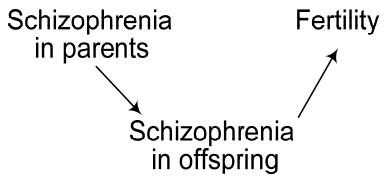


Figure 16 Illustration of a possible relationship between schizophrenia in parents and offspring fertility.

Paper II is an individually matched cohort study. The members of the sib-pair unit were matched on the potential confounders age, birth cohort and gender. It should be noted that the study individuals (the siblings of the proband) were matched to avoid confounding, whereas the probands were matched in an attempt to reduce misclassification of exposure. In a cohort study, if the exposed and unexposed study

subjects do not differ with respect to a variable, then that variable cannot be a confounder. In a matched cohort study, the crude measure of association is unconfounded by the matching variable. In a matched case-control study, the crude measure of association is biased, since the exposure distribution among the controls is more similar to the exposure distribution among the cases. A matched analysis must be performed, for example by using conditional logistic regression.

In Paper III, we were unable to include covariates, except for birth order, in our statistical model. The genetic contribution to SGA may be partly explained by such well known maternal risk factors for SGA births, such as smoking and preeclampsia [154]. To examine whether our results might be confounded by these factors, we performed a restricted analysis of non-preeclampic and non-smoking women. These analyses did not affect the size of the effect estimates, suggesting that the familial effects are explained by other means. In Paper IV, maternal parity, preeclampsia, height, BMI, country of birth, cohabiting with the infant's father, smoking, age and education, were included in our model estimating the sibling risks. The fully adjusted model only marginally changed the odds ratios between siblings, indicating that the covariates could not explain the genetic and environmental effects making the siblings similar.

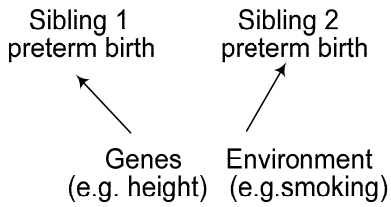


Figure 17 Illustration of the scenario investigated in Paper IV: are sibling risks for preterm birth explained by known risk factors?

A covariate's potential to account for familial clustering of a disease depends on the strength of association between covariate and disease, and the degree of familial correlation of the covariate [132]. In Paper IV, the covariates had either no effects or weak effects on the odds ratios between siblings. These results are perhaps not unexpected, considering that unless the covariate is associated with extreme relative risks and is highly correlated in families, it is unlikely that the risk factor would explain familial aggregation of disease [155]. For example, it was estimated by Khoury et al.[155] that for a covariate with relative risk 10 and a familial correlation 0.5, the maximum sibling recurrence-risk would not be higher than 2.01.

8.1.5 External validity

External validity concerns the extent to which the study results can be generalized to populations beyond the study subjects. The papers in this thesis are population-based cohort studies based on nationwide registers. Thus, the findings should be largely transferable to the Swedish population. External validity also concerns the generalizability to other time periods. In Paper I, we study the fertility in patients with schizophrenia and their first-degree relatives. For example, the affected generation was born 1932-1941, and it is possible that changes over time in treatment facilities and

medication patterns have affected the patient's abilities to mate and become parents. It is perhaps less likely that such changes would have had major effects on the reproductive pattern of the first-degree relatives of the patients. Also, Paper I and II are based on data from the Hospital Discharge Register. The tendency to treat younger patients of schizophrenia in out-patient facilities limits the generalizability of the results in the analyses of later cohorts.

8.2 FINDINGS AND IMPLICATIONS

8.2.1 Fertility of first-degree relatives of patients with schizophrenia: a three generation perspective (Paper I)

It has been suggested that schizophrenia genotypes are maintained in the population because of a heterozygote advantage, offering a compensatory higher fertility in healthy relatives of patients with schizophrenia [71, 72]. We found reduced fertility in patients with schizophrenia and among their offspring, that was not compensated by higher parental or sibling fertility. Furthermore, selection bias of larger families was accounted for in the analyses of parental fertility. Unlike earlier studies [74-78], which didn't control for family size, we did not find a difference in the fertility between parents of patients with and without a diagnosis of schizophrenia.

Providing a satisfactory answer to the question of how schizophrenia can persist, with current incomprehensive understanding of the genetic mechanisms in schizophrenia, is a futile task. However, several alternative explanations for how schizophrenia is maintained in the population have been proposed, some of which are discussed in the introduction of this thesis (section 2.1.3). Little is known about ancestral schizophrenia and even less is known about fertility in ancestral schizophrenia. Thus, most theories are based on theoretic reasoning and the hypotheses are hard to test empirically.

Most researchers now agree that schizophrenia is a complex trait where multiple genes, each with minor influences on overall population risk, are operating together with environmental and/or epigenetic factors [156]. In an extensive review by Keller and Miller [60], the authors put schizophrenia in an evolutionary genetic framework, and conclude that susceptibility alleles are maintained by polygenic mutation-selection balance at many different loci. Thus, the current model of transmission of the schizophrenia phenotype makes the reproductive advantage hypothesis redundant [60, 157].

8.2.2 Familial aggregation of schizophrenia: the moderating effect of age at onset, parental characteristics and season of birth (Paper II)

Schizophrenia is a multifactorial disorder with a highly familial nature. The life-time risk is almost ten times higher in first-degree relatives of patients with schizophrenia compared to the general population [3, 4] and twin studies indicate that the heritability is over 80% [4]. Heritability averages over a lot of complexity and the underlying mechanisms between genes and schizophrenia probably comprise both genetic and environmental factors. If these factors differ across populations, cohorts or environmental conditions, then heritability estimates – and even the genes contributing to the heritability – might also differ across these factors [5].

Consistent evidence of gene-environment interplay in schizophrenia from molecular genetic research is still sparse [158]. Instead a number of studies have examined gene-environment interplay using indirect measures of genetic risk, such as genetic relatedness to a patient with schizophrenia. Findings from studies using familial risk as

a proxy genetic risk factor, suggest that the familiality of schizophrenia can be modified by urbanicity [55], migration [159], family environment [53] and obstetric complications [160].

The power to detect interactions depends on the choice of scale on which the differences are measured. An ongoing discussion in epidemiological research concerns the proper choice of scale [161-163]. The sibling recurrence-risk ratio captures by definition differences on a multiplicative scale (the risk is almost ten *times* higher in siblings). Thus, interaction was measured in terms of departure from this multiplicative model. In a recent review on gene-environment in schizophrenia, van Os et al. states that "traditional notions of multiplicative interaction are probably not appropriate for 'real world' interventions" [52]. We have applied a matched cohort design as described by Liang and Beauty [132] (a "Family case-control design" in the terminology of Liang and Beauty). Following the analytical strategy proposed by the authors, we test for gene-environment interactions by adding in an interaction term in a logistic regression model.

In conclusion, we found that sibling recurrence risk remained high across levels of risk factors for the disease. Thus, as already known, individual variation in susceptibility to schizophrenia is largely genetic [3, 4]. However, the current findings, with large variation in the estimates depending on different levels of other risk factors, highlight the importance of environmental risk factors in schizophrenia and challenge the assumption of a uniform population-wide sibling risk. Some of these risk factors might themselves influence, or be influenced by genetic factors. Age at onset is probably one example of such a genetically influenced risk factor. Nevertheless, this study suggests that increased exposure to the potential environmental risk factors paternal age and migration status significantly reduces the familial vulnerability. Advances in molecular genetics might allow direct assessment of specific genes for schizophrenia, allowing more refined and powerful analyses of gene-environment interplay. At least, our study suggests that genetic influences alone will never provide an answer to the disease panorama.

8.2.3 Familial aggregation of small-for-gestational age births: the importance of fetal effects (Paper III)

Our results are in agreement with previous findings that familial factors influence risk of SGA[11, 102, 164]. Further, we could show that approximately 46% of the variation in liability to giving birth to a SGA offspring can be explained by genetic factors, of which fetal genes constitute 37% and maternal genes 9%.

To our knowledge, this is the first study which has been able to separate the effects of fetal and maternal genetic factors. Several intergenerational studies have shown that mothers who were themselves SGA or small at birth have an increased risk of giving birth to SGA children [100, 101]. The statistically significant increased odds ratios between brothers and brother-sisters found in this study, suggest that the familial component of SGA might be heritable also through the father. Our results have recently been given support by a study indicating that there are intergenerational effects of small for gestational age birth also from father to offspring [165]. The importance of fetal genes for SGA births is in accordance with the results from studies on normal birth weight:

Lunde et al. [93] estimated that fetal genetic factors explained 31% and maternal genes another 14% of the normal variation in birth weight. Mi *et al* .[166] observed a significant correlation between birth weights of paternal cousins, and other studies have shown that paternal birth weight had an independent contribution to infant's weight at birth[167,168].

A limitation of our study is that in our definition of SGA, we cannot distinguish infants who are constitutionally small from infants subjected to fetal malnutrition. The importance of this distinction has been stressed by Bakketeig and Hoffman[86], who reported that deviation from the expected growth pattern, rather than decreased fetal growth in itself, increased risk of perinatal mortality. For example, despite that infants of Chinese and South Asian origin, on average, have higher rates of SGA than Caucasian infants, the infant mortality is lower throughout gestation [169]. To accommodate this issue, it has been proposed that customized growth charts with ethnic-specific standards should be created. Kierans et al [169] found an improved coherence between SGA and perinatal mortality when ethnic-specific standards were used, suggesting that the ethnic differences are physiologic rather than pathologic. In this study, intrauterine growth curves were estimated separately for boys and girls [98]. Finally, we did not estimate the maternal and paternal contributions to the fetal genetic effect. In mammals, imprinted genes are important in feto-placental development and studies in mice suggest that paternally expressed genes tend to stimulate intrauterine growth while maternally expressed genes have the reverse effect [170-172].

Our results suggest an important role of maternal and fetal genes on the risk of giving birth to a SGA infant. The genetic aetiology of SGA births remains unknown, and future research has yet to identify the specific genes that mediate susceptibility to fetal growth restriction.

8.2.4 Maternal effects for preterm birth: common risk factors of importance (Paper IV)

Similar to others[10, 94, 101, 110-114], we have shown that familial factors influence the risk of preterm births. Sisters of women who had a preterm delivery were themselves at increased risk of having a preterm delivery. No increase in risk was observed in families joined by brothers. Maternal genetic factors accounted for 25% of the variability among individuals in their susceptibility to preterm birth, whereas fetal genetic factors only marginally influenced the variation in liability. Further, the increase in risk between offspring of sisters was independent of maternal risk factors for preterm birth, suggesting that maternal genetic effects are not explained by these well-known risk factors.

We estimated that 25% of the variation in liability for preterm births was attributable to maternal genetic effects. This is of same order of magnitude as the heritability estimates of 27% and 34% from analyses of Australian and Swedish twin data [11, 118], and also similar to the 34% heritability of gestational age implied by data from the Netherlands Twin Registry [173]. We found only a weak and non-statistically significant indication of preterm birth being heritable through the father, with an estimate of the fetal genetic effect of only 5%. This is lower than results from Lunde et al., who estimated the

relative importance of fetal genes to 11% [93]. However, it is possible that preterm births are under a different genetic and environmental control than term births.

We hypothesised that maternal risk factors would mediate the genetic contribution to preterm delivery. When the sibling risks were adjusted for several known risk factors, the fully adjusted model for sibling risks gave an almost identical pattern as the non-adjusted model. We can only speculate what other effects might explain the similarity in preterm births between offspring of sisters, but not brothers. The uterine environment is regulated by the maternal genotype and genetic association studies have suggested several functional polymorphisms within immune response genes associated with a predisposition to preterm birth [117, 174, 175].

There are limitations of our study that deserve consideration. We were unable to include other covariates than birth order in the statistical model evaluating the genetic and environment contributions. Instead, we modelled the pairwise odds ratios for preterm birth between offspring of siblings, while controlling for risk factors for preterm birth. The studied risk factors had either no effects or weak effects on the odds ratios between siblings, suggesting that the familial effects are mediated by other means. Another possible limitation is our decision to not discriminate between subtypes of preterm delivery (i.e. spontaneous versus induced preterm birth, very preterm versus moderately preterm birth). It is possible that a covariate's effect on familial aggregation of preterm birth differs by type of preterm delivery; for example preeclampsia mediating familiality of the induced, but not spontaneous preterm births. On the other hand, different clinical presentations of preterm birth may represent similar etiological entities and most risk factors show homogeneity across spontaneous and medically indicated preterm birth [176].

In conclusion, our results suggest that maternal genes are important for the risk of preterm birth. These maternal effects are independent of well known risk factors for preterm birth. In contrast, fetal genes explain only a small fraction of the total variation in liability to preterm birth. Our results support the use of genetic association studies focusing on the maternal genome, and less emphasis on collecting data on paternal and/or fetal genes.

8.3 CONCLUDING REMARKS

The findings from this thesis raise many questions and also provide inspiration for future studies.

Family studies [177, 178] indicate that there is a co-morbidity between schizophrenia and bipolar disorder, and that this is partly explained by genetic effects [179, 180]. It would be interesting to study the fertility in this context. Patients with bipolar disorder are overrepresented among the first-degree relatives of patients with schizophrenia [177, 178] and little is known about fertility of these individuals [181].

Another interesting issue, although not addressed in this thesis, is the question of why a reduction in fertility is observed in patients with schizophrenia. For example, can the differences between male and female patients be explained by an earlier average age at onset in male patients? We have not studied the fertility before and after age at onset. As indicated by Paper II, the familiality of schizophrenia seems to be stronger in the earlier forms of the illness. Is this reflected also in the reproductive pattern of the patients? Another aspect concerns the effects of changing medication habits on fertility. Perhaps fertility is a parameter worth considering in the evaluation of side effects of antipsychotic drugs.

In Paper II, we have examined gene-environment interplay in schizophrenia by use of register-derived variables as proxies for environmental exposure. A similar study design could be applied on data with more detailed information on exposures. We did not find a statistically significant effect of seasonality of birth on the familiality on schizophrenia. However, data on specific factors associated with winter-birth, such as prenatal infection [182], vitamin D-status [183] and sunlight exposure [184], would perhaps be more powerful in elucidating interactions. Likewise, migration status could be studied in further detail to distinguish migrants who have experienced war trauma from political refugees and labour migration.

An obvious limitation in Paper II is that we did not investigate if obstetric complications affect the sibling recurrence risk. Detailed data on obstetric complications is provided from the Swedish Medical Birth Register, but unfortunately many of these complications are quite rare, at least if the aim is to investigate the familial aggregation of schizophrenia among individuals who has experienced a specific obstetric complication. Also, the Medical Birth Register only comprises births from 1973 onwards, further decreasing the statistical power.

Due to computational challenges, we were unable to include covariates, except for birth order, in the statistical model evaluating the genetic and environment contributions for SGA and preterm birth (Paper II and IV). Recently, a new method allowing the inclusion of covariates while modelling the familial effects, have been developed by Yip et al. [185]. Instead of analyzing the full cohort, Yip et al.[185] sampled only informative families with at least two affected members, together with control families, thereby reducing the computational complexity. Interestingly, when the method was demonstrated on SGA data, the effects of both maternal and fetal genes were decreased after inclusion of maternal smoking status, preeclampsia and BMI.

9 CONCLUSIONS

- In a three generation perspective study, we found reduced fertility in patients with schizophrenia and among their offspring, that was not compensated by higher parental or sibling fertility.

- The sibling recurrence-risk in schizophrenia was statistically significantly reduced by higher age at onset, schizophrenia in parents, advancing paternal age and immigrant status of parents. Nevertheless, the sibling recurrence-risk ratio was significantly increased across all levels of risk factors of the disease.

- Genetic factors accounted for 46% of the variation in liability to have small for gestational age births. Fetal genetic effects were more important than maternal genetic effects.

- 25% of the variation in liability of preterm birth was explained by maternal genetic factors, whereas fetal genetic factors only marginally influenced the variation in liability. The increased odds ratio between offspring of sisters was independent of maternal risk factors for preterm birth, suggesting that maternal genetic effects are not explained by these well-known risk factors.

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