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Karolinska Institutet, Stockholm, Sweden

**Socioeconomic Disadvantage in Childhood and  
Later Risk of Schizophrenia and Other Psychoses**  
*National Register-Based Studies*

Susanne Wicks



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*Till min familj*

## ABSTRACT

*Aim:* The aim of this thesis was to analyse the association between various types of indicators of socioeconomic disadvantage in childhood and the risk of later developing schizophrenia and other psychoses. Furthermore, the importance of socioeconomic disadvantage was explored in relation to immigration, school performance, and an indicator of genetic liability for psychosis.

*Methods:* The study populations were based on register linkages of several Swedish registers. They were identified in the Multi-Generation Register and were followed in the National Patient Register regarding admissions for schizophrenia and other psychoses. Exposure of up to seven different indicators of childhood socioeconomic disadvantage (housing, single-parent household, parental socioeconomic classification, parental employment, households receiving social welfare benefits, parental early retirement, and parental education) was obtained via linkage to the national Population and Housing Censuses performed every 5 years between 1960 and 1990, and the Income and Taxation Registers. School performance data was obtained via the School Register. Hazard Ratios were estimated by multivariate Cox proportional hazard models.

*Results:* Five of seven indicators of childhood socioeconomic disadvantage were associated with later risk of schizophrenia and other psychoses (fully adjusted HRs from 1.2 to 1.7) (study I-IV). The risks increased with increasing number of exposures to the different indicators of socioeconomic disadvantage (study I, IV). First and second generation immigrants had increased risks for schizophrenia and other psychoses (HRs 1.4-3.1 and 1.0-2.0 respectively), compared with the Swedish majority population. These risks decreased considerably after adjusting for indicators of socioeconomic disadvantage (study II). In an adoption design (study III) both indicators of genetic liability (HR=4.7) and disadvantaged socioeconomic position (HRs 1.2-2.0) were independently associated with an increased risk for non-affective psychosis. The risk was considerably higher among adoptees exposed to both types of indicators (HRs from 5.7 to 15.0). Synergy indexes were larger than 1 (3.2, 2.6, 1.2). In study IV, risks were increased for schizophrenia (HR=1.9), other non-affective psychoses (HR=3.0), and affective psychoses (HR=2.3) in association with poor average grade, compared with those with a midrange average grade at graduation from compulsory school. Adjustments for socioeconomic position of the family reduced these estimates marginally (schizophrenia: HR=1.7, other non-affective psychoses: HR=2.8, affective psychoses: HR=2.1).

*Conclusion:* The results indicate that socioeconomic disadvantage during childhood or foetal life contributes to the risk of developing schizophrenia and other psychoses. Furthermore, this risk may even be relatively higher in individuals with a genetic liability for psychosis. Thus, influencing the social situation in childhood may have beneficial effects on the occurrence of psychosis. Socioeconomic disadvantage may also contribute to the increased risk of psychoses in immigrants. However, childhood socioeconomic disadvantage did not substantially affect the risk of psychoses associated with low school performance. In summary, there is support for social disadvantage in the aetiology of psychosis. This knowledge may open up for preventive methods on a societal level, perhaps targeting vulnerable groups as immigrants and individuals with genetic liability.

**Key words:** Schizophrenia, psychoses, socioeconomic position, socioeconomic disadvantage, social factors, immigration.

## SAMMANFATTNING (SWEDISH SUMMARY)

*Syfte:* Syftet var att studera samband mellan olika typer av socioekonomiska faktorer i barndomen och risken att senare insjukna i schizofreni och andra psykoser, samt att belysa dessa samband i förhållande till immigration, skolprestationer och indikator på genetisk sårbarhet för psykos.

*Metod:* Studiekohorterna (indexpersonerna och deras föräldrar) togs fram genom samkörning av nationella register. De identifierades i Flergenerationsregistret och följdes upp i nationella Patientregistret med avseende på slutenvård för schizofreni och andra psykoser. Genom länkning till de nationella Folk- och Bostadsräkningarna som utfördes vart femte år mellan 1960 och 1990 samt registret över Inkomster och Taxeringar kunde indikatorer på socioekonomiskt ogynnsam situation i barndomen tas fram (boendeform, ensamhushåll, hushållets socioekonomiska indelning, ekonomiskt bistånd till hushållet, föräldrarnas sysselsättning, förtidspension och utbildning). Indikatorer på skolprestationer togs fram via Skolregistret. Risker (Hazard Ratios) estimerades med multivariata Cox regressionsmodeller.

*Resultat* Det fanns ett samband mellan fem av de sju socioekonomiska faktorerna och risken att senare insjukna i schizofreni och andra psykoser. Fullt justerade HR varierade mellan 1.2 och 1.7 för de olika indikatorerna (studie I-IV). Risken ökade i takt med att antalet ogynnsamma faktorer ökade (studie I, IV). Ökad risk för schizofreni (HR 1.4-3.1) och andra psykoser (HR 1.0-2.0) fanns bland invandrare jämfört med svenskar. Dessa risker minskade avsevärt efter justering för de socioekonomiska faktorerna (studie II). Med en adoptivdesign (studie III) visades att både indikatorer på socioekonomisk position i barndomen (HR 1.2-2.0) och genetisk sårbarhet för psykos (HR=4.7) var oberoende av varandra associerade med risken för att senare insjukna i icke-affektiv psykos. Risken var betydligt högre för adoptivbarn som exponerades för båda typerna av riskfaktorer (HR mellan 5.7 och 15.0) med synergi index (som mått på interaktion) på 3.2, 2.6 och 1.2. Förhöjd risk för schizofreni (HR=1.9), andra icke-affektiva psykoser (HR=3.0) och affektiva psykoser (HR=2.3) fanns i studie IV bland dem med lägst medelbetyg från utgången grundskola jämfört med dem med medelmåttiga betyg. Dessa risker minskade något efter analyser med justering för de socioekonomiska faktorerna (schizofreni: HR=1.7, andra icke-affektiva psykoser: HR=2.8, affektiva psykoser: HR=2.1).

*Slutsatser:* Resultaten tyder på att en socioekonomiskt ogynnsam situation i barndomen påverkar risken att senare insjukna i schizofreni och andra psykoser. Denna risk kan även vara relativt högre bland dem med en genetisk sårbarhet för psykos. Resultaten tyder också att den högre risken för psykos bland invandrare delvis förklaras av socioekonomiska faktorer. Däremot påverkades sambandet mellan skolprestation och psykos i mindre utsträckning av de socioekonomiska faktorerna. Då en förändring av den sociala situationen i barndomen möjligtvis kan påverka förekomsten av psykos så öppnas utsikterna för preventiva åtgärder på samhälls nivå.

## LIST OF PUBLICATIONS

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

- I. **Wicks S**, Hjern A, Gunnel D, Lewis G, Dalman C: Social adversity in childhood and the risk of developing psychosis: a national cohort study. *Am J Psychiatry* 2005; 162:1652-1657
- II. Hjern A, **Wicks S**, Dalman C: Social adversity contributes to high morbidity in psychoses in immigrants - a national cohort of two generations of Swedish residents. *Psychol Med* 2004;34:1025-1033
- III. **Wicks S**, Hjern A, Dalman C: Social risk or genetic liability for psychosis? A study of children born in Sweden and reared by adoptive parents. *Am J Psychiatry* 2010; 167:1240-1246
- IV. **Wicks S**, Allebeck P, Gustafsson J-E, MacCabe J, Dalman C: School performance at age 16 and later risk of schizophrenia and other psychoses - the role of parental socioeconomic position. Manuscript

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## LIST OF ABBREVIATIONS

Census	The National Population and Housing Census
CI	Confidence Interval
CDR	Cause of Death Register
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
ITR	Income and Taxation Register
HR	Hazard ratio
MGR	Multi-Generation Register
NPR	National Patient Register
OR	Odds Ratio
PAF	Population-Attributable Fraction
SEC	Socioeconomic classification
SEP	Socioeconomic Position
SI	Synergy Index
NSR	National School Register
TPR	Total Population Register



# 1 INTRODUCTION

Schizophrenia and other psychoses are serious mental disorders, often with disabling consequences. It can lead to long periods of absence from work, difficulty in finding and maintaining employment etc. Friends and family often have a heavy task in caring for the person. Psychiatric care is needed in many cases, inpatient care as well as outpatient care. This is all costly, both economically and in suffering, to the community, the family, and to the person him/herself.

The aetiology of schizophrenia is far from understood. While there is consensus about a substantial genetic component in schizophrenia, most often studied by using twin data, it is also clear that other components are important too, such as environmental factors. The aetiology is most likely of multifactorial nature, including both genetic and environmental aspects.

Previous studies have consistently shown that schizophrenia is more frequent in economically disadvantaged groups and deprived areas. However, such a serious disorder will undoubtedly have an effect on a person's life situation. By the time I started this thesis it was not clear whether the association between socioeconomic disadvantage and schizophrenia was only a consequence of the disorder itself, leading to a drift down the social class scale, or an aetiological factor increasing the risk of developing schizophrenia.

Environmental factors can be modified, and if the impact of genetic vulnerability could be reduced by beneficial environmental situations, there could be new openings for prevention. This could be beneficial not only for those with a risk for psychosis but maybe also for those with a risk for other mental illnesses.

The overall aim of this thesis was to contribute to a better understanding of the role of socioeconomic position in childhood, in the risk of later developing schizophrenia and other psychoses.

## 2 BACKGROUND

Schizophrenia and other psychoses are mental disorders, often with disabling effects within many areas such as in working life, family life, social life, and in the society as a whole. Schizophrenia is a serious disorder with symptoms such as hallucinations, delusions, disorganized speech, reduced motivation, and affective flattening (1). A Finnish study found a life time prevalence of nearly 2% for non-affective psychosis, equivalent percentage for schizophrenia was 0.87% (2). In a systematic review from 2005 the median lifetime prevalence of schizophrenia was 0.40% (with a large variation, 10%-90% quintile=0.16% and 1.21%) (3). The number of new cases per year varies between 7.7–43.0 (10%-90% quintile) with a median of 15.2 per 100,000 (4). There are large variations in the incidence in different groups, with for example a higher incidence among immigrants than natives and among people living in urban areas compared with rural areas. The incidence of schizophrenia is higher among men than among women, with a male to female incidence risk ratio of about 1.4 (5, 4). However, the possibility that schizophrenia may go unrecognized to a larger extent in women than in men has not been completely ruled out, but at least for more severe forms of schizophrenia there seems to be a sex difference.

Age at onset for schizophrenia is most commonly in early adulthood, but can occur during all ages (6, 7). The onset for women is usually a few years later than for men. A Swedish study of inpatient data 1978-1994 showed a peak for first inpatient episode at 25-29 years for men, and 30-34 years for women with non-affective psychoses (including schizophrenia) (7). The mean age for first admission for schizophrenia is 28 for men, and 32 for women (8). The admissions are often preceded by symptoms or early signs 1 to 5 years earlier (8). The early onset of the disorder is one reason for the serious consequences. Education and entrance into the working life for example gets interrupted.

Adding to a complicated picture, is that alcohol and drug abuse is also more common among those with a diagnoses of schizophrenia compared with the general population (8). The suicide risk is substantial and a recent review concludes that almost 5% of persons with a schizophrenia diagnosis will commit suicide during their lifetime (9).

The aetiology of schizophrenia is still largely unknown. However, there is consensus about a genetic component in schizophrenia. Twin studies comparing concordance for schizophrenia in monozygotic twins with concordance in dizygotic twins, but also a sibling study, have pointed towards a heritability estimate of 60-80% (10-13), which means that 20-40% is explained by other factors, such as environmental factors or a combination of genetic and environmental factors. The aetiology is most likely of multifactorial nature, including individual, biological, psychological and social/ societal factors, and interactions between these factors.

## **2.1 SOCIAL CAUSATION OR SOCIAL DRIFT - CAUSE OR CONSEQUENCE**

Previous studies have consistently shown that schizophrenia is more frequent in economically disadvantaged groups and deprived areas (14-17). Serious disorders, such as schizophrenia and other psychoses will undoubtedly have an effect on a person's life situation (18). Psychoses are often preceded by a period of functional decline, and the question is whether the association between socioeconomic disadvantage and schizophrenia is only a consequence of the disorder itself, leading to a drift down the social class scale (social drift), or an aetiological factor increasing the risk of developing schizophrenia. Thus, one very important factor is that the measurement of exposure (socioeconomic disadvantage) must be long before the onset of the disorder. Many researchers have therefore used socioeconomic position at birth, usually the father's occupation grouped into categories, so called socioeconomic classification (or sometimes called social class). Increased risk for schizophrenia has been found in association with high socioeconomic classification (19), middle (20), and low socioeconomic classification (21, 22). Another study found no associations (23). Methodological problems could be one explanation to the contradictory results. Most studies used only one indicator of socioeconomic disadvantage (the importance of using more than one indicator is described in the next section), many of the studies were not able to take alternative explanations into account (immigration, psychosis in parent, urbanicity etc. also described more in a later section), and some studies had too small populations. Since I started the work with this thesis a few more papers have been published where the researchers have access to more than one or two indicators of socioeconomic position in these kind of studies (24-26).

## **2.2 SOCIOECONOMIC POSITION-CONCEPT AND MEASUREMENTS**

Socioeconomic position could be defined as an aggregate concept that includes both resource-based and prestige-based measures (27, 28). The resource-based measures are material as well as social resources and assets, such as income, wealth, education and social network. Prestige-based measures are measures referring to the individuals' position within the structure of the society and are linked to their occupational prestige, income, and educational level. The concept could also be described as the social and economic factors that influence what positions individuals or groups hold within the structure of a society. Socioeconomic position includes aspects such as employment possibilities, occupational position, accommodation possibilities, and opportunities to influence your environment. There is of course no single measure of this complex construct that is suitable for all outcomes and study aims (29). There are studies showing that education, income, and occupational group cannot be used interchangeably (30-32). Thus, the choice of indicators is very important. Many studies of psychoses in relation to socioeconomic position have used only one or two indicators, usually the father's occupation grouped into social class.

It is probably impossible to have any clear distinctions between resource-based and prestige-based measures. Most often they include both aspects. For example, single parenthood could easily include both aspects. There is a clear financial resources

aspect, one adult in the household equal's one income compared with two incomes in a two-parent household, while the costs for accommodation for example is still nearly the same. There could also be a social prestige-based aspect of not belonging to the 'norm'. Other conditions like unemployment and receiving social welfare benefits have obvious financial and social resource-based aspects as well as prestige-based aspects. Attained education is another example of a measurement that includes resource (material and social) and prestige-based aspects, a higher education is in society most often evaluated with a higher rank, gives access to occupations with higher rank and higher income etc. It is however important to remember that these kinds of measurements are all indirect measures, and they could be on individual, household, family, neighbourhood level. In conclusion, in order to study socioeconomic position in childhood and the risk of later developing psychoses, it is important to consider as many different measures of social position as possible. By using only one or two measures much of the information about social position is still missing, and any results may be misleading. This is the case in all studies concerning the effects of socioeconomic position on different health outcomes.

### **2.3 IMMIGRATION AND SOCIOECONOMIC DISADVANTAGE**

Immigration is another risk factor for schizophrenia. Schizophrenia has been associated with several different groups of immigrants, both first and second generation immigrants (33-39). Several explanations have been suggested, such as cultural differences in drug abuse, cultural barriers in setting diagnosis, obstetric complications, selection of vulnerable individuals, racism, and social disadvantage (36). The fact that the risk varies across different immigrant groups suggests that social factors may be involved. A recent review did conclude that there may be a role for social factors in the aetiology of schizophrenia (39). Other explanations have been studied. Ethnic density has been associated with schizophrenia with an increased risk for those living in areas with a smaller proportion of their own ethnic group (40, 41). Negative identification with own ethnic group has also been associated with increased risk for schizophrenia in immigrants (42). Social exclusion has been associated with mental illness (43). Recent studies have found associations between psychosis and perceived discrimination. A Dutch study (44) found an increased rate of delusional ideation (BPRS-intervju) and perceived discrimination. A population-based case-control study of first-episode psychosis in Nottingham found that an increased risk for psychosis in a Black ethnic group was partly explained by perceived disadvantage measured by questionnaires, as well as by socioeconomic disadvantage (measured for example by employment) (45). Social disadvantage is more common among immigrants and is one possible aetiological hypothesis which had not yet been explored when I started the work for this thesis. Again, to be able to add anything to the discussion about the effect of social factors on the risk of psychoses in immigrants, it is very important to use several different indicators of social position.

## **2.4 GENETIC LIABILITY FOR PSYCHOSES AND SOCIOECONOMIC DISADVANTAGE**

In many studies, parental psychosis has been used as an indicator of genetic liability for psychosis. The problem is that there are many other factors involved. Living with a parent that has been diagnosed with a psychotic disorder does have social and psychological consequences. Thus, it is impossible to disentangle what is genetic and what is social exposure. In studies of gene-environment interactions it is of upmost importance that these indicators are separated. Interaction effects of socioeconomic disadvantage and genetic liability have not been studied before. However, there are studies of interaction effects showing synergistic effects between biological family history of psychosis and other environmental factors, such as urbanicity and parental rearing patterns (46-49). An ideal setting to study how socioeconomically disadvantaged conditions interact with genetic liability for psychosis is an adoption design, where children are reared in adoptive families (environmental factors) and there is information available about their biological parental psychotic illness (genetic indicator). Thus, indicators of social exposure and genetic liability are separated. Again, it is important to have access to more than one indicator of socioeconomic disadvantage.

## **2.5 SCHOOL PERFORMANCE AND LATER RISK OF PSYCHOSES – POSSIBLE EFFECTS OF SOCIOECONOMIC DISADVANTAGE**

Studies of the association between school performance and schizophrenia have had inconclusive results. Increased risk for schizophrenia has been associated with poorer school performance in sports and handicraft (50, 51), and better performance in languages, religion and arts (51). There are studies with associations between schizophrenia and excellent school performance (52, 53), poor school performance (54, 55), as well as no association between schizophrenia and school performance (56). The contradictory results could be due to methodological differences such as different school systems, school performance measured at different ages, different diagnostic groups, sex differences, sample sizes. However, one important factor that has not been considered yet is the role of parental socioeconomic position. School performance could be affected by the child's social situation.

## **2.6 POSSIBLE MECHANISMS**

The developmental model postulates that the aetiology of schizophrenia involves many factors which may interact from very early age and throughout life (57, 58). For example, early genetic or obstetric complications could be reasons for a vulnerability for psychoses. Exposure to environmental factors such as social stress or isolation during different times throughout life may increase the risk of onset of psychosis in vulnerable individuals. This model predicts prevention possibilities; nobody is predestined to become psychotic.

Similarly, the stress-vulnerability model postulates that the higher the degree of vulnerability is less exposure to environmental stressors is necessary for the individual

to express ill health, and vice versa, the lower the degree of vulnerability the more exposure is needed for the individual to reach the threshold for ill health(59).

The biopsychosocial approach emphasize that ill health is best understood by biological, psychological and social factors. For example subjective experiences and emotions can produce chronic or acute stress which in turn affect biology and, thus affects physical and mental illness.

According to the social causation hypothesis social adversity implies a larger stress in life and limited resources to cope with stress, and this could cause psychosis in genetically vulnerable individuals. The biological reaction when the human is exposed to stress is at first an immediate reaction with a hormone noradrenalin release at the nervendings, and adrenalin release into the blood system. The second reaction is that the release of the hormone cortisol. Stress is an emergency reaction where extra energy is needed. The brain is also affected by cortisol to make it more attentive. However, a prolonged high level of cortisol can be harmful to the brain (60). The individual vulnerability to cortisol levels may be genetically determined (61).

Several socioeconomic factors could be considered as indicators of social exclusion. One assumption is that those who are more socially included have greater access to resources that the excluded don't have. These resources include economy as well as resources which come from living within a society, i.e. educational opportunities, social networks, and support. Social exclusion can refer to individuals who are excluded, but also to for example an area. A socially excluded area could be segregated, disadvantaged, or stigmatized and this may influence everybody who lives in the area regardless of whether the individual him/herself is excluded. The individuals in the area are influencing the area and the area is influencing the individuals. This could be in line with the social defeat hypothesis. According the social defeat hypothesis chronic experiences of social defeat could lead to sensitisation and/or overactivity of the mesolimbic dopamine system (62). The neurotransmitter dopamine has since long been associated with schizophrenia (63). However, the mechanisms are still unclear.

## **2.7 UNIQUE OPPORTUNITIES**

The Registers in Sweden offer unique opportunities to perform studies where it is essential to have measurements of exposure long before the onset of the illness. This is important when studying the role of socioeconomic position on the risk of developing schizophrenia and other psychoses, since these disorders have such adverse effects on the person's life situation. Using measurements in close timing to the onset will mostly describe the consequence of having a psychosis, which is well documented. The Swedish databases offer the possibility to design studies where several indicators of socioeconomic position is analysed, while taking several confounders into account. Record linkage of different Swedish registers offered an opportunity to perform this thesis.



The overall aim of this thesis was to contribute to a better understanding of the role of socioeconomic position in childhood in the risk of later developing schizophrenia and other psychoses.

## **2.8 SIGNIFICANCE**

Schizophrenia and other psychoses are very serious disorders, often with adverse consequences and costs, both economically and in terms of suffering, for the society, the family, and especially for the person him/herself. How socioeconomic disadvantage is related to schizophrenia and other psychoses, and if there is an interaction with genetic liability for psychosis is important to understand. It's important both from a scientific point of view, by adding a piece of knowledge to the large puzzle of schizophrenia and psychoses aetiology, and for preventive purposes. If environmental factors influence the risk of developing psychosis this is a path to explore, environmental factors can most often be modified. By clarifying the role of social factors, there may be new openings for preventive methods that could be beneficial not only for people with schizophrenia but also for other vulnerable groups.

### **3 AIM**

The general aim of this thesis was to analyse the association between various types of indicators of socioeconomic disadvantage in childhood and the risk of later developing schizophrenia and other psychoses. Furthermore, the importance of socioeconomic disadvantage was explored in relation to immigration, school performance, and an indicator of genetic liability for psychosis.

The specific aims were:

1. To study if childhood socioeconomic disadvantage contributes to the risk of developing schizophrenia and other psychoses later in life (Study I).
2. To investigate risks of schizophrenia and other psychoses in immigrants in Sweden and whether socioeconomic disadvantage contribute to these risks (Study II).
3. To study how socioeconomic disadvantaged conditions in childhood interact with genetic liability for psychosis. (Study III).
4. To assess the association between school performance at age 16 and the risk of later developing schizophrenia and other psychoses, and how this association is affected by socioeconomic position of the family (Study IV).

## 4 MATERIALS AND METHODS

### 4.1 MATERIALS OF THE STUDIES

This thesis is based on a register linkage of several national registers held by Statistics Sweden and the National Board of Health and Welfare, via each individual's unique identification number. We identified four study populations in the Multi-Generation Register (MGR). Data regarding immigration, emigration, and death was obtained via Total Population Register (TPR) and the Cause of Death Register (CDR). The populations were followed in the National Patient Register (NPR) regarding admissions for psychoses. Exposure to socioeconomic disadvantage in childhood was obtained via linkage to the National Population and Housing Censuses performed every five years between 1960 and 1990, and the Income and Taxation Register (ITR). Finally, school performance data was obtained via the National School Registers (NSR). The major registers will be further described below.

The personal identification number (64) was introduced in 1947 when everybody resident in Sweden was given a unique personal identification number, to be kept for life. This number is since then used administratively in everyday life in Sweden for identification at school, at work, at the bank, at the hospital, etc. Children born in Sweden and immigrants get their new personal identification number. Initially it was administrated by the local parishes, but today it is administrated by the National Tax Agency. This number enables us to make register linkages like the ones in this thesis.

#### 4.1.1 The Multi-Generation Register

The populations were identified in the MGR, held by Statistics Sweden. It consists of persons who have been registered in Sweden at any time since 1961, and who were born in 1932 or later (65). They are called index persons. The register contains connections between index persons and their biological parents, and if relevant their adoptive parents. The MGR is a part of the Total Population Register (TPR), where information comes from the National Tax Agency. Additional information from older national registers is also added, beginning from the 2002 version, to make the MGR as complete as possible. Coverage of index persons is virtually complete for those who have been resident in Sweden since 1968. Coverage is good, but not as complete for those who were only residents 1961-1967. For our cohorts of persons born 1955-1984, the parental linkage is overall as good as complete for those born in Sweden (99-100% with a link to their biological mother and 97-99% to their father). Linkage to the biological parents for children born outside Sweden is dependent on whether their parents have immigrated to Sweden. As we are studying exposure in childhood we only include those who immigrated to Sweden in childhood, thus most often with their parents. In our data, 90% of children who immigrated before 18 years of age have a link to their biological mother and 74% have a link to their father. For those who immigrated before 13 years of age the corresponding figures are 96% and 80%. National adoptees have a link to their biological mother in 95% of the cases and to their biological fathers in only 60%.

#### 4.1.2 The National Patient Register

The outcomes were obtained via the NPR. It was started by The National Board of Health and Welfare in the early 1960's to collect information regarding inpatient care at public hospitals (66). The first year, 1964, contains data from somatic clinics in 6 out of 26 county councils in Sweden. More and more county councils participated in the registration, which was decided to be mandatory in 1984 by the Ministry of Health and Welfare together with the Federation of County Councils. The National Patient Register today includes all inpatient care in Sweden, with complete coverage of both somatic and psychiatric care from 1987. However, the coverage of psychiatric inpatient care is virtually complete from 1973 with a few exceptions 1984-1986 (five counties are missing 1984, two 1985, and one 1986). From 2001 the register also contains visits (doctor's) to specialised outpatient care from both private and public caregivers. The coverage of outpatient care contacts is of varying degree, and the registration of diagnoses is very low within psychiatric outpatient care before 2006. Thus only inpatient care was used in the four papers. The NPR contains data such as admission and discharge dates, main and contributory diagnoses, type of care, sex, and age.

Figure 1 below illustrates number of inpatient care episodes at psychiatric clinics reported to the National Patient Register.

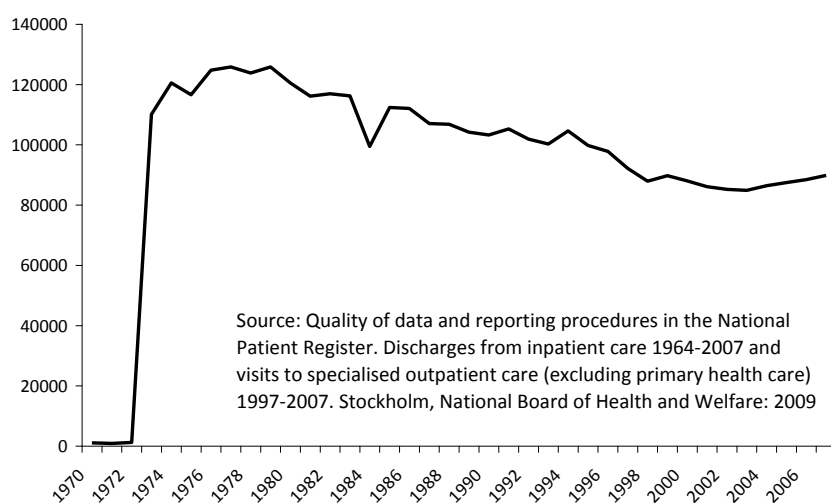


Figure 1.

The number on inpatient episodes at psychiatric clinics have decreased during the period of 1973-2008. This is probably due to changes in the health care system which has resulted in fewer hospital beds and expanded outpatient care facilities (67-69).

#### 4.1.3 The National Population and Housing Censuses 1960-1990

The indicators of parental socioeconomic position were obtained via the Swedish censuses that were performed every five years between 1960 and 1990 by Statistics Sweden. Data was collected via questionnaires to the total adult (16+) population, in combination with available registers. The contents include individual and household data such as employment, housing, type of household. The participation rate was more than 99% except for the last census of 1990 where 97.5% of the population participated (70). Similar data is today collected via a selection of different administrative registers and compiled into the database Longitudinal integration database for health insurance and labour market studies (LISA) (71).

#### 4.1.4 Income and Taxation Register

Statistics Sweden has yearly data about income and taxation in the ITR since 1968, although the contents are very sparse the earlier years with mainly variables such as income from employment and wealth data. Other kinds of data such as social welfare benefits, housing benefits are available from 1980 or 1985 and onwards (71).

#### 4.1.5 The National School Register

Statistics Sweden and the Swedish National Agency for Education administrate the NSR with national data from 1988. It contains subject specific grades on the leaving certificate for all pupils who graduated from nine years of compulsory school along with administrative data (72). In addition, there is similar information on those who graduate from upper secondary school (73). Upper secondary school consists of two or three years of schooling after compulsory school. Children attending schools for children with special needs or schools with other grading systems (e.g. international schools, schools with a special pedagogy) are not included in the register before 1995.

## 4.2 STUDY POPULATIONS

More detailed descriptions of the materials are available in each paper (I-IV).

### 4.2.1 Study I

With the aim to study if childhood socioeconomic factors contribute to the risk of developing schizophrenia and other psychoses, a population of 2.1 million Swedish children born 1963-1983 was identified. They were followed in the NPR from 1987 to 2002 regarding inpatient care for psychoses. Five indicators of childhood socioeconomic position (parental socioeconomic classification, adults in the household receiving social welfare benefits, parental unemployment, single-parent household, and housing situation) were obtained via linkage to the censuses from 1970 to 1990, with the adults in the household representing the child's socioeconomic position.

#### 4.2.2 Study II

The aim was to compare rates of schizophrenia and other psychoses in immigrants of different ethnic groups with the majority population in Sweden, in relation to socioeconomic disadvantage. A national cohort of all individuals living in family households with children in Sweden in the 1985 census was created, 1.47 million adults born 1929–1965 and 1.14 million children and youths born 1968–1979. The adults consisted of the Swedish majority population (Swedish-born) and first generation immigrants, which was defined as foreign-born persons that settled in Sweden after the age of 20 years. The children and youths consisted of the Swedish majority population (children and all adults in the household were Swedish-born) and a crude definition of second generation immigrants; Swedish and foreign born children in households where all the adults were foreign-born. The cohort was followed in the NPR 1991-2000 regarding admissions for schizophrenia and other psychoses. Five indicators of socioeconomic position were obtained from the national census of 1985 and 1990, in childhood for the children and youths, with the adults in the household representing the socioeconomic situation, and in adulthood for the adults (their own socioeconomic position). Countries of birth (own country of birth for the adults and parental country of birth for the children and youths), were due to the number of cases categorised into five groups: 1) Sweden, 2) Finland, 3) Western (Norway, Denmark; Iceland, Germany, Great Britain, USA, Canada, and other western), 4) Eastern and Southern Europe (Poland, Hungary, other eastern countries, Yugoslavia, Greece, Italy, and other southern Europe), 5) Non-Europeans (Turkey, Iran, Iraq, Asia, Chile, other Latin America, and Africa).

#### 4.2.3 Study III

To study how socioeconomic disadvantage interact with genetic liability for psychosis, an adoption design was used where the effect of environmental factors was separated from genetic components. The population of 13,116 children born in Sweden between 1955 and 1984, and reared in Swedish adoptive families was followed in the NPR 1973-2006 regarding admissions for non-affective psychoses (including schizophrenia). Three indicators of socioeconomic position in childhood (in the rearing family) were obtained via linkage to the national censuses from 1960 to 1985. The indicator of genetic liability (biological parental inpatient care for non-affective and affective psychoses) was obtained via further linkage to the NPR. To keep the two types of exposure (indicators of genetic liability and childhood socioeconomic position) as disentangled as possible, children were excluded if they lived with a biological parent at any 5-year-point when they were 1–15 years old (via linkage to the censuses 1960-1990, and the Register of Total Population in 1995). Children with adoptive parents with inpatient care for mental illness were excluded. As a comparison and to gain statistical power, a population of 2.9 million non-adoptees was identified in the same registers.

#### 4.2.4 Study IV

This study was performed with the aim to assess the association between school performance at age 16 and the risk of developing schizophrenia and other psychoses, and how this association is affected by socioeconomic position of the family. A study population of 184,806 children born 1972 and 1977 were followed in the NPR 1973-2006 regarding admissions for schizophrenia, other non-affective psychoses, and affective psychoses. Seven indicators of socioeconomic position of the family were obtained via the censuses, and ITR of 1985 and 1990. The population was linked to the NSR to obtain school performance data. To avoid measuring only the effect of psychotic illness on school performance we excluded those who were hospitalized for psychosis before, or at any time during the first five years after completed compulsory school. Inclusion of immigrants was limited to those who immigrated no later than two years before completing compulsory school, as possible language problems otherwise could affect the grades.

### 4.3 OUTCOMES AND EXPOSURES

#### 4.3.1 Diagnoses

The outcomes were obtained via individual record linkage to inpatient data in the NPR, schizophrenia, other non-affective psychoses, and affective psychoses. During the follow-up periods three different diagnostic systems have been used, the Swedish versions of ICD-8 (74), ICD-9 (75) and ICD-10 (76). The classifications used in the four studies are presented in table 1. Schizophrenia included all types of schizophrenic disorders except schizoaffective disorder, schizophreniform disorder, and latent schizophrenia. Non-affective psychoses included schizophrenia, schizoaffective and schizophreniform disorder, latent schizophrenia, and delusional disorders. Affective psychoses included bipolar disorders and other mood disorders with psychotic symptoms. Other non-affective psychoses included schizoaffective disorder, schizophreniform disorder, latent schizophrenia, and delusional disorders.

Table 1. Diagnostic classifications according to a main or contributory diagnosis in the National Patient Register

Diagnosis (study)	ICD-8 (1973-1986)	ICD-9 (1987-1996)	ICD-10 (1987-)
Schizophrenia (I, II, IV)	295 (excluding 295.40, 295.50, 295.70)	295 (excluding 295E, 295F, 295H)	F20
Non-affective psychoses, including schizophrenia (III)	295, 297, 298.20-298.99, 299.99	295, 297, 298C-X	F20-F29
Affective psychoses (IV)	296 (excluding 296.00)	296 (excluding 296A, 296B)	F31, F302, F323, F333
Other non-affective psychoses (IV)/Other psychoses (I <sup>1</sup> , II <sup>2</sup> )	295.40, 295.50, 295.70, 297, 298.20-298.99	295E, 295F, 295H, 297, 298C-298X	F21-F29

<sup>1</sup> 298B was included

<sup>2</sup> 298B, F302, F312, F315, F333 was included

#### 4.3.2 Indicators of childhood socioeconomic position

Seven indicators of parental socioeconomic position in childhood were available via linkage to the National Population and Housing Censuses 1960-1990 and Income and Taxation register 1985 and 1990.

- Single-parent household (used in study I-IV)
- Housing coded as rent apartment, own apartment, and own house (used in study I-IV)
- Parental employment (used in study I-IV)
- Household receiving social welfare benefits (used in study I, II, IV)
- Socioeconomic classification of the household coded as blue collar, white collar, self-employed, and others (used in study I, II, IV)
- Parental highest attained education coded as less than 9 years, 9 years, 10-12 years, and more than 12 years (used in study IV)
- Parental early retirement (used in study IV)

The seven indicators were chosen from the perspective to represent a socioeconomic disadvantaged situation that could affect the children in the family. They all include financial, psychological, and social aspects. For example, unemployment and early retirement means exclusion from the workforce, and to a large extent other daily social contacts to make you feel part of the community (reduced social resources). In addition, the reduced financial resources also limit the families' possibilities of recreation and recovery (reduced social resources). Living in a household that needs economic support includes reduced financial resources and may generate feelings of lack of control and lower self-esteem. Single-parent household has obvious financial



consequences, and the social situation could be experienced as more stressful with feelings of lone responsibility, lack of everyday support, and exclusion from ‘the norm’.

The indicators of socioeconomic position partly overlap and partly have unique aspects. The degree of association is presented in table 2, tested with correlation coefficients for non-parametric data. The analyses are based on data from study IV.

Table 2. Association<sup>1</sup> between the different indicators of socioeconomic position.

Indicators	Single-parent household	Housing	Employment	Social welfare benefits	SEC	Education
Single-parent household						
Housing	0.41					
Employment	0.21	0.15				
Social welfare benefits	0.22	0.27	0.26			
Socioeconomic classification (SEC)	0.27	0.19	0.77	0.31		
Education	0.12	0.16	0.10	0.12	0.29	
Early retirement	0.01	0.05	0.14	0.07	0.15	0.11

<sup>1</sup>Tested with the phi-coefficient, and when both variables have more than two categories, Cramer’s V. All coefficients are significant at  $p < 0.0003$ .

#### 4.3.3 School performance data

Subject specific grades for each individual were obtained through linkage to the National School Register. The register for compulsory school contains grades for a maximum of 20 subjects on the leaving certificate for all pupils who graduated from nine years of compulsory school. At this point in time the relative grading system was used in the Swedish schools, based on a scale of 1-5, where 1 was the lowest and 5 the highest grade. This was a grading system where the distribution of grades was supposed to follow a normal distribution; with an average grade of 3 and a standard deviation of 1 (77). English and Mathematics was given in advanced and general courses. To make the grades equivalent in advanced and general courses, one extra point was added to the grades achieved in the advanced course (78). The average grade (arithmetic mean of the subject specific grades) was calculated for each person and split into quintiles, boys and girls separately. Pupils with grades on less than 8 subjects were excluded. Data was also obtained about completed upper secondary school, which was another two or three years of schooling after compulsory school.

#### 4.3.4 Possible confounders

There are other factors that may influence the results. We were able to take several other explanations into consideration in the analyses. They were parental inpatient care for psychosis (study I, II, IV, part of the methodology in study III), parental inpatient care for substance abuse (study I-II), urbanicity (study I, II, IV), foreign-born parents (study I, IV, part of the methodology in study II and III), and paternal age (study I).

### 4.4 STATISTICAL ANALYSES

#### 4.4.1 Cox proportional hazards models

Sex- and age-adjusted hazard ratios with 95% confidence intervals were estimated using Cox proportional hazards models of time in the study, with schizophrenia, non-affective psychosis, other psychoses, or other affective psychoses as the outcome variable. Time in the study was calculated from the starting date (1987 in study I, 1991 in study II, 1973 or at age 16 in study III, and at age 21 in study IV), until the first hospital admission recorded in the NPR, or date of death recorded in the CDR, or date of emigration, or end of follow-up (2002 for study I, 2000 in study II, 2006 for study III and IV), whichever came first. Persons were excluded if inpatient episodes for psychoses existed before the age of 16 in study III as childhood psychosis could affect rearing family socioeconomic position. To avoid measuring only the effect of psychotic illness on school performance in study IV we excluded those who were hospitalized for psychosis before, or at any time during the first five years after completed compulsory school, i.e. before the age of 21. Multivariate analysis with adjustments were performed for urbanicity (study I, II, IV), paternal age (study I), parental inpatient care for substance abuse (study I, II), foreign-born parents (study I, IV, not relevant for II, III), and parental inpatient care for psychosis (study I-IV).

#### 4.4.2 Logistic regression

Logistic regression was used to estimate ORs and 95% CIs in analysing the association between socioeconomic disadvantage and possible confounders in study I. Logistic regression was also used in analysing the association between indicators of socioeconomic disadvantage and average grade in study IV.

#### 4.4.3 Population-attributable fraction

Population-attributable fraction (PAF) is defined as the proportion of cases in a population that would be avoided if the risk factor was eliminated, assuming that it's causally related to the disease (79). This assumption can of course most often not easily be made. Furthermore, many diseases are caused by multiple risks which mean that eliminating one risk factor may have effect on others, thus interpretations of PAFs must be made with caution. Complete removal of most risk factors is also unrealistic.

Population-attributable fractions were estimated in study I according to the formula  $p(\text{hazard ratio}-1)/p(\text{hazard ratio}-1)+1$ , where  $p$  was the proportion of the population that was exposed.

#### 4.4.4 Synergy Index

Synergy indexes with 95% CIs were calculated as an estimate of an interaction effect between the indicators of genetic liability for psychosis and socioeconomic disadvantage (study III). Assuming an additive model the following formula was used:  $(HR_{11}-1)/([HR_{10}-1]+[HR_{01}-1])$  (80-82). A synergy index of 1 indicated no biological interaction effect (i.e., the risk was the same for those exposed to both risk factors  $[HR_{11}]$ , as the sum of risks for those exposed only to the disadvantaged socioeconomic status in childhood risk  $[HR_{10}]$  and those exposed only to the genetic liability risk, alternatively familial history of psychosis  $[HR_{01}]$ ). Thus, a synergy index greater than 1 was expected if an interaction effect was present, (i.e., the risk for those exposed to both risk factors was expected to exceed the sum of risk 1 and risk 2).

#### 4.4.5 Chi-square statistics

Possible differences between adoptees with an identified biological father and those without identified biological father were tested with chi-square statistics ( $\chi^2$ ) (study III).

### 4.5 ETHICAL CONSIDERATIONS

All registers including this kind of data are very sensitive and must be handled correctly and cautiously. Data was treated according to recommendations of the Swedish Data Inspection Board. All studies have been approved by the Regional Ethical Review Board at Karolinska Institutet in Stockholm, Sweden.

## 5 RESULTS

Patient characteristics are presented in Papers I-IV. The main results from each study are presented here, more information can be found in the papers.

A short summary of the four studies is presented in table 3.

Table 3. Short summary of study I-IV: aim, population, outcomes, exposures, main findings, and conclusions.

Study	I	II	III	IV
Aim	To study if childhood socioeconomic disadvantage contribute to the risk of subsequent psychosis	To study risk of psychosis in immigrants in relation to socioeconomic disadvantage	To study how childhood socioeconomic disadvantage interact with genetic liability for psychosis	To study association between school performance and risk of subsequent psychosis, in relation to parental socioeconomic position
Population	2.1 million persons born 1963–1983	1.47 million adults born 1929–1965 and 1.16 million children and youth born 1968–1979	13,116 intra-country adoptees and 2.9 million non-adoptees born in Sweden 1955-1984	184,806 persons born 1972 and 1977
Outcomes	Schizophrenia and other psychoses	Schizophrenia and other psychoses	Non-affective psychoses (including schizophrenia)	Schizophrenia, other non-affective psychoses, and affective psychoses
Exposures (parental and household)	Employment, housing, single-parenthood, social welfare benefits, and socioeconomic classification	Employment, housing, single-parenthood, social welfare benefits, and socioeconomic classification	Employment, housing, single-parenthood, and genetic liability for psychosis	Employment, housing, single-parenthood, social welfare benefits, socioeconomic classification, early retirement, and education
Conclusions	Childhood socioeconomic disadvantage is associated with subsequent psychoses	Childhood socioeconomic disadvantage is associated with high morbidity of psychoses in immigrants	Childhood socioeconomic disadvantage and genetic liability is associated with risk of subsequent psychoses. There seems to be an interaction effect.	The association between school performance and subsequent psychoses is to a smaller extent explained by parental socioeconomic position

## 5.1 CHILDHOOD SOCIOECONOMIC DISADVANTAGE IS ASSOCIATED WITH SUBSEQUENT PSYCHOSES (STUDY I)

The population consisted of 2,130,376 persons in Sweden born 1963-1983. We identified 4,109 cases of schizophrenia and 6,043 cases of other psychoses during the follow-up period of 1987 to 2002.

There were increased risks for schizophrenia and other psychoses in association with all childhood socioeconomic indicators. However, there was one exception in the measurement parental socioeconomic classification, where blue collar worker and self-employed did not differ from white collar worker. The final multivariate model included adjustments for all socioeconomic indicators and possible confounders (urbanicity, foreign-born parents, paternal age, and parental inpatient care for psychosis and alcohol/drug abuse), results are presented in figure 2. The results for other psychoses were similar to those for schizophrenia.

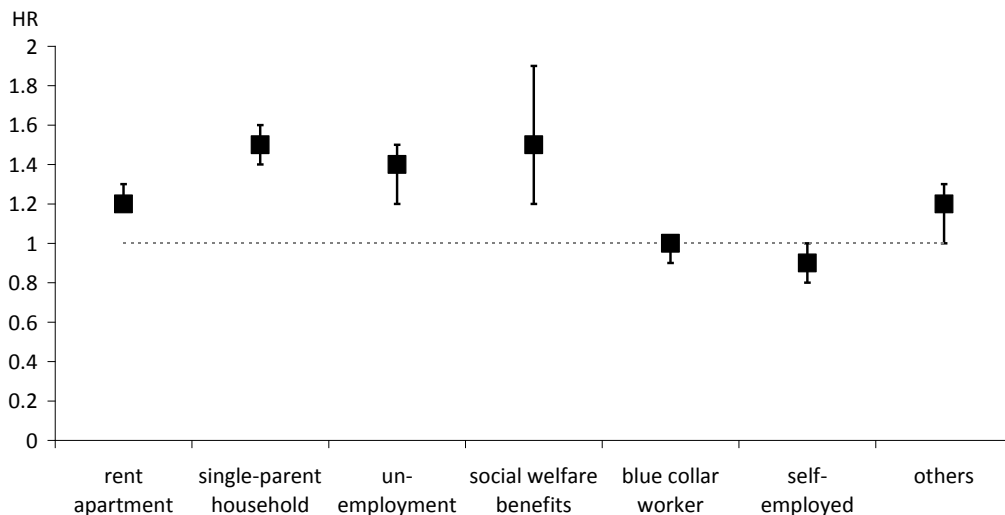


Figure 2. Indicators of childhood socioeconomic disadvantage and hazard ratios with 95% CI for Swedish people with inpatient care for schizophrenia.

Hazard ratios for schizophrenia increased with an increasing number of exposures to socioeconomic disadvantage (figure 3), from HR=1.2 (95% CI=1.1-1.3) for those with exposure to one indicator of childhood socioeconomic disadvantage to 2.7 (95% CI=2.3-3.3) for those exposed to four, compared with those exposed to none. Again, the results for other psychoses were similar.

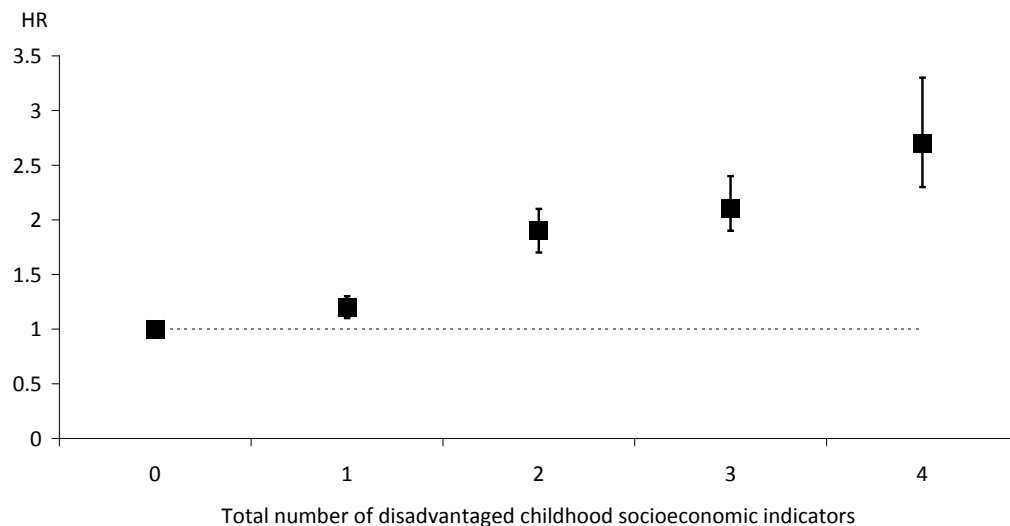


Figure 3. Hazard ratios with 95% CI for schizophrenia in relation to number of indicators of childhood socioeconomic disadvantage.

## 5.2 CHILDHOOD SOCIOECONOMIC DISADVANTAGE CONTRIBUTE TO HIGH MORBIDITY OF PSYCHOSES IN IMMIGRANTS (STUDY II)

The adult population consisted of 1,472,335 persons in Sweden born 1929-1965, 1,268 cases of schizophrenia and 7,142 persons with other psychoses. The children and youths consisted of 1,144,213 persons in Sweden born 1968-1979, 1,588 cases of schizophrenia and 3,096 cases of other psychoses. The indicators of socioeconomic disadvantage represented the situation in adulthood for the adults and in childhood for the children and youths.

Increased risks for schizophrenia and other psychoses were found in all immigrant groups, and in both first and second generation immigrants. Adjustments for the socioeconomic factors reduced the estimates considerably, especially in the non-European group where the risk among first generation immigrants was reduced to be lower than the risk for the Swedish majority population. However, the risks remained increased for the Finnish immigrants, and for those from Eastern and Southern Europe. The results for schizophrenia are presented in figure 4 and figure 5. The results for other psychoses were similar, only at a lower level before adjustments, and at the same level as schizophrenia after the adjustments for socioeconomic disadvantage.

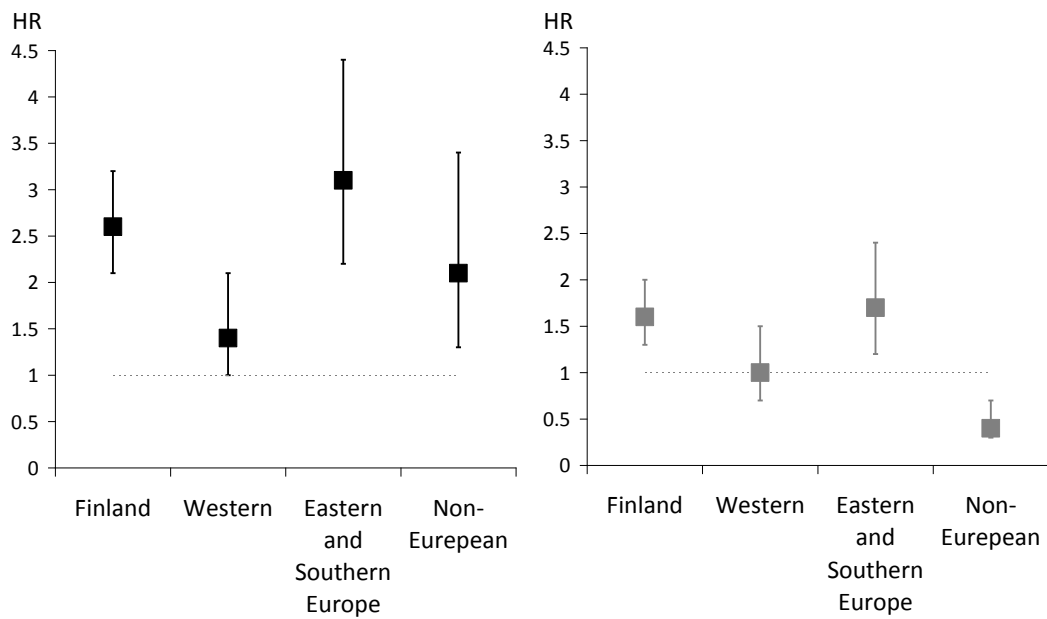


Figure 4. Hazard Ratios with 95% CI for schizophrenia in first generation immigrants compared with the Swedish majority population. Age and sex adjusted estimates to the left (black boxes), and additional adjustments for socioeconomic disadvantage to the right (grey boxes).

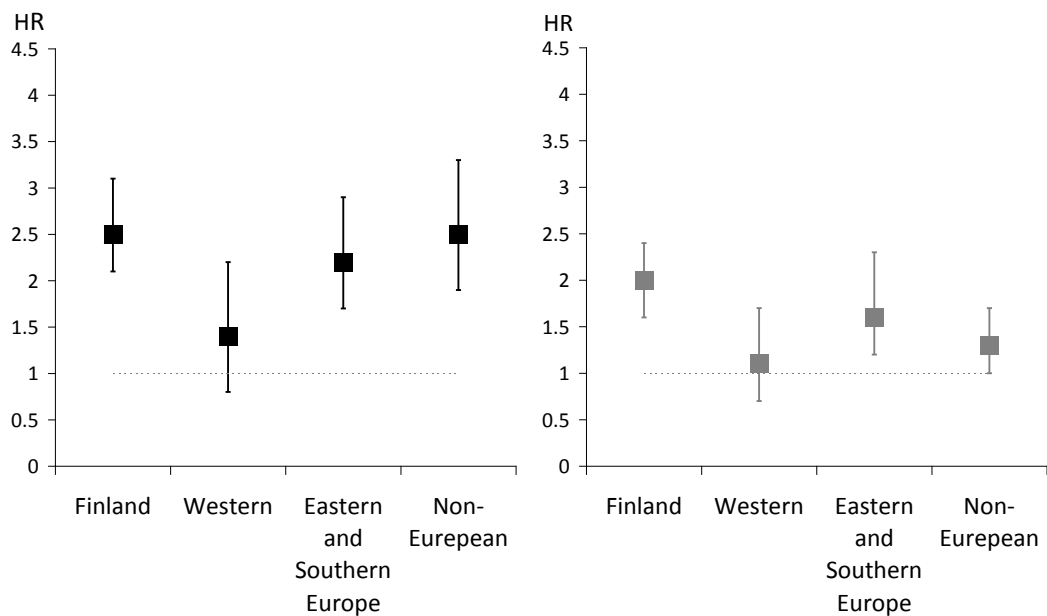


Figure 5. Hazard Ratios with 95% CI for schizophrenia in second generation immigrants compared with the Swedish majority population. Age and sex adjusted estimates to the left (black boxes), and additional adjustments for childhood socioeconomic disadvantage to the right (grey boxes).

### **5.3 CHILDHOOD SOCIOECONOMIC DISADVANTAGE AND GENETIC LIABILITY CONTRIBUTE INDEPENDENTLY AND JOINTLY TO THE RISK OF DEVELOPING PSYCHOSIS (STUDY III)**

An adoption design was used to study how socioeconomic disadvantage interact with genetic liability for psychosis. Consequently, the environmental factors were separated from the genetic components. Among 13,116 children born in Sweden 1955-1984 and reared in Swedish adoptive families, 230 were hospitalized for non-affective psychoses including schizophrenia during the follow-up period.

Separate analyses were performed for the three different socioeconomic variables. In each analysis, the adoptees were grouped into whether they were exposed only to the socioeconomic indicator, only to the indicator of genetic liability, or to both indicators of socioeconomic disadvantage and genetic liability and compared to the unexposed persons. There was some support that both genetic and socioeconomic indicators were independently associated with an increased risk of psychosis. Adoptees reared in families with parental unemployment (hazard ratio=2.0, 95% CI=1.0–4.2), in single-parent households (hazard ratio=1.2, 95% CI=0.6–2.6), or living in apartments (hazard ratio=1.3, 95% CI=1.0–1.8) and were without the presence of genetic liability had increased risk for psychosis. The risk for non-affective psychosis among persons with genetic liability for psychosis alone (without exposure to a less advantaged socioeconomic position in childhood) was increased (hazard ratio=4.7, 95% CI=3.1–7.2). The risks when being exposed to both types of indicators (socioeconomic disadvantage and genetic liability) were considerably higher. Thus, synergy indexes were estimated to test for an interaction effect between socioeconomic disadvantage and genetic liability. A synergy index larger than 1 indicated that the risk for those being exposed to both socioeconomic (rearing parental unemployment/single-parenthood/housing) and genetic (biological parental inpatient care for psychoses) factors was larger than the sum of the two risks for those being exposed to only one of them. There was some support for an interaction effect with the three synergy indexes being larger than 1, although only one of them was statistically significant (SI=3.2, 2.6 and 1.2). Analyses in the non-adoptive population supported these results.

### **5.4 SCHOOL PERFORMANCE WAS ASSOCIATED WITH LATER RISK OF SCHIZOPHRENIA AND OTHER PSYCHOSES, AND WAS TO A SMALLER EXTENT EXPLAINED BY PARENTAL SOCIOECONOMIC POSITION (STUDY VI)**

The study population consisted of 184,806 persons. During the follow-up period 222 cases of schizophrenia, 400 cases of other non-affective psychoses, and 282 cases of affective psychoses were identified.

Increased risk for psychosis was found in association with lower compared with midrange average grade (HR=1.9, CI=1.2-2.8 for schizophrenia in the lowest quintile, HR=3.0, CI=2.2-4.2 for other non-affective psychoses, and HR=2.3, CI=1.6-2.4 for affective psychoses). Increased risk was also found in the highest quintile for other non-affective and affective psychoses, but not for schizophrenia (HR=0.8, CI=0.6-1.3 for schizophrenia, HR=1.6, CI=1.1-2.3 for other non-affective psychoses, and HR=1.6,



CI=1.1-2.5 for affective psychoses). Adjustments for the socioeconomic indicators reduced the estimates somewhat.

Increased risks among those who did not complete upper secondary school, compared with those who did, were found for schizophrenia (HR=3.3, CI=2.5-4.3), other non-affective psychoses (HR=2.6, CI=2.1-3.2), and affective psychoses (HR=2.0, CI=1.5-2.6). Adjustments for average grade at age 16 reduced the estimates somewhat. Additional adjustments for socioeconomic position reduced the estimates to HR=2.6 (CI=1.9-3.5) for schizophrenia, HR=1.8 (CI=1.4-2.3) for other non-affective psychoses, and HR=1.7 (CI=1.3-2.3) for affective psychoses.

## 6 DISCUSSION

### 6.1 MAIN FINDINGS

#### 6.1.1 Childhood socioeconomic disadvantage was associated with later risk of psychoses

In these large population-based cohorts of two generations of Swedish residents, five out of seven indicators of childhood socioeconomic disadvantage were associated with later risk of schizophrenia and other psychoses. This was consistent in all the studies. Furthermore, a stronger association was found with an increasing number of exposures, suggesting a dose-response relationship. When this thesis was started most studies included only one, or perhaps two indicators of socioeconomic position in childhood or at birth, and the results were contradictory (21, 19, 20, 22, 23). One of the most commonly used measures, parental education, was not associated with psychosis at all in our data. Another often used indicator is socioeconomic classification (SEC). The only group within this classification with an increased risk for psychoses in my studies was the group 'others', which included those who were unemployed, had non-classified occupations, etc. All other groups in this classification refers to those in work (blue collar, white collar, self-employed), and may therefore not be an appropriate measure to use in studies of socioeconomic risk factors and psychoses. It is also possible that the group 'others' to a larger extent than the other groups, consists of people with more health problems. The results underline the importance of using more than just one or two indicators to capture the whole spectrum of the social situation. In contrast to earlier studies we had the possibility to study up to seven indicators of socioeconomic position in childhood. The majority of the different socioeconomic indicators used in study I-IV had a substantial part that was unique (table 2), with two exceptions. The correlation coefficient for single-parent household and housing was 0.41, and 0.77 for the association between employment and socioeconomic classification. Single-parent household and housing still have large unique aspects not covered by the other, while employment and socioeconomic classification (SEC), due to the construction of SEC, to a larger degree include the same aspects. The final model in study I (where several potential confounders were considered) show that the majority of the indicators of socioeconomic disadvantage were independently associated with an increased risk of schizophrenia and other psychoses (rented apartments, single-parent households, parental unemployment, and households receiving social welfare benefits). A few more studies of this subject including more than one indicator have been published since I started this work and they are at large in accordance with our results (24, 25). A review published in 2007 concludes that social factors may play an etiologic role in the development of schizophrenia (83).

By using an adoption design we were able to separate the indicator of genetic liability for psychosis (biological parental inpatient care for psychosis) from exposure to the indicators of socioeconomic disadvantage in childhood (measures of the rearing parents). Both the indicator of genetic liability and the indicators of childhood socioeconomic position were independently associated with an increased risk for psychosis. In addition, the risk for non-affective psychosis was further increased for

adoptees with genetic liability who also were reared in disadvantaged socioeconomic situations in childhood. This risk, when being exposed to both types of indicators, was larger than the sum of the two individual risks, suggesting an interaction effect. Interaction effects of socioeconomic disadvantage and genetic liability have not been studied before, but the results are in agreement with earlier studies of interaction effects between biological family history of psychosis and other environment factors such as urbanicity and parental rearing patterns (46-49). The results suggest that influencing the socioeconomic situation in childhood may have a positive effect on the risk of developing psychosis for children both with and without genetic liability for psychosis.

#### 6.1.2 Socioeconomic disadvantage contributes to the risk of developing psychoses among immigrants

First and second generation immigrants in diverse ethnic groups had increased risks of schizophrenia and other psychoses compared with the Swedish majority population. The increased risks found here are in accordance with several other studies from different countries (33-39). Notably, these risks were considerably reduced after adjusting for socioeconomic disadvantage, suggesting that socioeconomic disadvantage in the receiving country is part of the explanation of the increased risks for psychoses among immigrants. Other studies of first generation immigrants have also found this association with socioeconomic disadvantage (84, 85), which in contrast to second generation immigrants obviously could be due to social drift. The Finnish and the Eastern and Southern European immigrants had increased risks of schizophrenia and other psychoses even after adjusting for the socioeconomic factors and parental psychotic illness. The risks among non-Europeans and among those from Western countries were after adjustments reduced to the same level or lower compared with the Swedish majority population, suggesting that for these two groups, socioeconomic factors rather than ethnicity was the explanation for the increased risk. In first generation immigrants this could very well be due to social drift. Controlling for parental psychotic illness did not alter the results. The majority of first generation immigrants from Finland and Western countries immigrating before 1971 while the majority of the non-Europeans immigrated after 1970. Being the newest group of immigrants (nearly 37% immigrated between 1981 and 1985) the non-Europeans were more exposed to socioeconomic disadvantage due to the immigration situation.

The explanation for the increased risk, even after adjustments for socioeconomic disadvantage, in the Finnish people is difficult to identify. Cultural barriers, stressors of being a newcomer to the country, or exclusion due to ethnicity are not likely explanations. The Finnish immigrants could be considered as quite an assimilated group as they have an immigration history in Sweden since 1950s when they started to immigrate due to increased demand of labour in Sweden. Almost 68% of the Finnish immigrants in study II immigrated before 1971. Finland also has a Swedish speaking minority and many Finns were taught Swedish at school. On the other hand, as they are a comparatively assimilated immigrant group they live in areas where they are ethnically a smaller proportion, i.e. they are exposed to being a minority. A higher incidence of schizophrenia has been found in certain parts of Finland where many

immigrants originated (86). Selective migration, those who migrate are as a whole healthier than their origin population (87), could perhaps be part of an explanation in the sense that immigrants who become ill in Sweden may be less likely to return (migrate back) to their country of origin. However, further research is needed to understand the reasons for the increased risk for psychoses among first and second generation Finns.

### 6.1.3 School performance was associated with later risk of schizophrenia and other psychoses, and was to a smaller extent explained by parental socioeconomic disadvantage

Increased risks for schizophrenia, other non-affective psychoses, and affective psychoses were found in association with lower average grade on the leaving certificate from nine years of compulsory school. This is in accordance with another large Swedish study (55). A Finnish study showed no association between school performance and later psychoses (56). However, there are methodological differences. In the Finnish study they compared pupils with the average grade dichotomized into above and below the mean. Our data was classified into quintiles, thus the first quintile consisted of pupils with much lower average grades compared with a group with the cut-off below and above the mean. Increased risks were also found for other non-affective psychoses and affective psychoses in association with a high average grade on the leaving certificate. In contrast to two other studies (52, 53), no indication of such an association was found for schizophrenia, neither for men nor for women. The risk estimates were only to a smaller extent reduced after taking parental socioeconomic position into account.

Increased risks for psychoses were also found among those who did not complete upper secondary school compared with those who did. There is a social selection into upper secondary school and university (88), thus parental socioeconomic position could be part of an explanation. Adjustments for parental socioeconomic position represented by seven indicators reduced the estimates somewhat, suggesting that parental socioeconomic position is only a minor explanation of the association between psychoses and school performance.

## 6.2 POTENTIAL EXPLANATIONS FOR THE MAIN FINDINGS

Several of the socioeconomic factors can also be considered as indicators of different degrees of social exclusion. Unemployment among parents for example, means exclusion from the workforce and, to a large extent, other daily social contacts. It could also generate feelings of being excluded from contributing to the society, feelings of being needed, useful, etc. Poor financial resources limit the family's possibilities of housing accommodation, physical and social activities necessary to feel included in the society. The possibilities of recreation and recovery are also reduced. Notably, it is the social factors related to exclusion which are associated with increased risk of psychoses throughout the studies. Thus, it may be that it is not the gradient of socioeconomic position, but rather the excluding situation that influences the risk of developing psychoses. It was only the group 'others' (including

unemployment), in the measurement socioeconomic classification, that showed an association with increased risk for psychoses while the other groups, that indicates different work positions (blue collar, white collar, self-employed), were not associated with risk. Social exclusion has been associated with mental illness (43), as have several kinds of perceived discrimination such as skin colour, age, gender, and disability (44). To be part of a minority group could also be seen as an indicator of social exclusion. Perceived discrimination has also been associated with psychological distress (89). The size of the minority groups has also been associated with schizophrenia, with a greater incidence of schizophrenia among people of ethnic minorities living in areas with a smaller proportion of their own ethnic group (40, 41). Psychosis has also been associated with perceived disadvantage (45) and negative identification with your ethnic group (42), and feelings of social defeat (62).

In summary, a disadvantaged socioeconomic situation could lead to social exclusion, isolation, alienation, feelings of social defeat, and a stressful life situation. In a stressful life situation, there may also be fewer opportunities for social support and recreation, and these situations may be of importance in the development of psychosis in people with a biological vulnerability. Possible biological mechanisms, among several, could be the potential harmful effects by increased levels of the stress hormone cortisol. The individual vulnerability to cortisol levels may, in turn, be genetically determined (61). Another possibility is that stressful situations may influence the genetic expression (i.e., epigenetics) (90). The hypothesis that chronic experience of social defeat leads to disturbance of the mesolimbic dopamine system in the brain, which increases the risk for schizophrenia, has also been put forward (62).

The causal direction in the association between socioeconomic disadvantage and psychoses always has to be interpreted with caution since psychotic disorders have such obvious social effects that may precede the onset of the illness and may result in social downward drift. Goldberg even proposes that social drift may extend over several generations through hereditary factors (16). This was addressed in several ways in my studies. Firstly, by including two generations and using indicators of socioeconomic disadvantage in childhood based on information about the household/family the child lived in at the time (study I-IV). Thus, exposure is measured long before the onset of the outcome. Secondly, in study II the focus was on immigrants. First generation of immigrants tend to be exposed to socioeconomic disadvantage only due to the fact of being a newcomer to the country, rather than through social drift in generations. Thirdly, in study III an adoption design was applied to separate the indicator of genetic liability for psychoses (biological parental inpatient care for psychoses) from environmental exposure (socioeconomic indicators of the rearing parents). Finally, biological parental inpatient care for psychoses was considered in all analyses. This of course is not only an indicator of genetic liability. There are many social consequences of being reared by a parent with psychosis, such as your parent being socioeconomically disadvantaged, hospitalized and away from home. Thus, I believe that we have minimised the space of the social drift and that the results cannot readily be explained by social drift theory.

Several other possible explanations were explored, although the results were not markedly altered. Increased risks for schizophrenia has been associated with being

born in an urban area as well as living in an urban area (91, 4, 49, 92), with possible explanations such as greater risk of infections, polluted air, crowding, or selective migration from rural to urban areas. Urbanicity may also be associated with an increased risk for socioeconomic disadvantage, thus urbanicity was considered in study I, II, IV. Immigration was studied separately in study II, was not relevant in study III as the population consisted of Swedish-born persons only, and analyses were adjusted for immigration status in study I and IV. Advanced paternal age at the birth of the child (93-97) was considered in study I where it had no effect. Cannabis has been associated with schizophrenia (98) and with immigrants in Sweden (99). Parental inpatient care for substance abuse was considered in study I and II, although the effect may be underestimated because only a minor part of this diagnostic group has contact with inpatient care. Parental psychotic illness was part of the method in study III in we separated the indicator of genetic liability (biological parental psychoses) from environmental factors of the rearing parents, while excluding children with rearing parents with inpatient care for mental disorders. Biological parental inpatient care for psychosis was used as a crude indicator of genetic liability in the other studies, but it is obviously at the same time an indicator of all environmental factors that comes with being reared by a parent with psychosis. We did not consider parental age at the time of exposure, which in retrospect would have been beneficial as education, socioeconomic classification, and perhaps housing are dependent on age. However, as our populations are families the parental age-range is still limited and it is unlikely that this alone would explain the results. Thus, none of the above possible alternative explanations were valid.

All the indicators of socioeconomic position in this study were measurements in childhood (apart from the measurements for first generation immigrants), but it is likely that there is a strong correlation between exposure in early childhood and exposure in utero. We were not able to adjust for obstetric complications (100-102), maternal stress (103, 104) and infections (105-108). Thus, factors acting throughout foetal life and early life cannot be excluded. However, a recent study on Swedish data showed that the association between school performance and schizophrenia was not explained by obstetric complications (55).

### **6.3 STRENGTHS AND WEAKNESSES**

#### **6.3.1 Common to all studies**

These studies have some major advantages. Firstly, the studies are based on large national population-based cohorts, thus minimizing selection effects and allowing multivariate analyses due to sufficient number of cases. The number of cases in studies of schizophrenia and other psychoses has in earlier studies often been a problem. Secondly, exposure to socioeconomic position in childhood was measured long before the onset of adult psychoses, thus minimizing the effect of social drift. This is particularly important when studying the role of social factors on the risk of developing schizophrenia and other psychoses since the disorders have such adverse effects on the person's social situation. Using measurements in close timing to the onset will mostly describe the consequence of having schizophrenia, which is well documented. Thirdly, several different indicators of socioeconomic position were

used, thus covering a broader spectrum of socioeconomic position in comparison to using only one or two indicators. Finally, adjustments for several potential confounders were possible.

Socioeconomic position is a multidimensional construct consisting of several different factors which cannot be used interchangeably (30-32), thus the choice and the selection of included indicators of socioeconomic position is important. The studies in this thesis included a large number of different socioeconomic factors. However, these socioeconomic factors were crude and indirect measures. For example, most people who live in apartments or single-parent households do not suffer from social disadvantage, however it is likely that a larger proportion of those who for example live in single-parent households do, compared with those who live in two-parent households. The most disadvantaged variables available were social welfare benefits and unemployment. Thus, the effects of socioeconomic disadvantage could be underestimated. Furthermore, age at time of exposure varied and duration of exposure was not known. It is possible that exposure at a certain time in childhood is more important than other times (critical periods). Perhaps accumulation (found with other risk factors (109)), or cumulative exposure at one time, or during life (110) makes a difference. We did find a stronger association with an increasing number of exposures.

Possible sex differences in the association between socioeconomic position in childhood and later risk of developing schizophrenia and other psychoses was not elucidated in the analyses in study I or study II. However, additional analyses stratified for sex in study I showed no sex differences. The effect of the five indicators of socioeconomic disadvantage on the risk of developing schizophrenia and other psychoses was similar for men and women.

There are variations in coverage of inpatient care for psychoses for our populations due to the length of follow-up period in the NPR (1973-2006). For example, the youngest persons born in 1984 were only 22 years old at the end of follow-up. It is reasonable to assume that several will have their first inpatient episode at a later stage in life. Consequently, the results could be weaker due to some misclassification of the outcome.

The Swedish healthcare system has changed during the time of observation (68, 69). The policy today is to whenever possible treat patients in outpatient care rather than in inpatient care. Consequently, the outpatient care facilities have expanded and the number of hospital beds has shrunk. As a result, the less serious cases are treated in outpatient care today, whereas they may have been treated in inpatient care the earlier years. This misclassification probably means risk for more attenuated results. However, a recent Swedish study with access to psychiatric inpatient and outpatient care in Stockholm County showed that 75% of the patients (18-64 years of age) with non-affective psychoses were identified also in the inpatient care during the observation time of 1973 to 2006 (111). Thus, using inpatient data during this period is still valid.

Three diagnostic systems have been used during the time of the studies follow-up periods (ICD-8, ICD-9, and ICD-10). A Stockholm study found a decline from 1978 to

1994 in first admission rates for schizophrenia, but not for schizophrenia and paranoid psychoses combined (7). The authors concluded that this may be explained either by a true decline, or just as likely by changes over time in the application of clinical diagnoses. On the other hand, in a study of incidence in Nottingham during three time periods from 1978 to 1999 the authors concluded that there were indications that there has been a change in the syndromal presentation of non-affective disorders, away from schizophrenia towards other non-affective psychoses (112). Whether there are true changes in incidence, or changes due to the application of the different diagnostic systems or over time, it seems important to include more diagnostic groups than just schizophrenia, which is done in all the studies in this thesis.

We relied upon register-based clinical diagnoses of schizophrenia and other psychoses. The quality of these can be questioned, but several studies have shown that the validity in Sweden is appropriate for these types of epidemiological studies (113-115). Study II is sensitive to possible differences in the psychiatric care for immigrants. A review of British studies (116) showed some ethnic variation of pathways to care, while a Danish study did not find selective referral of immigrants to be of major importance (117). A Swedish study reported fairly equal access to care for ethnic minorities in Sweden (118). Another question is whether Swedish psychiatrists have a tendency to use the label schizophrenia more often if a psychotic patient belongs to an ethnic minority with different cultural norms, as studies in the USA have suggested (119, 120). Further studies are needed to address this concern in Sweden

### 6.3.2 Study specific strengths and limitations

#### 6.3.2.1 *Study II*

The concept of second generation immigrants could be questioned as 35% of the children and youths had been exposed to immigration themselves, although the majority before school age (21%). Nevertheless, multivariate analyses within this group, comparing those born in Sweden with those born outside Sweden, indicated that the experience of immigration in itself during childhood was of little importance for the risk of developing psychoses.

As schizophrenia and other psychoses are such rare disorders we had to create large groups of heterogenic ethnicity, with the exception of the Finns. Conclusions about the specific groups are therefore limited.

The study population consisted of individuals living in households with children. Since it is quite possible that families are particularly important as sources of social support for immigrants and the situation of elderly immigrants differs from younger immigrants, the results cannot be generalised to immigrants in households without children, nor to the elderly or to the recently settled.

It could be argued that the analyses for the second generation immigrants in study II should have included adjustments for parental inpatient care for psychosis in a model before adjustments for socioeconomic position, due to possible confusion of genetic and environmental factors (parental social drift due to parental psychoses). However,



reanalyses in this order did not change the results. The major reduction of the estimates was introduced with the adjustments for childhood socioeconomic disadvantage, not with parental inpatient care for psychosis. The same relates to study IV, although the effect of the socioeconomic position was at a lower level.

#### *6.3.2.2 Study III*

The strength was the adoption design which enabled separation of socioeconomic position during childhood (in the rearing family) and genetic liability for psychosis (biological parental psychotic illness), allowing us to study the effect of socioeconomic position in childhood and genetic liability independently, as well as to study potential interaction effects of being exposed to both. Several methods were used to separate the two types of exposure as much as possible. Children were excluded if they lived with a biological parent at any census during 1–15 years of age, if their rearing parents had psychiatric admissions during the adoptees childhood or early adulthood, if they were not living in family households between 1-5 and 6-10 years of age, or if they were adopted by a grandparent or sibling. Age at adoption was unknown, but 97% of the children lived with their adoptive parents at their first census. Other studies have shown that the majority of the adoptees were adopted very early, most of them in infancy (121, 122).

Since the children were born between 1955 and 1984 their parents were of various ages during the time of national coverage of psychiatric inpatient care in the NPR (1973–2006). In addition, a considerable number of biological fathers were unidentified (41%), although not unexpected in a population of intracountry adoptees at this time. There were no differences between those with identified biological fathers relative to those with unidentified biological fathers regarding the proportion of maternal psychosis or the adoptee's own psychotic illness. However, the proportion of adoptees with genetic liability for psychosis is most likely underestimated which in turn would attenuate the results rather than overestimate them.

The potential impact of adoption (unwanted child, non-optimal pregnancy, risk of poor antenatal care, increased occurrence of psychiatric illness, etc.) was controlled for by making analyses only within the population of adopted children (i.e., they were all exposed to the circumstances of adoption). However, it is possible that adopted children relative to the general population are more sensitive to environmental adversities as a result of the possible impact of adoption. As a comparison and to gain statistical power the total Swedish population of non-adoptees was analysed. These analyses supported the result in the adoptee population, although the interaction effect sizes were smaller (but significant), because of the more imprecise indicator familial history of psychosis.

#### *6.3.2.3 Study IV*

In this study two indicators of school performance were used, average grade at graduation from compulsory school and completion of upper secondary school. It is important to keep in mind that school performance is a complex measure which includes several different aspects such as cognitive ability as well as language capacity, motivation, and capability to adjust to the school system.

To avoid reversed causation, i.e. the effect of psychosis on school performance, we excluded those who had inpatient episodes for psychosis before, or at any time during the first five years after completed compulsory school, i.e. all individuals were psychoses free (no inpatient care for psychoses) until five years had passed since graduation. We would most likely have had higher estimates had we dropped this inclusion criterion.

A newly immigrated student will at first be concentrating on learning Swedish, and the grades may be negatively affected due to language difficulties. Other aspects of being new in a country will probably also influence the school performance. Consequently, the inclusion criterion for immigrants was for the immigration date to be earlier than two years before graduation from compulsory school.

## **6.4 CONCLUSIONS**

To conclude, the main results of these national population based cohort studies of two generations indicates that socioeconomic disadvantage during childhood or foetal life contributes to the risk of developing schizophrenia and other psychoses. Furthermore, this risk may even be relatively higher in individuals with a genetic liability for psychosis. Thus, influencing the social situation in childhood may have beneficial effects on the occurrence of psychosis. Socioeconomic disadvantage may also contribute to the increased risk of psychoses in immigrants. However, childhood socioeconomic factors did not substantially affect the risk of psychoses associated with low school performance. In summary, there is support for social disadvantage in the aetiology of psychosis. This knowledge may open up for preventive methods on a societal level, perhaps targeting vulnerable groups as immigrants and individuals with genetic liability. Apart from the obvious individual gains of reduced suffering, this could lower the community's costs for inpatient days, outpatient visits, medication, sick-leave and pension costs, but also the cost of a young person perhaps not working (loss of productive years) etc. Prevention programs at community/society level could possibly be beneficial not only for people at risk for psychoses but also for other vulnerable groups.

## **6.5 FUTURE DIRECTIONS**

These studies underline the importance of using more than one indicator of socioeconomic disadvantage. They are all measuring different aspects. Five out of the seven measures may contribute to the risk of developing psychoses later in life. It would be useful with studies of a more qualitative design to elucidate exactly what the important aspects behind these indicators are.

It would also be interesting to investigate how neighbourhood socioeconomic disadvantage during childhood is associated with psychoses, to use measures on an individual and neighbourhood level.

It would also be of importance to further investigate the unexplained increased risk for psychoses among the Finnish immigrants. If the explanation is found perhaps a directed preventive program could be developed.

It is difficult to assess what the different independent aspects of the socioeconomic factors represent in register studies like these. Further research with a more qualitative design is needed to elucidate the mechanisms underlying the observed patterns of association.

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