Clinical Phenotype and Genetic Epidemiology of Schizophrenia in a Finnish Isolate

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Academic Dissertation

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Appendix 1 Operational Criteria Checklist for Psychotic Illness 88
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Skitsofrenia on vakava mielenterveyden häiriö. Skitsofreniaa esiintyy kaikkiällä maailmassa. Skitsofrenian esiintyvyys vaihtelee, mutta elinaikainen sairastumisriski on keskimäärin 0,4-0,7%. Perinnöllinen alttius on sairauden merkittävä riskitekijä. Jos perheen molemmat vanhemmat ovat sairaita, on lapsen sairastumisriski 50-kertainen väestötason riskiin nähden.


Väitöskirjatyössä keskityttiin tutkimaan skitsofrenian elinaikaisesta esiintyvyyttä, ilmaantuvuutta ja diagnoosien luotettavuutta sekä skitsofrenian ilmisuuta ja periytyviä piirreominaisuuksia (fenotyypiä) Kuusamosta lähtöisin olevissa perheissä. Tämä väitöskirjatyö on osa laajempaa Kansanterveyslaitoksen vakavien mielenterveyden häiriöiden geneettistä epidemiologiaa ja molekyyligenetiikkaa koskevaa hanketta, jota toteutetaan Mielenterveyden ja Alkoholitutkimuksen osastolla yhteistyössä Molekyylilääketieteen osaston kanssa.


Skitsofrenian esiintyvyys oli isolaatissa kansainvälisesti korkea sekä rekisterien (1,5%), konsensusdiagnoosien (0,9-1,3%) että haastattelun (0,7-1,2%) perusteella. Skitsofreniadiagnoosi piti konsensusdiagnoosin perusteella paikkansa 69%:lla ja haastattelun perusteella 63%:lla niistä potilaista, joilla oli rekisteritietojen perusteella skitsofrenia, skitsoaffektiivinen tai skitsofreniforminen psykoosi. Ne skitsofreniaa sairastavat potilaat, joilla oli sairaita sisarukseja, edustivat familiaalista skitsofreniaa. Siitä liittyi korostetusti skitsofrenian negatiivisista oireista tunteiden latistumista ja puheen köyhtymistä. Toisaalta isolaatista lähöisin olevien potilaiden oirekuvassa oli vähemmän skitsofrenian positiivisia oireita eli aistiharhoja ja harhaluuloja kuin koko maan monisairaiden perheiden potilailla. Rekisteritietojen mukaan terveistä sisarukseista 16% sairasti haastattelun perusteella psykoottista häiriötä. Heistä 7,7%:lla oli ollut psykoottisia oireita jo ennen rekisteritietojen seulontaa ja lisäksi 8,7% oli saanut psykoosidiagnoosin suhteellisen pian seurannan aikana ennen tutkimuksen alkua.

Yhteenvetona todetaan, että skitsofrenian esiintyvyys oli tarkasti geneettisesti määriteltyssä isolaatissa kansainvälisesti korkea kolmella eri menetelmällä arvioituna. Uusina löydöksinä tuli esiin myös se että, isolaatin potilaiden oirekuvassa oli vähemmän harhaluuloja ja aistiharhoja kuin koko maan monisairaiden perheiden potilaissa. Tämä ilmiasu saattaa ilmentää skitsofrenian periytyvää piirreominaisuutta. Pelkästään rekisteritietojen ei voida käyttää skitsofreniaa sairastavien potilaiden terveiden sisarusten seulontaan geneettisissä tutkimuksissa varten, koska 7,7%:lla terveistä sisarukseista oli haastattelun perusteella psykoottisia oireita jo ennen seulontaa. Geneettisiä tutkimuksia varten rekisteridiagnosin vaihtoehtoista on siten varmennettavaa diagnostisella haastattelulla tai sairauskertomuksista johdettavan konsensusdiagnoosin avulla. Strukturoitua haastattelua suositellaan myös kliiniseen käyttöön parantamaan diagnoosien luotettavuutta sekä silloin, kun skitsofreniaa sairastavan potilaan lähiomainen hakee apua päihde- tai mielenterveyden ongelmiin.

Asiasanat: skitsofrenia, esiintyvyys, diagnoosi, oireet
ABBREVIATIONS

APA       American Psychiatric Association
BPRS      Brief Psychiatric Rating Scale
CI        Confidence Interval
CODE-295  Register diagnosis of schizophrenia, schizoaffective or schizophreniform disorder
CPRS      Comprehensive Psychopathological Rating Scale
DSM       Diagnostic and Statistical Manual of Mental Disorders
DSM-III   Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-III-R Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised
DSM-IV    Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
GAF       Global Assessment of Functioning
GEE       General Estimation Equations
ICD       International Classification of Diseases
ICD-8     International Classification of Diseases, Eight Edition
ICD-9     International Classification of Diseases, Ninth Edition
ICD-10    International Classification of Diseases, Tenth Edition
IM        Isolate Multiplex patients
IS        Isolate Singleton patients
MSSS      Major Symptoms of Schizophrenia Scale
NOS       Not otherwise specified
NM        National (whole country) Multiplex patients
OCCPI     Operational Criteria Checklist for Psychotic Illness
OPCRIT    Computer program for the OCCPI
OR        Odds Ratio
p, p-value Significance Probability
PANSS     Positive and Negative Syndrome Scale
PSE       Present State Examination
RDC       Research Diagnostic Criteria
SANS      Scale for the Assessment of Negative Symptoms
SAPS      Scale for the Assessment of Positive Symptoms
SCID      Structured Clinical Interview for DSM
SD        Standard Deviation
SDS       Schedule for the Deficit Syndrome
WHO       World Health Organization
1. ABSTRACT

Schizophrenia is a severe mental disorder, its prevalence averaging 0.4-0.7% worldwide. The largest and best documented risk factor related to the development of schizophrenia is genetic risk. The lifetime risk of schizophrenia increases with each affected relative, up to nearly 50% when both parents are affected. Schizophrenia is a complex clinical syndrome. It can be recognized and defined with reasonable agreement but we have no laboratory or other objective test to diagnose it. The present study focuses on the assessment of prevalence of schizophrenia, on the reliability of the schizophrenia diagnosis, on phenotype analysis, and on the signs and symptoms of schizophrenia in an isolate. We also investigated whether siblings of patients with schizophrenia can be identified as not having any psychotic disorder using health care register information only. This study is part of a larger investigation called "The Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland", conducted at the National Public Health Institute as a collaboration between the Department of Mental Health and Alcohol Research and the Department of Molecular Medicine.

In our study we utilized three nationwide health care registers: 1) the Hospital Discharge Register, 2) the Free Medication Register, and 3) the Disability Pension Register, plus the National Population Register, in order to identify all schizophrenia patients born from 1940 to 1976 (N=33731) in Finland, and their first-degree relatives. Patients with at least one parent born in a specific genetic homogeneous isolate in north eastern Finland were identified, as well as familial schizophrenia patients with at least two affected siblings from the whole country. In addition, the study included a population-based comparison group derived from the Health 2000 Study. Between 1991 and 2002 we contacted all isolate patients (N=658) and multiplex patients (N=4904) from the whole country with at least two affected siblings in the family in order to take blood samples for genetic studies. We also collected case records and reassessed the register diagnosis. Were recontacted the isolate patients and a random sample of multiplex patients from the whole country in 1998-2002 to make diagnostic clinical interviews and to assess
the negative and positive symptoms and signs of schizophrenia for phenotype studies. We also interviewed siblings of schizophrenia patients who were initially healthy according to the Hospital Discharge Register. We followed them for seven to 11 years to monitor any emergence of psychotic disorders.

Our main findings were that the prevalence of schizophrenia was relatively high based on register (1.5%), case record (0.9-1.3%), and interview data (0.7-1.2%). Of those with a register diagnosis of schizophrenia, schizoaffective or schizophreniform disorder, 69% received a record-based consensus diagnosis and 63% an interview diagnosis of schizophrenia. Schizophrenia patients with first-degree relatives with psychotic disorder had more severe affective flattening and alogia as negative symptoms than those who were the only affected individuals in their family. However, isolate patients had less positive symptoms than the whole Finland familial patient group. When we interviewed the initially healthy siblings of schizophrenia patients, the emergence of illness in these siblings during a relatively short follow-up was high (8.7%). In addition, 7.7% of siblings had psychotic symptoms already before the register diagnoses were identified in 1991.

The prevalence of schizophrenia in the genetically homogeneous isolate assessed using three methods was relatively high. A novel finding was that the isolate patients, regardless of their familial loading for schizophrenia, had less delusions and hallucinations than the whole country familial patients, which may be related to the genetic homogeneity in the isolate. This phenotype feature encourages the use of endophenotypes in genetic studies instead of reliance of diagnoses alone. In addition, we found that the absence of register diagnosis cannot be used in molecular genetic studies to confirm that siblings are healthy. For genetic research the register diagnosis should be reassessed using either a structured interview or a best-estimate case note consensus diagnosis. Structured clinical interview methods should be used also when first-degree relatives of schizophrenia patients seek help for any mental, alcohol or substance use problems.

Keywords: schizophrenia, prevalence, diagnosis, familial, phenotype, symptoms, isolate
2. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications.


3. INTRODUCTION

Schizophrenia is a severe mental disorder, the prevalence of which varies from 0.4 to 0.7% worldwide (Saha et al. 2005). Schizophrenia often begins early in life and leads to severe psychosocial impairment. It brings great suffering for both patients and their families. First degree relatives of schizophrenia patients have 10-fold risk of developing schizophrenia compared to the general population (Austin 2005, Gottesman 1994, Kendler et al. 1993a,b, 2000, Varma 1997). Certain environmental risk factors also increase the risk of schizophrenia. Some of these risk factors operate on an individual level and some on a societal level, but all need to be considered in the context of schizophrenia as a lifelong brain disorder (Cannon and Clarke 2005). However, the etiology and pathophysiology of schizophrenia remain to be elucidated.

It has become relatively simple to localize and characterize genes for monogenic disorders. However, the situation is quite different in complex psychiatric disorders, which are influenced by multiple genes and their interactions. Finding susceptibility genes for complex disorders may be possible by using trait-like variables associated with the disorder as phenotypes in genetic studies. This effort to identify intermediate phenotypes or endophenotypes is driven by the idea that they involve the same biological pathways as the disorder but are closer to the relevant gene action than the categorical diagnoses, thus adding power to genetic studies. The endophenotypes are assumed to have a simpler genetic architecture than their corresponding disorder (Freedman et al. 1999). An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, neuropsychological or a personality trait, and it may provide simpler clues to the genetic and environmental underpinnings than the disease syndrome itself. Hence, in patients and their apparently healthy first-degree relatives it should be more prevalent than in the general population (Weiser et al. 2005b).

The signs and symptoms of schizophrenia are diverse and almost every aspect of cognition and behavior are affected (see Appendix 1, 2 and 3). No single one of these many signs and symptoms can be considered to be pathognomonic. Unfortunately, we have no laboratory or other objective tests to diagnose schizophrenia and thus accurate observation and recording of signs and symptoms is generally the only way of forming a reliable diagnosis of schizophrenia. However, each symptom is present in some patients, but none is present in all. Schizophrenia is a heterogeneous "group of schizophrenias" (Andreasen 1995, Andreasen et al. 1995a). The complexity of schizophrenia is so great that some early
investigators challenged whether it could be defined with adequate precision to achieve good reliability among clinicians and investigators (Kreitman et al. 1961, McCormick and Flaum 2005). However, the World Health Organization and the American Psychiatric Association produced criterion-based systems for diagnosing schizophrenia that have been shown to improve reliability. The most recent versions were used in this study (World Health Organization 1993, American Psychiatric Association 1994).

"The Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland" project, was initiated in 1988. For our study we selected one of the largest rural municipalities in the eastern part of Finland, known to have a high prevalence of schizophrenia. Its population (17000) has a history of isolation, making it genetically homogeneous and thus providing an excellent basis for genetic studies. It also has a straightforward health service system ideal for clinical study purposes. The current thesis forms part of that project.
4. REVIEW OF THE LITERATURE

4.1 Epidemiology of schizophrenia

4.1.1 Prevalence of schizophrenia

Although schizophrenia occurs throughout the world, its prevalence has been reported to vary considerably. Torrey (1987) published a review article including 70 prevalence studies. In the latest systematic review of the prevalence of schizophrenia Saha and colleagues (2005) identified 188 studies from 46 countries published 1965-2002. The median values per 1000 persons (10%-90% percentiles) for the distributions of point, period, lifetime, and lifetime morbid risk were 4.6 (1.9-10.0), 3.3 (1.3-8.2), 4.0 (1.6-12.1), and 7.2 (3.1-27.1), respectively (Saha et al. 2005). Studies with the highest quality scores had significantly higher prevalence estimates. The median value for lifetime prevalence of schizophrenia was 0.40%, with a range of 0.2-1.2%. Prevalence estimates varied considerably. The review paper of Goldner and colleagues (2002) estimated the prevalence rates from 18 studies. The lifetime prevalence of schizophrenia varied from 0.12% (Chen et al. 1993) to 1.6% (Canino et al. 1987) and that of schizophrenia spectrum disorders from 0.4% (Oakley-Brown et al. 1989) to 2.2% (Lehtinen et al. 1990). In the Goldner et al. (2002) study, the best-estimate rate for lifetime prevalence of schizophrenia, 0.55% (0.37-0.8), was higher than Saha and colleagues (2005) found. The lifetime prevalence varied 13-fold. The lowest prevalence rates of schizophrenia were found in Asian populations (Hwu et al. 1989, Oaklay-Brown et al. 1989).

In Finland the lifetime prevalence of schizophrenia was 1.3% in the Mini-Finland Health Survey, which used the Present State Examination interview (Lehtinen et al. 1990), and 1.2% in our earlier register based study (Hovatta et al. 1997). Geographically, the prevalence is highest in eastern and northern Finland and lowest in the southwest (Salokangas et al. 1987, Lehtinen et al. 1990, Hovatta et al. 1997, Korkeila et al. 1998). In addition, the prevalence of schizophrenia was reported to be 1.7% in one isolate in North Sweden, which was founded by three Finnish families in the early 17th century (Böök et al. 1978, Jokipii 1992).

In isolated populations, the lifetime prevalence has varied from 0.1% (Chen et al. 1993) to 2.2% (Hovatta et al. 1997). Some religious groups have very low prevalence estimates, e.g. 0.03% for Amish (Egeland and Hostetter 1983) and 0.13% for Hutterite individuals (Nimgaonkar et al. 2000). There is also small area variation in the prevalence rates of schizophrenia within homogeneous populations, such as communities in rural Ireland (Youssef et al. 1999, Scully et al. 2004).
4.1.2 Incidence of schizophrenia

The incidence of a disease is a measure of the number of new cases that occur in a population over a given period of observation. Cumulative incidence is an estimate of the probability of the occurrence of an outcome over a specified period of time. The incidence of schizophrenia was estimated in a systematic review article of McGrath et al. (2004a). They analyzed 55 core studies from 33 countries finding, a median value (10%-90% percentiles) for incidence of 15.2 (7.7-43.0) per 100 000 person years. Males had a significantly higher incidence rate than females, while urban born and migrants had higher rates than rural and native-born individuals.

In Finland, the incidence of schizophrenia and schizophreniform disorder was estimated to be 36 per 100 000 person years by Salokangas (1993), and 69 per 100 000 person years for all non-affective psychotic disorders based on the Finnish Hospital Discharge Register (Korkeila et al. 1998). According to a register based study of Finnish birth cohorts born 1954-1965, the incidence of schizophrenia has declined in Finland (Suvisaari et al. 1999), which suggests that some risk factors may have diminished in intensity.

4.1.3 Schizophrenia and migration and geographical variation in occurrence of schizophrenia

The meta-analysis and review by Cantor-Graae and Selten (2005) confirmed that personal or family history of migration is a risk factor for schizophrenia.

The rural/urban disparity in the occurrence of schizophrenia is marked; prevalence and incidence rates are repeatedly found to be higher in urban areas (Mortensen et al. 1999, Schelin et al. 2000, McGrath et al. 2004a). Both urban birth and upbringing have been associated with increased risk of developing schizophrenia in adulthood (Lewis et al. 1992, Marcelis et al. 1998, Mortensen et al. 1999, Van Os et al. 2001). However, Saha and colleagues (2005) found significant difference in incidence but no difference in prevalence of schizophrenia between urban, rural and mixed sites. Native-born and individuals from "least developed countries" had lower prevalences of schizophrenia than immigrants or individuals from "emerging" or "developed" countries.

Finland appears to be an exception in this regard, as both the prevalence and incidence rates of schizophrenia have been higher in rural areas (Suominen 1975, Lehtinen et al. 1990). However, in a more recent study the incidence among cohorts born 1965-1969 seemed to be already higher in urban-born than rural-born individuals, contrasting with a higher incidence in rural cohorts born in the 1950s (Haukka et al. 2001).
4.1.4 Gender differences in prevalence and age of onset of schizophrenia

In a meta-analysis Aleman and colleagues (2003) analyzed 38 studies and provided evidence for a sex difference in the risk of developing schizophrenia. The risk remained significantly higher in men after controlling for potentially confounding factors. However, Saha and colleagues (2005) found no difference between males and females in their systematic review of the prevalence of schizophrenia.

Depending on the operational definition of illness onset, age at onset was 3.2-4.1 years higher for women than men (Häfner 2003). However, several previous Finnish studies have found no gender differences in the age of onset (Hovatta et al. 1997, Salokangas 1993, Suvisaari et al. 1998).

4.2 Methods of assessing genetic and environmental risk factors

4.2.1 Family studies

Family studies of schizophrenia have established that schizophrenia strongly aggregates in families. The lifetime risk increases with each affected relative, to nearly 50% when both parents are affected (McGuffin et al.1995).

Pooled data from more than 40 Western European systematic family and twin studies between 1920 and 1987 suggest that the lifetime risk of schizophrenia in siblings of schizophrenic probands is about 9% (Gottesman 1994). The Roscommon study (Kendler et al. 1993a), which interviewed patients with schizophrenia and their first-degree relatives, found a 9.2% morbid risk of schizophrenia in siblings. The overall risk of an interview-based diagnosis of schizophrenia was 6.5% among relatives. The risk for all non-affective psychosis was 10.0%. Varma and colleagues (1997) found that the morbid risk of schizophrenia in siblings was 8.7% in a study of 1089 first-degree relatives of schizophrenic patients.

The current evidence suggests that familial liability to schizophrenia increases not only the risk of schizophrenia as narrowly defined, but also that of personality disorders of the schizophrenia spectrum and probably several psychotic illnesses, including major depressive disorder with psychotic features (Kendler et al. 1993a,b, 2000, Cardno et al. 2002a, Chang et al. 2002, Weiser et al. 2005a).

In high-risk studies, individuals - usually the offspring of schizophrenia patients - with higher risk of developing schizophrenia than in the general population, are identified in childhood and followed to adulthood through the risk period for developing schizophrenia. The best known high-risk studies are the Copenhagen High Risk Project (Cannon and Mednick 1993), the New York High-Risk Project (Erlenmeyer-Kimling et al. 1997), and the Israeli
High-Risk Study (Ingraham et al. 1995); the cumulative incidence of schizophrenia in these studies was 16.2%, 13.1%, and 8.0%, respectively. Results from all the high-risk studies support the familial liability to schizophrenia.

Finland’s Helsinki High-Risk Study analyzed offspring born between 1960 and 1969 to mothers with schizophrenia, schizoaffective disorder, other schizophrenia-spectrum disorders, or affective disorders. The cumulative incidence of schizophrenia was 6.7% among the offspring of mothers with schizophrenia. The offspring of mothers with a psychotic disorder had a heightened risk of developing a wide range of severe mental disorders (Niemi et al. 2004).

### 4.2.2 Twin studies

Twin studies are based on the assumption that monozygotic (MZ) and dizygotic (DZ) twins share a common environment to approximately the same degree. However, MZ twins are genetically identical, whereas DZ twins are like siblings and have on average only half of their genes in common. Sullivan and colleagues (2003) assessed in their meta-analysis of 12 published twin studies of schizophrenia that the point estimate of heritability in liability to schizophrenia was high, at 81% (95% CI 73%-90%), and they also determined that there was small but significant and interesting common environmental effect on liability to schizophrenia: 11% (95% CI 3%-19%). In a Finnish twin cohort born from 1940 to 1957 with 2495 monozygotic and 5378 same-sex dizygotic twin pairs the lifetime prevalence of schizophrenia was 2%; the heritability estimate for liability to schizophrenia was 83% for genetic factors and the remaining 17% was due to unique environmental factors (Cannon et al. 1998). The heritability estimates in these studies are, of course limited to twins.

### 4.2.3 Adoption studies

Adoption studies can clarify the role of genetic and environmental factors in the transmission of schizophrenia by examining two kinds of rare but informative relationships: individuals who are genetically related but do not share a familial-environmental factor, and individuals who share familial-environmental factors but are not genetically related (Kendler 2000).

The largest study to use the affected adoptee design was the Danish Adoption Study of schizophrenia (Kendler and Gruenberg 1984, Kety et al. 1994). The findings included a 10-fold greater prevalence of schizophrenia among biological than control relatives of adoptees with chronic schizophrenia as well as other schizophrenia spectrum disorders.

The largest study using the affected biological parent design was the Finnish Adoptive Study of Schizophrenia (Tienari and Wynne 1994, Tienari et al. 2000, 2003), which found a significantly greater lifetime prevalence, 6.7%, among 164 index adoptees compared with a 2% prevalence of schizophrenia among 197 control adoptees. The genetic liability extended to a broad spectrum of other psychotic and non-psychotic disorders.
4.3 Symptoms and signs of schizophrenia

The signs and symptoms of schizophrenia are complex and diverse, encompassing almost every aspect of cognition and behavior. To simplify the complexity, schizophrenia has been divided into negative and positive symptoms (Andreasen 1983, 1984) (see also Appendix 2 and 3). However, when the inter-relationship between these negative and positive symptoms was studied using factor analysis, it was recognized that positive symptoms should be further subdivided into "psychotic" and "disorganized" groups (Andreasen et al. 1995a,b). Grube and colleagues (1998) also found these three factors in their meta-analysis, which included 10 factor analytic studies from the years 1982 to 1993. Further, subdivisions of symptoms and signs of schizophrenia have been analyzed in several studies to improve the phenotype description for genotype studies. Positive symptoms have been divided into hallucinations and delusions. Kimhy and colleagues (2005) further divided delusions into three factors; delusions of influence, self-significance, and persecution. Negative symptoms have also been divided into several factors (Blanchard and Cohen 2005).

In a Helsinki High-Risk follow-up, 179 offspring were born to mothers with schizophrenia, schizoaffective disorder, other schizophrenia spectrum disorders, and affective psychoses. Maternal symptoms were analyzed and divided into four factors: negative, positive, catatonic and affective symptoms. High maternal positive symptoms were found less harmful to the child than other psychotic symptoms (Niemi et al. 2004). Salokangas (1997) analyzed 156 first-contact patients and re-examined them two and five years thereafter. He found five major dimensions: a fairly stable negative dimension, plus delusional, hallucinatory, disorganization, and depressive dimensions. The negative dimension was already present at the onset of the disorder. However, the syndrome structure was more complex and varied considerably with the duration of the illness.

A variety of instruments have been used to assess symptoms of schizophrenia. These instruments include the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (Kay et al. 1987), the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al. 1978), the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962, Hedlund and Vieweg 1980), the Major Symptoms of Schizophrenia Scale (MSSS) (Kendler et al. 1993a), and the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al. 1989).

We concentrated on studies which have used the Operational Criteria Checklist for Psychotic Illness (OCCPI) (McGuffin et al. 1991) or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984).
4.3.1. Studies based on the Operational Criteria Checklist for Psychotic Illness

The Operational Criteria Checklist for Psychotic Illness (OCCPI), is an instrument that has been widely used in phenotype definition (Table 1). It has a categorical definition of symptoms and no built-in positive or negative subscales. Most of the studies have found four or five factors in the factor analysis, including negative, positive and disorganized factors. Some of the findings are presented in Table 1. Familial aggregation was found for negative symptoms (Van Os et al. 1997, Cardno et al. 2001, Wickham et al. 2001), and for disorganized symptoms (Cardno et al. 1997, 2001, Wickham et al. 2001). Serretti et al. (1996) replicated the factor analysis in two independent large samples and found that the four-factor structure had strong construct and content validity. However, Serretti and Olgiati (2004) later added the negative factor to the symptomatology of major psychosis. Symptom factors also correlated with clinical variables (Van Os et al. 1999, Rosenman et al. 2000, McIntosh et al. 2001).

In addition, Kendler and colleagues (1998) combined the OCCPI and the Major Symptoms of Schizophrenia Scale (MSSS) and found that relatives had increased risk of schizophrenia but also of a wide range of psychotic disorders.
Table 1. Factor analytic studies based on Operational Criteria Checklist for Psychotic Illness (OCCPI)

<table>
<thead>
<tr>
<th>Authors and year of study</th>
<th>Country</th>
<th>N</th>
<th>Male %</th>
<th>Mean age years</th>
<th>Diagnostic method</th>
<th>Diagnoses Liability classes(6)</th>
<th>Number of included OCCPI items</th>
<th>Number and names of the factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardno et al. 1996</td>
<td>UK</td>
<td>102</td>
<td>67 %</td>
<td>45.1</td>
<td>DSM-III-R(1)</td>
<td>Lc 1</td>
<td>21</td>
<td>5: Paranoid, negative, disorganization, first-rank delusions, hallucinations</td>
</tr>
<tr>
<td>Serretti et al. 1996</td>
<td>Italy</td>
<td>1004</td>
<td>56 %</td>
<td>42.1</td>
<td>DSM-III-R(1)</td>
<td>Lc 1-4</td>
<td>38</td>
<td>4: excitement, depression, disorganization, delusion</td>
</tr>
<tr>
<td>Cardno et al. 1997</td>
<td>UK</td>
<td>66</td>
<td>58 %</td>
<td>36.6</td>
<td>RDC(2)</td>
<td>Lc 1-4</td>
<td>19</td>
<td>8: positive formal thought, first-rank delusions, hallucinations, inappropriate affect/ bizarre behavior, negative, grandiose/bizarre delusions, delusions of influence/ persecution, and other hallucinations</td>
</tr>
<tr>
<td>Van Os et al. 1997</td>
<td>UK</td>
<td>150+</td>
<td>64 %</td>
<td>26.4</td>
<td>RDC(2)</td>
<td>Lc 1-4</td>
<td>20</td>
<td>7: inappropriate-catatonia, delusions-hallucinations, mania, insidious-blunting, depression, lack of insight, paranoid delusions</td>
</tr>
<tr>
<td>Kendler et al. 1998</td>
<td>Ireland</td>
<td>343+</td>
<td>64 %</td>
<td>42.3</td>
<td>DSM-III-R(1)</td>
<td>Lc 1-4</td>
<td>64</td>
<td>6: classic schizophrenia, depression, schizophreniform, bipolar-schizomania, schizophrenia-depression, hebephrenia</td>
</tr>
<tr>
<td>Cardno et al. 1999</td>
<td>UK</td>
<td>191</td>
<td>70 %</td>
<td>42.0</td>
<td>DSM-IV(3)</td>
<td>Lc 1-2</td>
<td>26</td>
<td>4: positive, disorganization, negative, first-rank delusions</td>
</tr>
<tr>
<td>Serretti and Olgiati 1999</td>
<td>Italy</td>
<td>108</td>
<td>41 %</td>
<td>52.2</td>
<td>DSM-III-R(1)</td>
<td>Lc 3, only delusional disorder</td>
<td>11</td>
<td>4: core depressive, hallucinations, delusions, irritability symptoms</td>
</tr>
<tr>
<td>Van Os et al. 1999</td>
<td>UK</td>
<td>706</td>
<td>57 %</td>
<td>36.0</td>
<td>RDC(2) and DSM-III-R(1)</td>
<td>Lc 1-4</td>
<td>46</td>
<td>5: Manic, depressive, negative, positive, disorganized symptoms</td>
</tr>
<tr>
<td>Rosenman et al. 2000</td>
<td>Australia</td>
<td>980</td>
<td>60 %</td>
<td>39.3</td>
<td>DSM-III-R(1)</td>
<td>Lc 1</td>
<td>64</td>
<td>5: dysphoria, positive, substance use, mania, negative</td>
</tr>
<tr>
<td>Cardno et al. 2001</td>
<td>UK</td>
<td>224</td>
<td>54 %</td>
<td>46.5</td>
<td>RDC(2)</td>
<td>Lc 1-4</td>
<td>18</td>
<td>6: positive, negative, disorganization, manic, depressive, general psychotic</td>
</tr>
<tr>
<td>McIntosh et al. 2001</td>
<td>UK</td>
<td>204</td>
<td>48 %</td>
<td>26.6</td>
<td>ICD-9(3)</td>
<td>Lc 1-4</td>
<td>39</td>
<td>4: manic, depression, disorganization, reality distortion (no negative items in analysis)</td>
</tr>
<tr>
<td>Serretti et al. 2001</td>
<td>Italy</td>
<td>2241</td>
<td>45 %</td>
<td>41.7</td>
<td>DSM-IV(3)</td>
<td>Lc 1-4</td>
<td>46</td>
<td>4: excitement, delusions, depression, disorganization (negative)</td>
</tr>
<tr>
<td>Wickham et al. 2001</td>
<td>UK</td>
<td>155</td>
<td>52 %</td>
<td>40.0</td>
<td>RDC(2)</td>
<td>Lc 1-4</td>
<td>53</td>
<td>5: depressive, manic, reality distortion, disorganization, psychomotor poverty</td>
</tr>
<tr>
<td>Serretti and Olgiati 2004</td>
<td>Italy</td>
<td>1294</td>
<td>45 %</td>
<td>41.7</td>
<td>DSM-IV(3)</td>
<td>Lc 1-4</td>
<td>29</td>
<td>5: mania, positive, disorganization, depression, negative</td>
</tr>
<tr>
<td>Murray et al. 2005</td>
<td>UK</td>
<td>387</td>
<td>50 %</td>
<td>42.8</td>
<td>ICD-9(3) and ICD-10(7)</td>
<td>Lc 1-4</td>
<td>62</td>
<td>4: depression, reality distortion, mania, disorganization</td>
</tr>
</tbody>
</table>

1) Diagnostic and Statistical Manual of Mental Disorders, Third Edition - Revised (American Psychiatric Association 1987)
2) Research Diagnostic Criteria (Spitzer et al. 1978)
6) Liability classes: class 1=schizophrenia, class 2=schizoaffective disorder, class 3=schizophreniform, delusional, shared psychotic, and brief psychotic disorder, psychotic disorder not otherwise specified, class 4=affective psychotic disorder, class 0=all other mental disorders
7) Major Symptoms of Schizophrenia Scale (Kendler et al. 1994a)
4.3.2 Studies based on the Scale for Assessment of Positive and Negative symptoms of schizophrenia

The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen and Olsen 1982, Andreasen 1982, 1983) was the first instrument applied to comprehensive assessment of negative symptoms of schizophrenia. SANS and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984) have been widely used for clarifying the heterogeneity of the clinical picture in schizophrenia. SANS and SAPS factor analyses have been applied to "global scores", but there is a risk of missing relationships between individual symptoms. Here, studies analyzed at item level to achieve a more detailed view of signs and symptoms of schizophrenia are referred.

Factor analysis of SANS and SAPS since 1993 has resulted in 3-11 factors (Table 2). Malla et al. (1993) found that the emergence of three factors was not explained by medication. It was found that the factor symptoms showed familial aggregation (McGrath et al. 2004b) and that especially the negative symptoms were resistant to cultural influences (Emsley et al. 2001). Peralta and Cuesta (1999) found 11 symptom factors and suggested that the factor structure is more complex than assumed.

However, several factor analysis studies of SANS have demonstrated that the structure of negative symptoms is not one-dimensional (see Table 2 references: Minas et al. 1994, Peralta and Cuesta 1999). Studies on the factor structure of SANS have found two to five factors (Mueser et al. 1994, Peralta and Cuesta 1995, Sayers et al. 1996). The precise number of factors that best represent negative symptoms measured by SANS is unclear; however, the most reliable factors are diminished expression and a combined anhedonia-asociality factor (Blanchard and Cohen 2005).
Table 2. Factor analytic studies based on the Scales for the Assessment of Positive (SAPS) and Negative (SANS) Symptoms

<table>
<thead>
<tr>
<th>Authors and year of study</th>
<th>Country</th>
<th>Number of subjects</th>
<th>Male %</th>
<th>Mean age years</th>
<th>Diagnostic method</th>
<th>Diagnoses Liability classes</th>
<th>Number and names of the factors of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malla et al. 1993</td>
<td>UK</td>
<td>155</td>
<td>76 %</td>
<td>34.2</td>
<td>DSM-III-R²</td>
<td>Lc 1 chronic</td>
<td>3: disorganization, psychomotor poverty, reality distortion</td>
</tr>
<tr>
<td>Minas et al. 1994</td>
<td>Australia</td>
<td>114</td>
<td>63 %</td>
<td>27.3</td>
<td>DSM-III¹</td>
<td>Lc 1-4 acute/chronic</td>
<td>5: negative signs, social dysfunction, delusions, hallucinations, thought disorder</td>
</tr>
<tr>
<td>Andreasen et al. 1995a</td>
<td>USA</td>
<td>243</td>
<td>70 %</td>
<td>32.0</td>
<td>DSM-III-R²</td>
<td>Lc 1, 3 chronic</td>
<td>3: positive, disorganized, negative</td>
</tr>
<tr>
<td>Vazquez-Barquero et al. 1996</td>
<td>Spain</td>
<td>86</td>
<td>50 %</td>
<td>15-54</td>
<td>PSE⁴</td>
<td>Lc 1 first episode</td>
<td>4: negative, non-paranoid, paranoid, disorganized</td>
</tr>
<tr>
<td>Toomey et al. 1997</td>
<td>USA</td>
<td>549</td>
<td>98 %</td>
<td>49.0</td>
<td>DSM-III-R²</td>
<td>Lc 1-0 chronic</td>
<td>5: diminished expression, disorganization, disordered related, bizarre delusions, auditory hallucinations</td>
</tr>
<tr>
<td>Peralta and Cuesta 1999</td>
<td>Spain</td>
<td>660</td>
<td>54 %</td>
<td>36.0</td>
<td>DSM-III-R²</td>
<td>Lc 1-4 acute/chronic</td>
<td>11: poverty of affect/speech, thought disorder/inappropriate affect, other delusions, paranoid delusions, bizarre behavior, non-auditory hallucinations, auditory hallucinations, manic thought disorder, attention</td>
</tr>
<tr>
<td>Emsley et al. 2001</td>
<td>South Africa</td>
<td>422</td>
<td>75 %</td>
<td>38.2</td>
<td>DSM-IV³</td>
<td>Lc 1 chronic</td>
<td>5: diminished expression, disordered relating, psychosis, thought disorder, bizarre behavior</td>
</tr>
<tr>
<td>McGrath et al. 2004b</td>
<td>USA</td>
<td>1043</td>
<td>64 %</td>
<td>39.6</td>
<td>DSM-III-R²</td>
<td>Lc 1-2 chronic</td>
<td>5: positive, negative, disorganized, affective, early onset/developmental</td>
</tr>
<tr>
<td>Niehaus et al. 2005</td>
<td>South Africa</td>
<td>208 (sibpairs)</td>
<td>81 %</td>
<td>37.8</td>
<td>DSM-IV³</td>
<td>Lc 1 chronic</td>
<td>5: negative, positive thought disorder, bizarre behavior, affective</td>
</tr>
</tbody>
</table>

2) Diagnostic and Statistical Manual of Mental Disorders, Third Edition - Revised (American Psychiatric Association 1987)
4) Present State Examination, PSE (Wing et al. 1974)
5) Liability classes: class 1=schizophrenia, class 2=schizoaffective disorder, class 3=schizophreniform, delusional, shared psychotic and brief psychotic disorder, psychotic disorder not otherwise specified; class 4=affective psychotic disorder; class 0=all other mental disorders
4.3.3 Negative symptoms and family history of schizophrenia

Family history of schizophrenia has been associated with pronounced negative symptoms in twin (Dworkin and Lenzenweger 1984, Cardno et al. 2001), adoption (Cardno et al. 2002b), and sibling pair studies (Burke et al. 1996, Hwu et al. 1997, Kendler et al. 1997). However, two studies (DeLisi et al. 1987, Cardno et al. 1999) reported no significant concordance in sibling pairs for negative symptoms. Neither did Ritsner and colleagues (2005), when negative symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) and controlled using additional variables like age of onset, baseline ratings, insight and side effects of medication. However, other studies have found that negative symptoms associate with the familial form of schizophrenia (Verdoux et al. 1996, Van Os et al. 1997, Kirkpatrick et al. 2000, Wickham et al. 2001). The deficit form of schizophrenia, characterized by enduring, primary negative symptoms, has also been associated with family history of schizophrenia (Malaspina et al. 2000, Ross et al. 2000, Kirkpatrick et al. 2001).

4.4 Reliability of the schizophrenia diagnosis

4.4.1. Accuracy and reliability of register diagnosis

Access to data from case registers makes it possible to design powerful studies of disease incidence and prevalence, treatment outcomes and service utilization (Tansella 2000, Byrne et al. 2005). Byrne and colleagues (2005) assessed the validity of registers used in psychiatric research in their systematic review. They included fourteen studies, seven of which concerned Scandinavian registers and five schizophrenia. They were unable to find an established gold standard for the assessment of register quality. Three studies compared register data with case notes, testing the reliability of data transfer to the register. One of these studies concerned the Finnish Hospital Discharge Register (Keskimäki and Aro 1991). The authors assessed the accuracy of 2211 discharges. The accuracy of the principal diagnosis in the register was 94.6%. However, for schizophrenia the accuracy was 99%, and subsidiary diagnoses, too, were most accurate in psychiatric hospitals (83%). The remaining eleven studies assessed case notes to determine a diagnosis, which was then compared with the register. Several studies reduced researcher subjectivity by employing operationalized diagnostic criteria. Byrne and colleagues (2005) studied the quality of these studies by assessing sample number, randomization, blinding (both of the researchers to each other and to the relevant register data), methods used for assessing validity, and use of inter-rater reliability. The studies of Isohanni et al. (1997) and Mäkikyrö et al. (1998) used operationalized DSM-III-R, and the latter also employed OCCPI diagnoses in the case note review and consensus diagnosis procedure. Study samples were not randomized, but all cases were included in the Northern Finland 1966 Birth Cohort. Neither inter-rater reliability nor blinding was stated. Isohanni et al. (1997) found 100% true positive and 48% false negative cases. The sensitivity was 0.52 and specificity 1. Mäkikyrö et al.
(1998) found 93% positives when schizophrenia, and schizophrenia spectrum disorders were included. The positive predictive value was 0.87 and the negative 0.82. It has been found in several studies that Finnish clinicians have a persistent tendency to apply a narrow definition of schizophrenia, with a tendency to false negative rather than false positive case diagnoses (Kuusi 1986, Pakaslahti 1987, Salokangas 1997, Isohanni et al. 1997, Taiminen et al. 2001, Moilanen et al. 2003). Dalman et al. (2002) examined the validity of the Swedish National Inpatient Register diagnoses of schizophrenia among young cases: 76% of diagnoses fulfilled the DSM-IV criteria for schizophrenia.

Byrne and colleagues (2005) concluded that despite the widespread use of registers, there is little empirical literature on their validation and the existing studies vary in conceptual sophistication and methodology. They emphasized the importance of blindness in research settings. Statistical methods varied from assessing percentage levels of agreement between case note and register, to the calculation of specificity and measures of correlation. The representativeness of the study populations varied too, with most of the studies concerning inpatient samples.

4.4.2 Reliability of consensus diagnosis

To achieve final best-estimate diagnoses, Leckman et al. 1982 used a sample of 1878 individuals in their methodological study. They formed lifetime psychiatric diagnoses using direct interviews, family history from multiple informants, and medical records. They were able to examine the agreement between two raters using a best estimate diagnostic procedure based on a review of all available information in both interviewed and non-interviewed samples of patients and their relatives. They concluded that best-estimate diagnoses were reliable either using interview or all available information including case notes. McConville and Walker (2000) assessed the reliability of case register diagnoses, but also the inter-rater reliability of case note diagnoses. They assessed forty-five randomly selected case notes, and the inter-rater reliability across all diagnostic categories was kappa=0.71 (p<0.001). Goodman et al. (1984) also assessed inter-rater reliability and the kappa value was 0.58. Craddock et al. (1996) compared the OCCPI diagnoses and DSM-III-R plus RDC consensus best-estimate diagnoses in 100 cases. The agreement between the consensus best-estimate diagnoses was kappa=0.80 for DSM-III-R and 0.72 for RDC.

4.4.3 Reliability of interview diagnosis

Spitzer et al. (1978) assessed the reliability of Research Diagnostic Criteria (RDC) using joint interviews, whereby one rater conducted the interview and the other observed. Both made independent ratings. They also used the test-retest method. For schizophrenia the kappa in joint interviews was 0.80, and in test-retest 0.65. Skre et al. (1991) assessed fifty-four audio taped SCID interviews rated independently by three raters. Agreement was highest (0.93) for schizophrenia and major depressive disorder (0.92). Interrater reliability was generally good for combinations of two diagnoses, but poorer when three
were combined. Williams et al. (1992) analyzed 592 subjects with a test-retest method to calculate the reliability of SCID-III-R interviews. For most of the major lifetime diagnostic categories the overall weighted kappa was 0.68, for schizophrenia it was 0.68. Miller (2001) showed that structured interviews like SCID and Computer Assisted Diagnostic Interview (CADI) (Miller 2001) were significantly more accurate than unstructured traditional diagnostic assessments for making inpatient diagnoses, using consensus diagnoses as the golden standard. Fennig et al. (1994) compared best-estimate and structured SCID-III-R interview diagnoses in a study of first-admission psychosis at entry and six months later. They concluded that the SCID interview, when administered by closely supervised experienced non-psychiatrist clinicians and incorporating information from other sources, can produce reliable diagnoses of schizophrenia and bipolar disorder.

The reliability of SCID-II for personality disorders was tested in 69 patients (Weertman et al. 2003) and the overall kappa was 0.63. Osone and Takahasi (2003) used the test-retest reliability assessments for DSM-IV personality disorders. The overall kappa was 0.87. Farmer and Chapman (2002) found in their study of 149 persons that the SCID-II (DSM-IV) personality questionnaire may perform well as a screening tool for personality disorder diagnoses. This SCID-II finding suggests generally modest levels of both comorbidity and covariation across personality disorder concepts. However, the inter-rater reliability was excellent.

4.5 Summary of the literature

Schizophrenia exists worldwide, its mean prevalence varying around 0.4-0.7% (Saha et al. 2005). However, in isolated populations, the lifetime prevalence has varied from 0.1% (Chen et al. 1993) to 2.2% (Hovatta et al. 1997).


The signs and symptoms of schizophrenia are complex, encompassing almost every aspect of cognition and behavior. Unfortunately, we have no laboratory or other objective tests to diagnose schizophrenia and thus accurate observation and recording of signs and symptoms is generally the only way of forming a reliable diagnosis. However, the phenotype of schizophrenia is heterogeneous and several studies have attempted to divide it into subtypes or dimensions to identify risk factors. Recently the symptoms and signs of schizophrenia and psychotic disorders have been divided into four or five dimensions:

Several studies have found that negative symptoms associate with the familial form of schizophrenia in twin (Dworkin and Lenzenweger 1984, Cardno et al. 2001), adoption (Cardno et al. 2002b), and sibling pair studies (Burke et al. 1996, Hwu et al. 1997, Kendler et al. 1997) and other studies (Verdoux et al. 1996, Van Os et al. 1997, Kirkpatrick et al. 2000, Wickham et al. 2001). The deficit form of schizophrenia, characterized by enduring, primary negative symptoms, has also been associated with family history of schizophrenia (Malaspina et al. 2000, Ross et al. 2000, Kirkpatrick et al. 2001).

Accurate diagnoses are essential for genetic studies of schizophrenia. However, the literature on register data validation for research is sparse (Byrne et al. 2005). It has also been found in several studies that Finnish clinicians have a persistent tendency to apply a narrow definition of schizophrenia, with a tendency to false negative rather than false positive case diagnoses (Kuusi 1986, Pakaslahti 1987, Salokangas 1997, Isohanni et al. 1997, Taiminen et al. 2001, Moilanen et al. 2003).
5. AIMS OF THE STUDY

The present investigation forms part of the study "The Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland", which was initiated in 1988 at the National Public Health Institute’s Department of Mental Health and Alcohol Research in collaboration with the Department of Molecular Medicine. The general aim of this study was to identify clinical phenotypes of schizophrenia for molecular genetic studies in isolate families representing a homogeneous population with high prevalence of schizophrenia.

The specific aims of the present thesis were:

I. To reassess the register-, case record- and interview-based lifetime prevalence of schizophrenia and schizophrenia spectrum or associated psychotic disorders, the cumulative incidence and reliability of the schizophrenia diagnoses in a genetically homogeneous isolate birth cohort born between 1940 and 1969.

II. To examine using Operational Criteria Checklist for Psychotic Illness (OCCPI) factor analysis the psychotic and affective signs and symptoms of schizophrenia in the genetically homogeneous isolate population, and to compare the factor solutions in the isolate and among individuals with schizophrenia from multiplex families identified from the whole country.

III. To examine using the Scales for the Assessment of Negative and Positive Symptoms (SANS and SAPS) the signs and symptoms of schizophrenia in a genetically homogeneous isolate and a nationwide multiplex family sample, and to investigate the symptom dimensions and their association with the degree of familial loading for psychotic disorders and with consanguinity.

IV. To investigate whether siblings of patients with schizophrenia can be identified as not having any psychotic disorder using health care register information only, to analyze the emergence of psychotic disorders among siblings of patients with schizophrenia during seven to 11 years of follow-up, and to compare the prevalence of psychiatric disorders between siblings of patients with schizophrenia and a random population sample.
6. SUBJECTS AND METHODS

6.1 Identification of the isolate and families from the isolate and the whole country

6.1.1 Identification of the isolate

The project was initiated in 1988, and subsequently the research and sample collection for genetic studies was started in 1991. Kuusamo (population 17000) was known to have a high prevalence of schizophrenia and a population history of isolation excellent for genetic studies. The principal investigators of the project were Professor Jouko Lönnqvist and Professor Leena Palotie. The study protocol was approved by the Ethics Committee of the National Public Health Institute, and by the Ministry of Social Affairs and Health.

The population history of Finland and this isolate is well known: multiple bottlenecks and 36 monogenic diseases have been identified as enriched in the Finnish population (Peltonen et al. 1999, Varilo and Peltonen 2004). The expansion of the Finnish population was based on agriculture and animal husbandry thought to have been introduced by eastern Uralic speakers 4000 years ago and settlers from the south 2000 years ago. Since then, Finland has been relatively isolated for geographic, linguistic and cultural reasons (Nevanlinna 1972, Peltonen et al. 1999). The northern and eastern parts of the country were settled from the south relatively recently, in the 16th and 17th centuries.

The study isolate was genetically formed in north-eastern Finland by only 39 families during this late settlement, and it remained almost completely isolated by distance until the 1940s (Varilo et al. 2003). In 1940-1960 there was substantial emigration to Sweden, although the population remained stable (Korkiasaari 1989). The inhabitation of the isolate is documented since 1676, and precise details of all births, deaths, marriages and movements have been found from the exceptionally well kept local church records (Hovatta et al. 1997, Varilo et al. 2003).

The isolate developed from a rural municipality in the 1940s and has a present population of about 17000. However, there are still only 3.5 inhabitants per square kilometer (see municipal data at http://www.kuusamo.fi). Kuusamo also has a simple service system: one health care center with a hospital closely associated with the university hospital in Oulu, north-western Finland.
6.1.2 Identification of isolate and multiplex families from the whole country

First, we utilized three nationwide health care registers to identify all schizophrenia patients with a diagnosis of schizophrenia, schizoaffective or schizophreniform disorder in at least one of the registers who were born from 1940 to 1969. Later we widened the Hospital Discharge Register data to patients born 1940-1976 and updated the Hospital Discharge Register information from 1991 to 1998. We identified altogether 33731 patients from the Finnish Hospital Discharge Register, the Disability Pension Register, and the Free Medicine Register (Figures 1 and 2).

We identified the first-degree relatives for each patient from the National Population Register, which was created in 1969 using local church registers and verified in 1973. Personal identification codes for every citizen were introduced earlier, in 1964. However, the family information was not found for 6079 patients and they were excluded. Over 80% of excluded patients were born from 1940 to 1949.

The total number of isolate patients in 1998 was 658, in 379 families. The total number of isolate patients is summarized in Figure 2. The inclusion and exclusion criteria varied in studies I-IV. In Study I we identified isolate birth cohorts, but in Studies II-IV we identified patients who had at least one parent born in the isolate. It took several years to collect the whole sample (Figure 1). Study II was done first, so we had register data only until 1991 and had not assessed all consensus diagnosis.

In the final isolate sample (Figure 2) we collected blood samples from 331 patients: 167 (25%) refused and 24 patients were not found. The studies by the Department of Molecular Medicine at the Public Health Institute have been reported in detail previously (Hovatta et al. 1997, 1998, 1999, Ekelund et al. 2000, 2001, 2004, Hennah et al. 2003, Paunio et al. 2001, 2004, Varilo et al. 2000, Varilo and Peltonen 2004). All patients and relatives gave their written informed consent, and the collection of blood samples was carried out as recommended in the Helsinki Declaration and amendments.

We reassessed the register diagnoses of 326 patients who participated in the genetic study. However, five patients remained without a consensus diagnoses because of insufficient or missing case records. A further 49 (15%) refused the interview and neuropsychological test, and a total of 257 patients participated in all analyses till 2002 (Figure 2). Their cognitive performance was assessed with a battery of neuropsychological tests (Tuulio-Henriksson et al. 2002, 2003, 2004, Paunio et al. 2004). 156 (24%) of 658 patients were deceased by 2002, concordant with the rate in a study of long-stay psychiatric patients in northern Finland (Räsänen et al. 2003).
Figure 1. Clinical examinations and diagnostic procedures

Hospital Discharge
Disability Pension
Free Medicine (1969-1985)
National Population

ISOLATE FAMILIES
At least one parent born in the isolate.
Patients born 1940-76 with a diagnosis of schizophrenia, schizoaffective or schizoaffective disorder (code 295)1)

WHOLE COUNTRY FAMILIES
At least two affected siblings in the family.
Patients born 1940-76 with a diagnosis of schizophrenia, schizoaffective or schizoaffective disorder (code 295)1)

II Blood samples 1991-2002
Genealogical research

III Case records:
Consensus diagnoses2) and OCCPI3) ratings
1995-2002

IV Clinical interviews:
SCID4), SANS5), SAPS6)
Neuropsychological tests
1998-2002

2) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association 1994)
3) Operational Criteria Checklist for Psychotic Illness (McGuffin et al. 1991)
4) Structured Clinical Interview I and II for DSM-IV (First et al. 1996, 1997)
5) Scale for the Assessment of Negative Symptoms (Andreasen 1983)
6) Scale for the Assessment of Positive Symptoms (Andreasen 1984)
33731 patients with a diagnosis of schizophrenia, schizoaffective- or schizophréniform disorder in at least one of the registers

6079 patients were excluded: no family information

ISOLATE PATIENTS
379 families
658 patients

136 deceased, 167 refused, 24 not found

Blood sample 331 patients
Genealogical research 263 families

No consensus 5 patients

326 patients (246 schizophrenia)
DSM-IV\(^1\) reassessed consensus diagnoses OCCPI\(^2\) ratings and diagnoses

49 refused, 20 deceased

257 patients (217 schizophrenia) with SCID-I-II\(^3\), SANS\(^4\) and SAPS\(^5\) interviews

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2) Operational Criteria Checklist for Psychotic Illness (McGuffin et al. 1991)
3) Structured Clinical Interview I and II for DSM-IV (First et al. 1996, 1997)
4) Scale for the Assessment of Negative Symptoms (Andreasen 1983)
5) Scale for the Assessment of Positive Symptoms (Andreasen 1984)
We also identified a total of 4904 whole country multiplex family patients with at least two affected siblings using the same registers. The study protocol was similar to that for the isolate sample (Figure 1), and we collected 1167 blood samples and made 945 consensus diagnoses and Operational Criteria Checklist for Psychotic Illness (McGuffin et al. 1991) (OCCPI) ratings. We then chose a random sample of 138 multiplex families from the whole country. We contacted 661 individuals, of whom 140 refused (21%) the interview and neuropsychological tests. Ninety-four of the interviewed patients had a consensus diagnosis of schizophrenia and were included in Study III.

6.2 Subjects in Studies I-IV

6.2.1 Subjects in Study I

We utilized the register information to identify all persons in the isolate born in the 1940-1969 birth cohorts, who had been hospitalized with a diagnosis of schizophrenia (295.0-3, 5-6, 8-9), schizoaffective (295.7) or schizophreniform (295.4) disorder, between 1 January 1969 and 31 December 1998. Code 295 refers here to these three disorders identified from the registers. We also used the Disability Pension Register until 1991 and the Free Medicine Register until 1986 to identify schizophrenia patients who had not been hospitalized (N=17). Of the 282 patients identified, 45 (16%) patients had died before 1998, leaving 237 patients to be included in our study.

Seventy-three of 237 patients did not receive a consensus diagnosis: 51 of them had not been willing to participate in the genetic study and 22 did not have a parent born in the isolate and were not included in the genetic study. We then contacted all 164 patients born in the isolate and with at least one parent also born in the isolate, who had a consensus diagnosis and had participated in our genetic studies of patients. We interviewed 131 of these patients, as six had deceased, 23 patients refused, and in four cases the doctor or nurse in charge of the patient’s care denied contact.

The corresponding birth cohorts of the isolate from 1940 to 1969 (N=14817), who were living in whole Finland and alive in 1998 (N=12368) were identified from the National Population Register, as were the number of deaths from 1940 to 1998 in the birth cohorts.
6.2.2 Subjects in Study II

For this study we included patients identified from the registers in 1991 who had a consensus diagnosis up to October 1, 2000. Patients were born from 1940 to 1969 and had a register diagnosis of schizophrenia (code 295), and at least one parent born in the isolate. We also included 28 extra families in the isolate study from a neighbouring municipality - previously part of Kuusamo and with a similar inhabitation history. In addition, four other families were identified by local doctors from the Kuusamo health center. In total there were 397 families and 588 patients. The 588 patients included 523 siblings, 38 mothers, 21 fathers and three families where both parents were affected. We collected and made consensus diagnoses and OCCPI ratings for 306 isolate patients and family members. 190 patients had a consensus diagnosis of schizophrenia in October 2000. Further, among these 190 patients with a consensus diagnosis we had 112 isolate singleton patients who were the only affected individuals in their family, and 78 isolate multiplex patients.

Schizophrenia multiplex families from the whole country with at least two affected siblings born between 1940 and 1969 were also identified to represent familial schizophrenia; there were 2239 families with 4904 patients. They were identified from the registers using the same protocol as for the isolate patients. The inclusion criteria for diagnosis were schizophrenia, and schizoaffective or schizophreniform disorder (code 295). We collected blood samples and made OCCPI ratings and consensus diagnoses reassessment using the same study protocol as in the isolate study (Figure 1). We had made 466 OCCPI ratings and consensus diagnoses of schizophrenia up till 1 October 2000 in the families from the whole country.

6.2.3 Subjects in Study III

In Study III we could identify more isolate patients than in Study II. Patients were born from 1940 to 1976 and we also had Hospital Discharge Register data from 1969 to 1998, i.e. seven years more compared to Study II. However, we did not include those 28 families from the neighbouring municipality.

The whole country multiplex patients were identified using the same health care registers as in the isolate study, but they had two or more affected siblings in the family (code 295). We identified for interviews a random sample of 138 families from the 4904 multiplex families in the whole country. We contacted 661 individuals and 140 refused (21%). Ninety-four interviewed patients had a consensus diagnosis of schizophrenia and were included in Study III.
Our final representative Study III sample contained 290 interviewed patients with a consensus diagnosis of schizophrenia. We divided them into three groups: 196 patients from the isolate, comprising 63 multiplex family patients and 133 isolate singleton patients, plus 94 multiplex family patients from the whole country. The criteria for multiplex patients were as follows: (1) at least one interviewed sibling with a DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association 1994) consensus diagnosis of schizophrenia (schizoaffective or schizophreniform disorder not included), and (2) at least one sibling with a diagnosis of schizophrenia or other psychotic disorder in registers or by consensus diagnosis. The interviewed singleton patients had no first-degree relatives with any psychotic disorder.

In addition, we linked the genealogical information from the isolate pedigrees to phenotype information and DSM-IV consensus diagnoses. To estimate the degree of familiality with each patient, we counted consanguineous patients through all common founders in four-generation pedigrees. We included the consanguineous patients from 263 families born 1940 to 1976, based on the liability classes of DSM-IV diagnoses (Figure 3). The genealogical research was conducted at the Department of Molecular Medicine. The ancestors of the schizophrenia patients in the isolate were traced back four to 12 generations and large four-generation pedigrees were constructed in accordance with published criteria (Figure 3)(Varilo et al. 1996, Hovatta et al. 1999, Varilo et al. 2003).

Figure 3. A large four-generation pedigree of families with schizophrenia in the isolate.

(next page)

Affected individuals of 263 families are in black. DSM-IV consensus diagnoses are shown in liability classes: class 1= schizophrenia, class 2= schizoaffective disorders, class 3= schizophreniform, delusional, shared psychotic and brief psychotic disorder, and psychotic disorder not otherwise specified, class 4= affective psychotic disorder, class 0= all other mental disorders.

○ = female, □ = male, ● = affected female, ■ = affected male, ◆ = multiple affected siblings.

LC= liability class of the youngest generation is marked below the pedigree, S= spouse with the respective number drawn elsewhere in the pedigree. Plain numbers= the number of affected offspring born 1940-76 of a given ancestral couple.
6.2.4 Subjects in Study IV

We followed-up siblings of schizophrenia patients in the isolate using the original register data from 1991 with 365 isolate families. These 365 isolate families had 446 patients born from 1940 to 1969, as in the Study II. However, the numbers are different because we did not include patients from the neighbouring municipality in the study. We contacted the patients and first-degree relatives from 1998 to 2002 and interviewed them using the Structured Clinical Interview for DSM-IV (SCID-I-II) (First et al. 1996, 1997), and the Scales for the Assessment of Negative Symptoms (SANS) and Positive Symptoms (SAPS) (Andreasen 1983, 1984).

For those 446 patients (code 295) identified in the isolate we identified a total of 1353 healthy isolate siblings born from 1940 to 1969 without a register diagnosis of psychosis (Figure 4). Information on the siblings was linked back to the health care registers to obtain data on their hospital admissions, pensions, and free medications. Of the total of 1353 healthy siblings, 280 were dead. 158 (18%) refused, 458 were not contacted, and in 78 cases we could not find the treating person for the affected sibling. Of the 379 initially healthy siblings who gave a blood sample, 248 were interviewed and tested. Ten were deceased and 53 (17%) refused, and three patients did not give permission to contact their five siblings. Because of time and budgetary limitations we could not interview the 63 initially healthy siblings who had participated in the genetic studies (Figure 4). Although we could not contact all healthy siblings, for every patient we aimed to interview and test at least one sibling close in age (Tuulio-Henriksson et al. 2003). This age criterion was set because we wanted to minimize age-related differences in neuropsychological performance between siblings.

The inclusion criteria for a patient were based on an interview diagnosis of schizophrenia or schizoaffective disorder, as well as fulfillment of the condition that the patient had a sibling without register diagnosis of psychosis and who was interviewed. 183 patients received a SCID interview diagnosis of schizophrenia or schizoaffective disorder. However, 59 patients were without an interviewed initially healthy sibling born from 1940 to 1969. In the end, therefore, we had 124 patients and 183 initially healthy siblings in 110 families.

Besides interviews, we also obtained information from the Finnish Hospital Discharge Register on all hospital treatments for mental disorders between 1991 and 1998 for both patients and siblings.
Figure 4. Identification of initially healthy siblings (study IV)

Isolate patients (N=446) (born 1940-69) with register\(^1\) diagnosis of schizophrenia, schizoaffective or schizophreniform disorder (code 295)

1353 siblings (born 1940-69) without diagnosis of psychotic disorder in registers\(^1\) in 1991

- 280 deceased
- 158 refused
- 78 not contacted because the person treating affected siblings was not found
- 458 not collected

379 blood samples

- 10 deceased
- 53 refused
- For 5 siblings of 3 affected siblings no permission given for interview
- 63 not collected

248 initially healthy siblings were interviewed\(^2\) and received neuropsychological tests

183 initially healthy siblings of 124 patients with interview diagnosis\(^3\) of schizophrenia or schizoaffective disorder in 110 families were included in the study

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2) Structured Clinical Interview I and II for DSM-IV (First et al. 1996, 1997)
6.2.4.1 Comparison group (Study IV)

The comparison group (N=111) was a representative sample of the Finnish general population aged 30-79. The sample was identified from the Health 2000 Survey, which is based on a nationally representative two-stage cluster sample of 8028 persons aged 30 or over (Aromaa and Koskinen 2004). Of the 161 subjects randomly selected from those who had participated in any of the study phases, 111 (69%) were interviewed with SCID-I during 2002-2004 and were taken as the comparison group for this study. Information on hospital treatments from 1974 to 2002 for any psychotic disorders was collected from the Hospital Discharge Register.

6.3 The Finnish Health Care Registers from 1969 to 1998

The Finnish Hospital Discharge Register covers all mental and general hospitals, as well as in-patient wards of local health centers, military wards, prison hospitals and private hospitals. It was computerized in 1968. We identified all patients who had been hospitalized between 1 January 1969 and 31 December 1991 (register codes 295.0-9), and later until 1998 (register codes F20.0-9, F23.1-2, F25.0-9). We also had Register data from two Social Insurance Institution Registers, namely the Disability Pension and the Free Medicine Registers. From the Disability Pension Register we collected data until December 1991; this register codes only the first three digits (295) of the diagnostic codes. The Free Medicine Register had its own code 12 for schizophrenia patients until the end of 1985, so we included patients according to this information from 1969 to 1985. The Hospital Discharge Register data consist of admission and discharge dates, primary and subsidiary diagnoses, and hospital identification codes for each inpatient. The Pension Register records the starting and ending dates and the primary diagnoses for disability pensions. The Free Medicine Register indexes the diagnoses of persons receiving state-subsidized outpatient medication. We used the unique personal identification numbers to link the data in these registers to the National Population Register, which has information on place of birth, date of death, place of current residence, marital status, and first-degree relatives of each Finnish citizen. The National Population Register was created in 1969 and updated in 1973 with family information, so the complete data on first-degree relatives can be found from 1973 for people born in the 1950s and later.

The diagnostic criteria of schizophrenia varied during the period 1969 to 1998 when the Hospital Discharge, Disability Pension and Free Medicine Registers were used for our study data. The criteria of schizophrenia used in Finland are presented in following sections.
6.3.1 International Classification of Diseases, Eighth Edition

The Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 8th Edition (ICD-8) (World Health Organization, 1967) provided no criteria for schizophrenia, but the ICD-8 glossary characterized the subtypes of schizophrenia. The simple type had oddities of conduct, difficulties in social contact, and decline in overall performance but without clear-cut positive symptoms of schizophrenia. The hebephrenic type had inappropriate affect, behavior often silly and empty of purpose and feeling, and prominent thought disorder. The catatonic type was characterized by catatonic symptoms, and the paranoid type by prominent delusions and hallucinations. The latent type was characterized by the emergence of symptoms not obviously schizophrenic but severe enough to raise a strong suspicion of schizophrenia. The residual type was characterized by a chronic residual state in which fragments of faded schizophrenic symptomatology occurred. Other and unspecified types did not fit into these subtypes. Acute schizophrenic episode was characterized by acute onset of schizophrenic symptoms often presenting as a dream-like state with slight clouding of consciousness and perplexity. The schizo-affective type included cases where both the affective and schizophrenic symptoms were pronounced. Infantile autism was also regarded as a part of schizophrenia. So the definition for schizophrenia was broad and based on the severity of social and personal dysfunction. There was also considerable overlap with personality disorders.

6.3.2 International Classification of Diseases, Ninth Edition

In the ninth edition of ICD (ICD-9) (World Health Organization, 1977, 1978) the childhood type of schizophrenia and infantile autism were removed from schizophrenic psychoses, but simple and latent schizophrenia remained. In Finland, however, the first four numbers in the diagnostic codes corresponded to the ICD-9 codes. We used the narrower DSM-III-R criteria and the fifth digit was similar to the third revised Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (American Psychiatric Association, 1987). However, the schizophreniform and schizoaffective disorders were still classified as schizophrenic psychoses, as in the ICD-8 and ICD-9.

6.3.3 International Classification of Diseases, Tenth Edition

The tenth edition of ICD (ICD-10) (World Health Organization, 1993) and its diagnostic codes and criteria have been used in Finland since 1996. Its diagnostic criteria of schizophrenia differ from those of the DSM-IV. The DSM-III-R (American Psychiatric Association, 1987) and the DSM-IV (American Psychiatric Association, 1994) require a six month duration of symptoms vs. only one month for ICD-10, and ICD-10 does not require deterioration from a premorbid level of functioning, whereas DSM-III-R and IV do. ICD-10 also has an exclusion criterion for mood disorder before the onset of schizophrenia, while DSM-IV requires that the total duration of all episodes of a mood syndrome has been brief
relative to the total duration of the active and residual phases of the disturbance. The ICD-10 diagnostic classification included negative symptoms prior to the publication of DSM-IV. Latent schizophrenia has now been removed from ICD-10 and nowadays patients having it might be classified with schizotypal personality disorder.

6.4 The research diagnosis of schizophrenia

In our study we used the DSM-IV criteria both in case record based consensus diagnosis assessments and in interviews. When we assessed interview based diagnoses, we used the Structured Clinical Interviews for DSM-IV: Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) (First et al. 1996) and Structured Clinical Interview for DSM-IV Personality Disorders, (SCID-II) (First et al. 1997) based assessments.

The DSM-IV is a classification of mental disorders developed for use in clinical, educational and research settings. It is a multiaxial system with five axes: I Clinical disorders and other conditions that may be a focus of clinical attention, II Personality disorders and mental retardation, III General medical conditions, IV Psychosocial and environmental problems, and V Global assessment of functioning (GAF). The five axes may help the clinician plan treatment and predict outcome, and it also facilitates comprehensive and systematic evaluation. The text of DSM-IV systematically describes each disorder: diagnostic features, subtypes and/or specifiers, recording procedures, associated features and disorders, specific culture, age and gender features, prevalence, course, familial pattern, and differential diagnosis.

SCID-I (First et al. 1996) and SCID-II (First et al. 1997) are semistructured interviews for DSM-IV diagnosis and have a one-time-use scoresheet containing DSM-IV diagnostic criteria and interview questions plus the GAF assessment scale. The majority of questions can be answered by a simple "yes" or "no"; however it is usually necessary to ask the patient to elaborate or provide specific examples. The clinician version covers only those DSM-IV diagnoses most commonly seen in clinical practice. It contains an overview and six modules: mood episodes, psychotic symptoms, psychotic disorders, mood disorders, substance use disorders, and anxiety and other disorders.

SCID-II covers all axis II personality disorders. In the interview the subject first filled out the personality questionnaire as a screening tool. In our study, for all items with a "yes" answer on the questionnaire the interviewer continued to ask all questions concerning that specific personality disorder.
6.4.1 The DSM-IV criteria for schizophrenia

The DSM-IV criteria for schizophrenia are shown in Table 3. DSM-IV divides schizophrenia further into five subtypes on the following algorithm: catatonic type is assigned whenever prominent catatonic symptoms are present (regardless of the presence of other symptoms); disorganized type is assigned whenever disorganized speech and behavior, and flat or inappropriate affect are prominent (unless catatonic type is also present); paranoid type is assigned whenever there is a preoccupation with delusions or frequent hallucinations are prominent (unless the catatonic or disorganized type is present). Undifferentiated type is a residual category describing presentations that include prominent active-phase symptoms not meeting criteria for the catatonic, disorganized, or paranoid type; and residual type is for presentations in which there is continuing evidence of the disturbance, but the criteria for the active-phase symptoms are no longer met.

Schizophreniform disorder has identical features to schizophrenia except for two differences: the total duration of the illness is at least one month but less than six months (See Table 3, criterion C), and impaired social or occupational functioning during some part of the illness is not required (See Table 3, criterion B). The specifiers: with good prognostic features or without good prognostic features, may be used to indicate the presence or absence of features that may be associated with a better prognosis.

The essential feature of schizoaffective disorder is an uninterrupted period of major depressive, manic, or mixed episode concurrent with symptoms that meet criterion A (See Table 3) for schizophrenia. In addition, during the same period of illness, there have been delusions or hallucinations for at least two weeks in the absence of prominent mood symptoms. The mood symptoms are also present for a substantial portion of the total duration of the illness. There are two subtypes: bipolar type, and depressive type - which includes only major depressive episodes.

In our study, we divided the diagnosis into six liability classes: class 1, schizophrenia; class 2, schizoaffective disorder; class 3, schizophreniform, delusional, shared psychotic, and brief psychotic disorder, and psychotic disorder not otherwise specified; class 4, affective psychotic disorder; class 5, organic psychotic disorders; and class 0, all other mental disorders.
Table 3. Diagnostic criteria for Schizophrenia (DSM-IV)

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

   (1) delusions
   (2) hallucinations
   (3) disorganized speech (e.g. frequent derailment or incoherence)
   (4) grossly disorganized or catatonic behavior
   (5) negative symptoms, i.e., affective flattening, alogia, or avolition

   note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person’s behavior or thoughts, or two or more voices conversing with each other.

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences).

D. Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Classification of longitudinal course (can be applied only after at least 1 year has elapsed since the initial onset of active-phase symptoms):

Episodic With Interepisode Residual Symptoms (episodes are defined by the reemergence of prominent psychotic symptoms); also specify if: With Prominent Negative Symptoms

Episodic With No Interepisode Residual Symptoms

Continuous (prominent psychotic symptoms are present throughout the period of observation); also specify if: With prominent Negative Symptoms

Single Episode in Partial Remission: also specify if: With Prominent Negative Symptoms

Single episode In Full Remission

Other or Unspecified Pattern
6.5. Case record based assessments

6.5.1. The Consensus diagnoses

We collected original case notes from the psychiatric hospitals based on data in the Hospital Discharge Register, which records all hospital treatments in Finland. The case notes from outpatient services were collected from Kuusamo outpatient service and the health care center. We also used hospital case records to identify outpatient services if the patient was living outside Kuusamo. If the hospital case notes were missing or insufficient we collected case notes from the municipalities where the patient had been living.

The mean follow-up time was 16.6 (SD 5.4) years from the first hospitalization until 1 October 2000 (Study II). However, the last consensus diagnoses were made in 2002. We validated and re-assessed the diagnoses of all patients and family members who participated in the genetic studies. Two researchers independently made best-estimate diagnoses using DSM-IV criteria (American Psychiatric Association 1994). Although they were blind to the register diagnoses, they knew the study protocol and could not be completely blind. In cases of disagreement, a third senior researcher reviewed the case to achieve the consensus diagnosis.

The consensus diagnoses for the isolate cases were made by the author with two other researchers. Altogether we made 406 consensus diagnoses including patients and first-degree relatives. For the multiplex families from the whole country the consensus diagnoses (N=945) were made in the same way by six researchers. In the isolate, the kappa values for the DSM-IV best-estimate diagnoses of schizophrenia were 0.95 (95% CI 0.84-1.0), for schizoaffective disorder 0.94 (95% CI 0.83-1.0), and for schizophreniform disorder 0.97 (95% CI 0.85-1.0). In the whole country multiplex family sample the kappa values were 0.85 (95% CI 0.79-0.92) for schizophrenia, and 0.73 (95% CI 0.60-0.85) for schizoaffective disorder and schizophrenia spectrum (schizoid, schizotypal and paranoid personality disorders, schizophreniform, delusional, and brief psychotic disorders and psychotic disorder NOS) (Ekelund et al. 2000). The consensus diagnoses were used as inclusion criteria: in Studies II and III we included all patients with a consensus diagnosis of schizophrenia, while in Study IV both schizophrenia and schizoaffective disorder were inclusion criteria. In Study I we assessed the reliability of consensus, register, and interview diagnoses.
6.5.2. The Operational Criteria Checklist for Psychotic Illness ratings

The Operational Criteria Checklist for Psychotic Illness 3.31 (OCCPI) was originally designed to facilitate a polydiagnostic approach to the diagnosis of psychotic and affective disorder for molecular genetic research. However, it has been used in a wide variety of clinical, epidemiological and biological research.

The OCCPI comprises a 90-item checklist of signs and symptoms and a suite of computer programs (OPCRIT)(Appendix 1). It has a glossary of clear and explicit descriptions of each constituent item and instructions for coding them. It generates diagnoses based on 12 different operational diagnostic systems including the 1) DSM-III (American Psychiatric Association 1980), 2) DSM-III-R (American Psychiatric Association 1987), 3) ICD-10 (World Health Organization 1993), 4) St. Louis criteria (Feigner et al. 1972), 5) Research Diagnostic Criteria (RDC) (Spitzer et al. 1978), and 6) Taylor and Abrams criteria (Taylor and Abrams 1978). The OCCPI also allows the diagnosis of schizophrenia to be made according to the 7) "flexible" criteria for schizophrenia of Carpenter (Carpenter et al. 1973), and 8) Schneider’s first-rank symptoms (Schneider 1959), and 9-11) according to three sub-typing classifications of schizophrenia (Tsuang and Winokur 1974, Crow 1980, Farmer et al. 1983), and 12) a version of the French criteria for non-affective psychosis (Pull et al. 1987). Farmer and colleagues (1992) compared these diagnoses and concluded that skilled clinical judgment remains the most reliable and valid tool the researcher possesses. In this study we used the case record-based DSM-IV consensus diagnoses in our analysis, not the operational diagnoses of OCCPI. In study II we analyzed by factor analysis the item level information on the OCCPI (Appendix 1).

The reliability of the OCCPI has been demonstrated in many studies (McGuffin et al. 1991, Craddock et al. 1996, Williams et al. 1996, Azevedo et al. 1999). Item-by-item agreement has been measured in only a few studies and the agreements between raters have been reasonable (McGuffin et al. 1991, Cardno et al. 2001).

To assess the diagnostic agreement, three psychiatrists independently made the OCCPI DSM-III-R diagnoses and the DSM-IV best-estimate diagnoses from the lifetime case notes for a random sample of 30 representative cases. All the OCCPI and DSM-III-R diagnoses were the same, and only one case note diagnosis was assessed in liability class 2 instead of class 1 by one of the researchers. The OCCPI item-by-item agreement was less good, however, as also in the study of Cardno and colleagues (2001). In our study the kappa values varied from 0.10 to 0.84. For the OCCPI factor analysis we chose 30 psychotic and affective items with kappa values exceeding 0.46.
6.6. Clinical interviews

6.6.1. Diagnostic interviews

For diagnostic assessments we used the SCID for axes I and II (First et al. 1996, 1997) and the GAF scale for Axis V, both based on the DSM-IV (American Psychiatric Association 1994). The Scales for the Assessment of Negative Symptoms (SANS, Appendix 2) and Positive Symptoms (SAPS, Appendix 3) (Andreasen 1983, 1984) were used to evaluate the signs and symptoms.

The interview questions and scoresheets were translated into Finnish. We added questions on smoking, place of birth and some sociodemographic variables to the overview scoresheet. We made all ratings on a lifetime basis and used all available information, including discussions with family members or health care personnel.

We first did a pilot study, interviewing and testing 39 patients. We started the interview with the overview and then went through all modules of SCID-I, including the GAF. The subjects then filled the SCID-II questionnaire, and for all items answered "yes" on the questionnaire the interviewer continued to ask all questions concerning that specific personality disorder. We continued with the SAPS interview if the subject had any psychotic symptoms in SCID-I. The SANS interview was done first for all patients, but we later used it for all subjects. The interview took approximately four hours on average. We also constructed a family tree including all core family members and relatives known by the subject. We generally completed the interview and performed the neuropsychological tests on the same day. We continued on another day if the subject wanted or was tired.

The study protocol required the clinical study teams to first-contact the doctor or the nurse in charge of the patient to obtain their participation in the study. All patients and relatives provided written informed consent after the procedure had been explained to them. The ethical review boards of Finland’s National Public Health Institute approved this study.

To contact all patients and their relatives around Finland we had four teams of field workers. The field workers, who contacted treating personal, patients and their relatives, were nurses, mental nurses and one doctor. All had been given extensive training in the use of the instruments. To increase reliability we used tape-recordings and the senior researcher reviewed the 20 first interviews of each fieldworker. The SCID-I-II, SANS and SAPS interviews were also discussed with the senior researcher, with whom the interviewers had regular consultations. The interviewers were blind to the consensus and register diagnoses.

We did not assess the reliability of SCID interviews in our studies, but in other studies the reliability of SCID-I (Skre et al. 1991, Williams et al. 1992, Miller et al. 2001) and SCID-II (Williams et al. 1992, Osone and Takahasi 2003, Weertman et al. 2003) has been
Nevertheless, it was difficult for the interviewers to remain completely blind to the status of family members because the participants often wanted to discuss the situation in their family and constructed the family tree.

### 6.6.2 Assessment of Negative and Positive Symptoms

SANS (Andreasen, 1983) (Appendix 2) consists of 25 items rated on a six-point scale (0-5) in the interview. The five subscales of SANS are affective flattening or blunting, alogia, apathy, asociality, and inattention. The signs of "affective flattening, alogia, and affective blunting", such as mobility of facial expression, response to a stimulus such as being smiled at, quality of eye contact, use of expressive gestures, etc, should be rated using observation rather than by subjective evaluation (Andreasen 1989, Andreasen et al. 1995b).

SAPS (Andreasen 1984)(Appendix 3) consists of 34 items and is divided into four subscales: hallucinations, delusions, bizarre behavior, and formal thought disorder.

All symptoms were rated based on the greatest lifetime-ever severity. We also used all other available information, including discussions with health care personnel or family members.

The reliability of the various SANS and SAPS items has been assessed repeatedly and found to be excellent, using both inter-rater and test-retest reliability measures, and they have been translated into many languages (Andreasen 1989, 1995b). However, Norman and colleagues (1996) found that levels of interrater reliability were lower than had been reported in earlier studies. Mueser and colleagues (1994) found that the reliability of SANS was good.

### 6.7. The genealogical studies in the isolate

We performed a genealogical search in accordance with published criteria for 263 families from the isolate who gave a blood sample for the genetic study. The ancestors of the patients were traced back for four to 12 generations from the local church registers and the National Archives of Finland to reveal all consanguineous relatives. To estimate the degree of familiality with each patient (Study III), we counted consanguineous patients through all common founders in four-generation pedigrees. We counted the number of consanguineous patients born 1940 to 1976 considering the liability classes of DSM-IV diagnoses (Figure 3).

An overview of total numbers of subjects in the isolate, in the whole country multiplex family and in Studies I-IV is presented in Table 4.
Table 4. An overview of methods and subjects in studies I-IV

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Samples</th>
<th>N</th>
<th>Male %</th>
<th>Mean age years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolate study total</td>
<td>Registers(^1), Case records(^2,4), Interviews(^3,5,6,7), Genealogical research(^8)</td>
<td>Registers</td>
<td>658</td>
<td>59 %</td>
<td>49.1</td>
</tr>
<tr>
<td></td>
<td>DSM-IV Consensus and OCCPI(^2,4)</td>
<td></td>
<td>326</td>
<td>64 %</td>
<td>49.9</td>
</tr>
<tr>
<td></td>
<td>Interview</td>
<td></td>
<td>257</td>
<td>60 %</td>
<td>51.8</td>
</tr>
<tr>
<td>Whole country multiplex</td>
<td>Registers(^1), Case records(^2,4), Interviews(^3,5,6,7)</td>
<td>Registers</td>
<td>4904</td>
<td>55 %</td>
<td>49.7</td>
</tr>
<tr>
<td></td>
<td>DSM-IV Consensus and OCCPI(^2,4)</td>
<td></td>
<td>945</td>
<td>57 %</td>
<td>49.2</td>
</tr>
<tr>
<td></td>
<td>Interview</td>
<td></td>
<td>284</td>
<td>56 %</td>
<td>49.5</td>
</tr>
<tr>
<td>Study I</td>
<td>Registers(^1), Case records(^2), SCID-I-II interviews(^3)</td>
<td>Registers</td>
<td>237</td>
<td>60 %</td>
<td>43.7</td>
</tr>
<tr>
<td></td>
<td>DSM-IV Consensus(^2)</td>
<td></td>
<td>164</td>
<td>67 %</td>
<td>43.7</td>
</tr>
<tr>
<td></td>
<td>Interview</td>
<td></td>
<td>131</td>
<td>66 %</td>
<td>43.6</td>
</tr>
<tr>
<td>Study II</td>
<td>Registers(^1), Case records(^2)</td>
<td>Isolate multiplex (IM)(^9)</td>
<td>78</td>
<td>74 %</td>
<td>50.6</td>
</tr>
<tr>
<td></td>
<td>Isolate singleton (IS)(^10)</td>
<td></td>
<td>112</td>
<td>67 %</td>
<td>47.1</td>
</tr>
<tr>
<td></td>
<td>Whole country (NM)(^11) multiplex</td>
<td></td>
<td>446</td>
<td>60 %</td>
<td>48.7</td>
</tr>
<tr>
<td>Study III</td>
<td>Registers(^1), Case records(^2), SCID-I-II, GAF(^5), SAPS(^6), SANS(^7), Genealogical research(^8)</td>
<td>Isolate singleton (IS)(^10)</td>
<td>113</td>
<td>66 %</td>
<td>47.5</td>
</tr>
<tr>
<td></td>
<td>Isolate multiplex (IM)(^9)</td>
<td></td>
<td>63</td>
<td>70 %</td>
<td>50.3</td>
</tr>
<tr>
<td></td>
<td>Whole country (NM)(^11) multiplex</td>
<td></td>
<td>94</td>
<td>59 %</td>
<td>46.3</td>
</tr>
<tr>
<td>Study IV</td>
<td>Registers(^1), SCID-I-II(^9), GAF(^5), SANS(^7) interviews</td>
<td>Isolate patients</td>
<td>124</td>
<td>65 %</td>
<td>46.0</td>
</tr>
<tr>
<td></td>
<td>&quot;Heathy&quot; siblings</td>
<td></td>
<td>183</td>
<td>49 %</td>
<td>46.1</td>
</tr>
<tr>
<td></td>
<td>Comparison group (Heath 2000)(^12)</td>
<td></td>
<td>111</td>
<td>50 %</td>
<td>50.3</td>
</tr>
</tbody>
</table>

1) Registers: The Hospital Discharge, Free Medicine and Disability Pension
2) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association 1994)
3) Structured Clinical Interview I and II for DSM-IV (First et al. 1996, 1997)
4) Operational Criteria Checklist for Psychotic Illness (McGuffin et al. 1991)
5) Global Assessment of Functioning
6) Scale for the Assessment of Negative Symptoms (Andreasen 1983)
7) Scale for the Assessment of Positive Symptoms (Andreasen 1984)
8) 263 isolate families
9) Isolate multiplex patients had at least one sibling with psychotic disorder
10) Isolate singleton patients had no first-degree relatives with any psychotic disorder according to register information
11) Whole country multiplex families have at least two affected sibling in the family
6.8. Statistical analyses

6.8.1 Statistical analyses in Study I

Using Survo MM 2.05 for Windows, the lifetime prevalence was calculated as the number of individuals born in the isolate and alive on 31 December 1998, who had received a diagnosis of schizophrenia at some point during their life, divided by the number of individuals born in the isolate and alive on 31 December 1998. The cumulative incidence was calculated as the number of individuals born in the isolate who received a diagnosis of schizophrenia at some point during their life divided by the number of individuals born in the isolate during the same years.

Using SPSS 11.0 for Windows, we calculated descriptive statistics for the sample and for frequencies of mental disorders. We also compared the three diagnostic assessments and made cross tabulations for patients with a DSM-IV consensus diagnosis and SCID-I and -II interview diagnosis, register and consensus diagnosis, and register and interview diagnosis.

6.8.2 Statistical analysis in Study II

All OCCPI symptom items were coded dichotomously (Appendix 1): a missing item score was assumed to mean no symptom. Items rated as present in at least 10% of subjects were included in the analysis. Then, on the basis of the kappa values exceeding 0.46, thirty OCCPI items were selected for use in the analyses. We thus excluded certain OCCPI items, including bizarre behavior and delusions, delusions of passivity, primary delusional perception, running commentary voices, other (non-affective) auditory hallucinations, and non-affective hallucination in any modality.

We compared the symptom items in different groups (isolate singletons, isolate multiplex, and multiplex family patients from the whole country) with the logistic regression model, and then the pattern of symptoms using classification tree analysis. That analysis produced a binary classification tree of response variable groups based on dichotomous OCCPI criteria (Breiman et al. 1984).

The factor structure analysis was calculated from the tetrachoric correlation matrix and rotated using VARIMAX rotation (Johnson and Wichern 1982). There was a good rationale for four factors, as the fifth factor accounted for less than 10% of the variance. The four factor solution was also common in other studies (Serretti et al. 1996, 1999, 2001, McGorry et al. 1998, Van Os et al. 1999, Cardno et al. 1999, McIntosh et al. 2001, Murray et al. 2005).
6.8.3 Statistical analysis in Study III

We analyzed the dimensional nature of the individual 19 SANS and 29 SAPS items, and excluded the global items (Study III, Appendix 2 and 3). We divided the material into three groups: Isolate multiplex (N=63), Isolate singleton (N=133), and nationwide (whole country) multiplex patients (N=94). First, we studied 3-7 factor solutions with VARIMAX rotation (Johnson and Wichern 1982) of the isolate and whole country separately, although the factor structures were fairly similar. Then, we calculated the scores of four factors produced by the pooled data and compared them between the three groups. Comparisons were made using linear regression models with group, sex, education, and age as explanatory variables. We also made the comparison using the same method, but using the number of affected consanguineous relatives as explanatory variable. Patients were divided into five groups according to the number of consanguineous affected relatives: 1-5, 6-10, 11-15, and over 15.

6.8.4. Statistical analysis in Study IV

Using SPSS 11.0 for Windows, we calculated the numbers and percentages of principal SCID-I-II diagnosis, co-morbid mental disorders, as well as sociodemographic and clinical characteristics in the groups of initially healthy siblings and the comparison group.

We took the within-family correlation into account by using conditional logistic regression and general estimation equations (Zeger and Liang 1986) in our analysis. We had family as the stratification variable, psychosis as the dependent variable, and age (40-49, 50-59, 60-69 years), sex, residence (city, population centers, rural), contact for mental health problems, contact for alcohol or substance use problems, and smoking as explanatory variables. We also tested the results of 113 SANS interviews of initially healthy siblings using the same logistic regression analysis, with the diagnosis of psychosis as the dependent variable and the SANS items without global ratings as explanatory variables. We also reanalyzed the register diagnoses seven years later.
7. RESULTS

7.1 Prevalence and diagnosis of schizophrenia based on register, case record and interview data in an isolated Finnish birth cohort born 1940-1969 (Study I)

7.1.1 Lifetime prevalence and cumulative incidence

The lifetime prevalence of schizophrenia and schizophrenia spectrum psychotic disorders in 1998 according to the Hospital Discharge, Disability Pension and Free Medicine Registers was 1.5%, and 1.9%, respectively. For schizophrenia spectrum psychotic disorders, it was highest (2.4%) in birth cohorts born from 1950 to 1964. The cumulative incidence was 1.90%. We also estimated the lifetime prevalences based on consensus diagnoses and interviews: the prevalences were 0.9-1.3% and 0.7-1.2%, respectively.

7.1.2 The register, case record, consensus and interview diagnoses of schizophrenia

In the Hospital Discharge Register, 191 (81%) patients had schizophrenia as register diagnosis. We identified only 17 (7%) patients in the Social Insurance Institution registers without a diagnosis in the Hospital Discharge Register. We then used case records to reassess the consensus diagnosis for 164 (69%) of 237 patients, 113 (69%) of whom had a DSM-IV consensus diagnosis of schizophrenia. Finally, we interviewed 131 patients and 83 (63%) of them had an interview diagnosis of schizophrenia.

7.1.3. Comparison of register, consensus and interview diagnoses

When we compared the register diagnosis of schizophrenia, schizoaffective and schizophreniform disorder (code 295 as inclusion criterion) with the DSM-IV consensus diagnosis in 164 cases and with the SCID interview diagnoses in 131 cases, 140 (85%) and 113 (86%), respectively, had a schizophrenia diagnosis in the Hospital Discharge Register (Tables 5 and 6).

The agreement between consensus and interview diagnoses in schizophrenia and schizoaffective disorder was good (a match in 91% of the cases, see Table 7).
Table 5. Comparison of register and consensus diagnoses (N=164)

<table>
<thead>
<tr>
<th>DSM-IV consensus diagnosis(^1)</th>
<th>Register 1 diagnoses(^2)</th>
<th>Lc 1</th>
<th>Lc 2</th>
<th>Lc 3</th>
<th>Lc 4</th>
<th>Lc 0</th>
<th>No dg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lc 1</td>
<td>101</td>
<td>20</td>
<td>2</td>
<td>13</td>
<td>4</td>
<td>140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lc 2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lc 3(^*)</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Register 2,3(^3)</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>24</td>
<td>5</td>
<td>16</td>
<td>5</td>
<td>1</td>
<td>164</td>
<td></td>
</tr>
</tbody>
</table>

2) Hospital Discharge Register diagnoses
3) Disability Pension and Free Medicine Register diagnoses
Liability classes: class 1= schizophrenia, class 2= schizoaffective disorder,
class 3= schizophreniform, delusional, shared psychotic, and brief psychotic disorder, and psychotic disorder NOS,
class 4= affective psychotic disorders, class 0= all other mental disorders
* only schizophreniform disorder

Table 6. Comparison of register and interview diagnoses (N=131)

<table>
<thead>
<tr>
<th>SCID-I-II interview diagnosis(^1)</th>
<th>Register 1 diagnoses(^2)</th>
<th>Lc 1</th>
<th>Lc 2</th>
<th>Lc 3</th>
<th>Lc 4</th>
<th>Lc 0</th>
<th>No dg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lc 1</td>
<td>79</td>
<td>19</td>
<td>1</td>
<td>13</td>
<td>1</td>
<td>113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lc 2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lc 3(^*)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Register 2,3(^3)</td>
<td>2</td>
<td></td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>23</td>
<td>3</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>131</td>
<td></td>
</tr>
</tbody>
</table>

1) Structured Clinical Interview I and II for DSM-IV (First et al. 1996, 1997)
2) Hospital Discharge Register diagnoses
3) Disability Pension and Free Medicine Register diagnoses
Liability classes: class 1= schizophrenia, class 2= schizoaffective disorder,
class 3= schizophreniform, delusional, shared psychotic, and brief psychotic disorder, and psychotic disorder NOS,
class 4= affective psychotic disorders, class 0= all other mental disorders
* only schizophreniform disorder

Table 7. Comparison of consensus and interview diagnoses (N=131)

<table>
<thead>
<tr>
<th>SCID-I-II interview diagnosis(^2)</th>
<th>Consensus diagnoses(^3)</th>
<th>Lc 1</th>
<th>Lc 2</th>
<th>Lc 3</th>
<th>Lc 4</th>
<th>Lc 0</th>
<th>No dg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lc 1</td>
<td>72</td>
<td>13</td>
<td></td>
<td>7</td>
<td></td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lc 2</td>
<td>6</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td></td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lc 3(^*)</td>
<td>2</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lc 4</td>
<td>4</td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lc 0</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diagnoses</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>23</td>
<td>3</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>131</td>
<td></td>
</tr>
</tbody>
</table>

2) Structured Clinical Interview I and II for DSM-IV (First et al. 1996, 1997)
Liability classes: class 1= schizophrenia, class 2= schizoaffective disorder,
class 3= schizophreniform, delusional, shared psychotic, and brief psychotic disorder,
psychotic disorder not otherwise specified.
class 4= affective psychotic disorder, class 0= all other mental disorders
7.2 Clinical phenotype of schizophrenia in a Finnish isolate (Study II)

7.2.1 Frequency of symptoms between isolate and whole country patient groups

We compared the presence of schizophrenia symptoms between the multiplex (N=78) and singleton (N=112) patients in the genetic isolate and the multiplex family patients (N=466) from the whole country and found significant differences between the three samples in 11 individual OCCPI items. However, the classification tree analysis did not discriminate the three patient groups from each other.

7.2.2. Clinical phenotype according to factor analysis

The factor analysis suggested that four distinct factors of the OCCPI variables accounted for 55% of the variance. The factors were "Delusions and hallucinations", "Manic symptoms and behaviour", "Negative" symptoms and "Depressive" symptoms. The basic phenotype structure of schizophrenia in the isolate was similar to that in the multiplex families representing familial schizophrenia in the whole of Finland.

7.3 Affective flattening and alogia associate with the familial form of schizophrenia (Study III)

7.3.1. Comparison between isolate and whole country patient groups

The isolate singleton (IS) patients had significantly less symptoms of affective flattening and alogia (factor 1) than isolate (IM) and nationwide (whole country) (NM) multiplex family groups (p=0.01 and p=0.001, respectively). In "delusions and hallucinations" (factor 3), there was again a significant difference, the IS (p=0.02) and IM patients (p=0.01) presenting less symptoms than the NM patients. The IS patients had significantly lower SANS scores than the two multiplex groups (p=0.02). In SAPS sums, the NM patients had significantly more symptoms than the IS and IM patients (p=0.00007).

The demographic and clinical characteristics of isolate and whole country multiplex patients are shown in Table 8.
Table 8. Demographic and clinical characteristics of isolate and whole country multiplex patients (N=290)

<table>
<thead>
<tr>
<th></th>
<th>Isolate singletons (IS)(1)</th>
<th>Isolate multiplex (IM)(3)</th>
<th>Multiplex whole country (NM)(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>N</td>
<td>133</td>
<td>88</td>
<td>45</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>47.5  (9.6)</td>
<td>46.4  (8.3)</td>
<td>49.8  (11.4)</td>
</tr>
<tr>
<td>Age of onset (SD)</td>
<td>23.0  (6.3)</td>
<td>22.3  (5.6)</td>
<td>24.3  (7.3)</td>
</tr>
<tr>
<td>Education, years (SD)</td>
<td>9.8   (2.9)</td>
<td>9.9   (2.6)</td>
<td>9.7   (3.5)</td>
</tr>
<tr>
<td>Hospitalization:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of admissions (SD)</td>
<td>15.6  (15.7)</td>
<td>14.8  (14.8)</td>
<td>17.1  (17.5)</td>
</tr>
<tr>
<td>Mean duration, days (SD)</td>
<td>111.8 (272.4)</td>
<td>138.5 (328.1)</td>
<td>60.9 (85.4)</td>
</tr>
<tr>
<td>GAF 1 year(4) (SD)</td>
<td>39.1  (15.3)</td>
<td>38.3  (14.8)</td>
<td>40.7  (16.2)</td>
</tr>
<tr>
<td>SANS(5) sum (SD)</td>
<td>50.9  (22.2)</td>
<td>51.2  (21.7)</td>
<td>50.3  (23.4)</td>
</tr>
<tr>
<td>SAPS(6) sum (SD)</td>
<td>41.5  (19.8)</td>
<td>42.1  (21.2)</td>
<td>40.4  (17.0)</td>
</tr>
</tbody>
</table>

1) Isolate singleton patients had no first-degree relatives with any psychotic disorder according to register information
2) Isolate multiplex patients had at least one sibling with psychotic disorder
3) Whole country multiplex families had at least two affected siblings
4) Global Assessment of Functioning
5) Scale for the Assessment of Negative Symptoms (Andreasen 1983)
6) Scale for the Assessment of Positive Symptoms (Andreasen 1984)

7.3.2 Phenotype according to factor analysis

The factor analysis resulted in four factors of which two were negative: "Affective flattening and alogia" and "Anhedonia and social dysfunction", plus "Disorganization" and "Delusions and hallucinations".

7.3.3. Influence of consanguinity

We observed no significant differences on the level of consanguinity (Figure 3), and neither did the mean number of affected consanguineous relatives differ significantly between the IS and (p=0.08) IM patients. Level of consanguinity did not correlate with any of the factor scores, in contrast to the family history.
7.4 Psychosis among initially healthy siblings of schizophrenia patients (Study IV)

7.4.1 Psychotic disorders of initially healthy siblings

In the SCID-I interview, 30 (16.4 \%) siblings received a diagnosis of psychotic disorder among the 183 siblings with no register diagnosis of psychotic disorder in 1991. Fourteen siblings (7.7\%) had had psychotic symptoms before 1991 and sixteen (8.7\%) developed psychotic symptoms during the follow-up.

Table 9. SCID-I-II\(^1\) diagnosis of 183 healthy siblings, and SCID-I diagnosis of 111 individuals from the comparison group.

<table>
<thead>
<tr>
<th></th>
<th>Isolate siblings</th>
<th>Comparison group(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>183</td>
<td>111</td>
</tr>
<tr>
<td><strong>Psychotic disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1 (1) 0.5 %</td>
<td>1 0.9 %</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>6 (2) 3.3 %</td>
<td></td>
</tr>
<tr>
<td>Delusional disorder</td>
<td>3 (1) 1.6 %</td>
<td></td>
</tr>
<tr>
<td>Psychotic disorder NOS</td>
<td>8 (4) 4.4 %</td>
<td></td>
</tr>
<tr>
<td>Alcohol-induced psychotic disorders</td>
<td>4 (3) 2.2 %</td>
<td>1 0.9 %</td>
</tr>
<tr>
<td>Other substance induced psychotic disorders</td>
<td>2 (1) 1.1 %</td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder with psychotic features</td>
<td>4 (1) 2.2 %</td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder I</td>
<td>2 (1) 1.1 %</td>
<td></td>
</tr>
<tr>
<td><strong>Other mental disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other depressive disorders</td>
<td>28 15.3 %</td>
<td>21 18.9 %</td>
</tr>
<tr>
<td>Personality disorders A(^{3,5}) *</td>
<td>7 3.8 %</td>
<td>not assessed</td>
</tr>
<tr>
<td>Personality disorders B(^{3,5})</td>
<td>4 2.2 %</td>
<td>not assessed</td>
</tr>
<tr>
<td>Alcohol use disorders</td>
<td>7 3.8 %</td>
<td>14 12.6 %</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>22 12.0 %</td>
<td>8 7.2 %</td>
</tr>
<tr>
<td>Other</td>
<td>1 0.5 %</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>99 54.1 %</td>
<td>45 40.5 %</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>84 45.9 %</td>
<td>66 59.5 %</td>
</tr>
<tr>
<td><strong>SUM</strong></td>
<td>183 99.9 %</td>
<td>111 100.0 %</td>
</tr>
</tbody>
</table>

\(^1\) Structured Clinical Interview I and II for DSM-IV (First et al. 1996, 1997)
\(^2\) Health 2000 study (Aromaa and Koskinen 2004)
\(^3\) Paranoid, schizotypal and schizoid personality disorders
\(^4\) Histrionic, narcissistic and borderline personality disorders
\(^5\) Avoidant, dependent and obsessive-compulsive and not otherwise specified personality disorders

* 5 siblings had SCID-II personality disorder without other diagnosis. Siblings had 43 (23\%) co-morbid diagnoses: 15 (8.2\%) alcohol use, 15 anxiety (8.2\%), and 6 (3.3\%) other depressive disorders, 5 (2.7\%) personality disorder (2 cluster A and 3 cluster B-C), one anxiolytic dependence disorder and one hypochondriasis. Comparison group had 10 (9.0\%) co-morbid diagnoses: 5 anxiety and 5 alcohol use disorders.
Of all 30 siblings with an interview diagnosis of psychotic disorder, only seven had a hospital treatment because of psychotic disorder between 1991 and 1998 according to the Hospital Discharge Register, even though they all had psychotic symptoms prior to 1998 according to interview. Less than half (43%) had current psychiatric treatment or medication and eight (28%) had current antipsychotic treatment.

### 7.4.2 Negative symptoms of initially healthy siblings

113 of 183 initially healthy siblings were interviewed with SANS (Appendix 2). Items 3 (Paucity of expressive gestures) and 15 (Impersistence at work or school) had statistically significant odds ratios of 4.6 and 3.0 (CI 1.1-18.4, p=0.004 and CI 1.6-5.9, p=0.001) respectively, and were associated with the diagnosis of psychotic disorder.

### 7.4.3 Siblings with initially no register diagnosis of psychosis compared to the comparison group

Initially healthy siblings had significantly more diagnoses of psychotic disorders (16% versus 2%, p<0.0001) than the comparison group (N=111), and 54% versus 41% had any mental disorder in the SCID-I interview. The comparison group had higher current GAF ratings (mean 79.2, SD 12.5 versus mean 73.7, SD 14.9, p=0.002) than the siblings.

An overview of aims and main results in different studies is given in Table 10.
Table 10. Overview of aims and main results in four studies.

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
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<tbody>
<tr>
<td><strong>Aims:</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prevalence of schizophrenia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cumulative incidence of schizophrenia, schizoaffective and schizophreniform disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reliability of diagnoses</td>
<td>Aim:</td>
<td>Aim:</td>
<td>Aim:</td>
</tr>
<tr>
<td><strong>Prevalence of schizophrenia</strong></td>
<td>Phenotype analysis of schizophrenia according to case record based OCCPI(^1) ratings</td>
<td>Phenotype analysis of schizophrenia according to interview based SANS(^3) and SAPS(^4) ratings</td>
<td>Mental health of siblings of schizophrenia patients</td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of schizophrenia was according to</td>
<td>Phenotype in the isolate was similar to whole Finland familial(^2) schizophrenia</td>
<td>Familial patients: more affective flattening and alogia than IS(^5) patients</td>
<td>30 (16%) of initially healthy siblings received diagnosis of some psychotic disorder</td>
</tr>
<tr>
<td>Register diagnoses 1.5% Consensus diagnoses 0.9-1.3%</td>
<td>Four factors were found: 1. &quot;Delusions and hallucinations&quot; 2. &quot;Manic&quot; 3. &quot;Negative&quot; 4. &quot;Depressive&quot;</td>
<td>Isolate patients: less positive symptoms than NM(^6) patients</td>
<td>14 (7.7%) of 183 initially healthy siblings had psychotic symptoms before 1991, and 16 (8.7%) developed symptoms during follow-up</td>
</tr>
<tr>
<td>Interview diagnosis 0.7-1.2%</td>
<td></td>
<td>Four factors were found: 1. &quot;Affective flattening and alogia&quot; 2. &quot;Disorganization&quot; 3. &quot;Delusions and hallucinations&quot; 4. &quot;Anhedonia and social dysfunction&quot;</td>
<td>54% of initially healthy siblings had a lifetime diagnosis of any mental disorder in the interview</td>
</tr>
<tr>
<td>Cumulative incidence for schizophrenia, schizoaffective and schizophreniform disorder was 1.9% according to register data</td>
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<td></td>
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<tr>
<td>Of those with register diagnosis of schizophrenia, schizoaffective or schizophreniform disorder 69% had a consensus and 63% an interview diagnosis of schizophrenia.</td>
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</tbody>
</table>

\(^1\) Operational Criteria Checklist for Psychotic Illness (McGuffin et al. 1991)

\(^2\) Two or more family members affected

\(^3\) Scale for the Assessment of Negative Symptoms (Andreasen 1983)

\(^4\) Scale for the Assessment of Positive Symptoms (Andreasen 1984)

\(^5\) Isolate singleton patients had no first-degree relatives with any psychotic disorder according to register information

\(^6\) Whole country multiplex families have at least two affected siblings in the family
8. DISCUSSION

Our main findings were that the prevalence of schizophrenia was relatively high in the isolate as ascertained using register, case record or interview data, as was the lifetime cumulative incidence. Of those with a register diagnosis of a schizophrenia-associated psychotic disorder, 69% received a record-based consensus diagnosis and 63% an interview diagnosis of schizophrenia. The isolate patients represented familial schizophrenia with affective flattening and alogia as negative symptoms, and they had less positive symptoms. Furthermore, 8.7% of initially healthy siblings received a diagnosis of psychotic disorder during a relatively short follow-up. In addition, 7.7% of siblings had psychotic symptoms already before the register diagnosis was identified.

8.1. Methods and methodological limitations

8.1.1. Registers and representativeness of study samples

The accuracy of the Finnish Hospital Discharge Register has been found to be excellent. The primary diagnoses in the register and hospital case notes were identical in 99% of schizophrenia cases (Keskimäki and Aro 1991).

Byrne et al. (2005) conducted a systematic review of studies investigating the validity of administrative registers used in psychiatric research. They concluded that there were relatively few high quality studies, and that methods and quality of studies varied considerable. However, no gold standard exists for the assessment of register data validity, and available studies mostly draw positive conclusions about the validity of registers. The accuracy of the Disability Pension and Free Medicine Registers has not been assessed. However, the proportion of patients who do not receive hospital treatment is relatively small, less than 10% (Lehtinen et al. 1990, Lehtinen et al. 1991). In our study, we identified from the Disability Pension and Free Medicine Registers just 17 patients (3% of all patients) who did not receive hospital treatment.

Patients with a register diagnosis of other non-affective psychotic disorder, e.g. delusional disorder or psychotic disorder not otherwise specified, were not included in the study. Previous studies (Isohanni et al. 1997, Moilanen et al. 2003) have found that a number of these patients actually have schizophrenia, so including these patients in our study would probably have raised the prevalence of schizophrenia in these birth cohorts. In addition, we excluded some schizophrenia spectrum disorders, e.g. paranoid, schizoid and schizotypal personality disorders, from the register survey. However, these patients might have manifested psychotic disorders and schizophrenia in the follow-up.
In 1969, when the first hospitalizations were registered in the National Hospital Discharge, Disability Pension and Free Medicine Registers, the patients born in 1940 were 29 years old. The mean age of onset was 28.2 years according to the register data, so we might have missed some patients who had no further relapses and, in addition, some at the other end with late onset of schizophrenia. In addition, the amount of psychiatric inpatient beds decreased dramatically in Finland in 1990s, and this might have lead to the more stringent indications of hospitalization. The prevalence might therefore have been even higher.

In our study, the patients from the isolate and whole country, isolate siblings and comparison group were all identified using the same unique representative extensive Finnish health care registers. However, the inclusion criteria varied in studies I-IV.

In Study I, we analyzed the birth cohort (N=282) identified from the national population register born from 1940 to 1969 in the isolate, contrary to studies II-IV with patients having at least one parent born in the isolate. However, the study project was originally designed mostly for genetic study purposes, and that placed on us the limitation that we had not identified for genetic studies all those patients who were born in the isolate. We had not contacted these patients without a parent born in the isolate or who refused from the genetic study, and we did not reassess their register diagnoses or interview them. So we had to estimate the lifetime prevalence based on interview and consensus diagnoses. Based on register information, individuals who refused to participate in the study were less severely affected than those who participated. Although this is a limitation in the clinical study, from the perspective of the genetic study it is an advantage that families having the most severely affected patients agreed to participate in the study.

In Study II, multiplex patients representing familial schizophrenia from the whole country were identified using the same registers. We compared the singleton and multiplex family patients from the isolate and whole country multiplex family patients; unfortunately we could not compare the isolate patients to singleton patients from the whole country or even to more heterogeneous populations (DeLisi et al. 2001). We included only consensus diagnosis ascertained schizophrenia patients in our study. This limits comparison with some other studies, which included schizophrenia plus other psychotic disorders (Kendler et al. 1998), but improves the validity of our analyses. In addition, we constructed extensive isolate pedigrees, which showed us all the complex genealogical connections in four generations. The information was used in analyses in Study III.

In Study III, we had the same limitation as in Study II, i.e. lack of a singleton patient sample from the whole country, and so could not compare our finding to the average schizophrenia rates found in Finland. The genealogical study designed to reveal all consanguineous relatives of schizophrenia patients was conducted exclusively in the isolate, so comparisons between the isolate and whole country multiplex family samples were not possible.
In Study IV, we could not contact or interview all healthy siblings (N=1353), which might have influenced our results. We aimed to interview at least one sibling nearest in age to every patient; however, we did not take into account the age differences between the siblings. We had 124 patients and 183 siblings with no register based diagnosis of psychosis in 110 families, and we took into account the within-family correlation in our statistical analysis.

The comparison group we had was a representative sample of the Finnish general population, but it might not be representative of the population originating from the isolate.

8.1.2 Case record collection and consensus diagnosis based assessments

We collected all available original case notes. The case notes were insufficient in five cases. In the isolate, kappa values for the best-estimate diagnosis were good to excellent, as they were also for the whole country multiplex family sample. Assessing consensus diagnoses in this way has emerged as reliable in many previous studies (Leckman et al. 1982, Goodman et al. 1984, Craddock et al. 1996, McConville and Walker 2000).

The reliability assessment of the register diagnoses we used in our diagnostic assessment is almost identical to that used by Isohanni et al. (1997) and Mäkikyrö et al. (1998). The study by Mäkikyrö and colleagues (1998) was based on the first 73 patients who participated in the genetic study in the early 1990s and, unsurprisingly, our results were quite similar. In the smaller sample, 87% of the patients obtained a diagnosis of schizophrenia, compared with 69% in our total sample, and 90% vs. 87% respectely had any schizophrenia associated psychotic disorder (Mäkikyrö et al. 1998). The most densely affected families were contacted first, which explains the slightly better reliability of register diagnoses found in that study.

In contrast, (Isohanni et al. 1997, Moilanen et al. 2003) found in the Northern Finland 1966 Birth Cohort that all persons who had received a register diagnosis of schizophrenia also fulfilled DSM-III-R diagnostic criteria for schizophrenia; however, there were 43% false negative cases having a register diagnosis of psychosis other than schizophrenia. Nevertheless, this cohort was substantially younger than ours and had shorter duration of illness. It had, more over, been treated during the era in Finnish psychiatry when it was customary not to give a diagnosis of schizophrenia after the first hospital treatments due to psychosis, even if the diagnostic criteria were met.

This was consistent with a studies of first-admission patients, which found that Finnish clinicians underdiagnosed schizophrenia (Pakaslahti 1987, Taiminen et al. 2001). Thus, in line with other studies, we conclude that the register diagnosis should be reassessed for genetic research (Moilanen et al. 2003, McConville and Walker 2000).
8.1.3 The Operational Criteria Checklist for Psychotic Illness ratings

Serretti and Olgiati (2004) summarized some limitations of existing studies. The samples are often too small and not adequately balanced in their composition. Too few non-psychotic symptoms are analyzed. The prevalence rates of symptoms are generally adequate in overall samples but not in individual diagnostic subgroups. Most studies include exploratory but not confirmatory factor analyses.

In our study, the Operational Criteria Checklist for Psychotic Illness (OCCPI) rating was based on the case notes for over 650 patients, blind to the register diagnosis. Thirty OCCPI items were selected for the analyses. However, the selection of OCCPI items also influences the factor structure (Kendler et al. 1998), and the exclusion of items may have affected our results derived from the four-factor solution. However, the results for all 80 psychotic and affective items also yielded a four-factor solution, which was very similar to the one with 30 items.

The choices made in analyses represent another potential influence on results. However, Serretti and colleagues (1999) replicated the factor analysis with four factors using two different methods (confirmatory and exploratory factor analysis) in two independent samples. We included only schizophrenia patients in this study, which limits the comparison to other studies, but improves validity. Only one study had exclusively schizophrenia patients (Wickham et al. 2001). However, RDC criteria for schizophrenia were used, which required a shorter duration of symptoms (only two weeks instead of six months of DSM-IV) and complicates comparisons.

8.1.4. Interview based assessments

We observed good diagnostic agreement between the register diagnosis of schizophrenia and SCID diagnoses, in contrast to the findings of Taiminen et al. (2001) with a sample of first-admission psychosis. However, the patients were younger in that study and the follow-up time was longer in ours.

Our interviewers were nurses, mental nurses and one doctor. We did not assess the reliability of SCID interviews, but we improved their reliability by intensive training and audio taping the first 20 SCID interviews of every interviewer. The agreement for SCID interview based schizophrenia diagnoses has been high, as assessed from audio taped material (Skre et al. 1991) and using the test-retest method (Williams et al. 1992).

The SCID interview assesses affective symptoms better than a consensus diagnosis made from case records, because in clinical practice affective symptoms among patients with severe positive psychotic symptoms are sometimes ignored (Taiminen et al. 2001). Further, Roy and colleagues (1997) pointed out in their methodological study of 134 patients from large multigenerational pedigrees densely affected by bipolar disorders or schizophrenia that
the most problematic diagnostic distinctions involved schizoaffective disorder, which is easily confused with schizophrenia, bipolar I and schizophreniform disorders.

In our study, 12 (40%) of siblings with no register diagnosis received a diagnosis of schizoaffective or affective psychotic disorder, but some of these siblings clustered in two families with several members with schizoaffective or affective psychotic disorders. However, several family studies have reported that families have high risk not only for schizophrenia and schizoaffective disorders but also for affective psychotic disorders (Kendler et al. 1993a,b, Chang et al. 2002, Maier et al. 2002).

8.1.5 Assessment of negative and positive symptoms

SANS covers 19 negative symptoms, compared with relatively few items assessing negative symptoms in OCPPI. Thus, using individual SANS and SAPS items instead of global scores gives a more detailed view of signs and symptoms of schizophrenia, especially negative symptoms. Ratings of affective flattening and alogia (diminished expression) reflect behaviors evident during direct observation within a clinical interview. These might vary more than anhedonia and social dysfunction, which are more of a reflection of global social engagement occurring in the community (Blanchard and Cohen 2005). However, to improve reliability, Andreasen (1989) has recommended that SANS and SAPS ratings should ideally be based on multiple sources of information. This is what we aimed to do.

8.1.6 Genealogical studies

Only the family history or status of first-degree relatives correlated with the factors "affective flattening" and "delusions and hallucination", contrary to the degree of familiality counted from four-generation pedigrees. However, on the basis of the genealogical study, all patients in the homogeneous isolate represented familial schizophrenia. We have also previously reported that practically all people in our isolate born before 1940s are in fact related to one another through numerous genealogical links (Hovatta et al. 1999, Varilo et al. 1996, 2003). The genealogical study was conducted exclusively in the isolate, which made the comparison with the multiplex families from the whole country impossible.

8.1.7 Statistical methods

In Studies II and III we included all items rated as present in at least 10% of subject for factor analysis. So, after OCCPI reliability assessments we included 30 OCCPI items, 19 SANS and 29 SAPS items in our analyses. All SANS and SAPS items were included except "Clanging" and "Inattentiveness during testing". In the OCCPI factor analysis, we dichotomized the items and excluded several of them, on the basis of the kappa values; this might have affected our results. However, our study was comparable with other investigations (Table 1). The factor analyses were calculated using VARIMAX rotation (Johnson and Wichern, 1982) and both analyses had good rationale for four factors, as in
many other OCCPI studies (Serretti et al. 1996, 1999, 2001; McGorry et al. 1998; Van Os et al. 1999; Cardno et al. 1999; McIntosh et al. 2001; see Table 1), but most SANS and SAPS factor analyses resulted in five factors (Toomey et al. 1997, Emsley et al. 2001, McGrath et al. 2004b, Niehaus et al. 2005) or even 11 factors (Peralta and Cuesta 1999, Table 2). However, the factors affective flattening and alogia, disorganization, delusions and hallucinations and anhedonia and social dysfunction are common to other studies, and there was a good rationale for four factors, while the fifth factor accounted for less than 10% of the variance. So, our results are consistent with other studies, showing that the methods were reliable.

In the isolate, multiple affected patients and siblings were from the same families and observations were thus not independent. We took the within-family correlation into account by using conditional logistic regression and general estimation equations (Zeger and Liang 1986) in our analysis. However, there were numerical convergence problems in some models, probably due to small cluster sizes, and we were able to model only part of the analysis using the general estimation equations method.

8.2 Lifetime prevalence and cumulative incidence (Study I)

For the birth cohorts born 1940-69 in the isolate, the lifetime register based prevalence of schizophrenia in 1998 was 1.5%, and of schizophrenia associated psychotic disorders was 1.9%. The cumulative incidence of schizophrenia associated psychotic disorders in the total birth cohort was also 1.9%. This is high compared to Goldner’s et al. (2002) systematic review analysis of best-estimate lifetime prevalence for schizophrenia of 0.55% (0.37 to 0.8), or for schizophrenia spectrum disorders of 1.45% (0.8 to 2.37). However, other isolates with high prevalence of schizophrenia have been described. In Puerto Rico, the lifetime prevalence for the age range 17-64 years in 1984 was 1.6% for schizophrenia and 1.8% for schizophrenia spectrum disorders (Canino et al. 1987). The prevalence in an isolated rural area of North Sweden in 1977 was also high, at 1.7% (Böök et al. 1978).

In our study, the register-based lifetime prevalence of schizophrenia (1.5%) among individuals born in the isolate was higher than in other parts of Finland. However, the DSM-IV consensus diagnosis- or SCID interview-based prevalences (0.9-1.3 and 0.7-1.2%) are rather similar to other Finnish studies: the cumulative incidence in the Northern Finland 1966 Birth Cohort was 0.9% (Isohanni et al. 2001), and the lifetime prevalence in the Mini Finland Health Survey was 1.3% for those aged 30 or over (Lehtinen et al. 1990).

Patients with a register diagnosis of other non-affective psychotic disorders, e.g. delusional disorder or psychotic disorder not otherwise specified, were not included in the study. In previous studies, it was found that a number of these patients actually have schizophrenia, so including these patients in our study would probably have raised the prevalence of schizophrenia.
In our study, the lifetime prevalence of schizophrenia was highest (2.4-2.5%) in the age groups 39-53 years born 1945-59 in the isolate. At that time, the study region was among the least developed parts of Finland. Moreover, during the 1950s infant mortality was high: 38.5 infant deaths per 1000 live births compared to 29.4 in the whole country (Palmgren, Official Statistics of Finland 1964). The occurrence of schizophrenia was lower in the birth cohorts of 1960-64 (1.5%) and 1965-69 (1.0%), which accords with the previously observed decline in the schizophrenia incidence in birth cohorts born from 1954 to 1965 (Suvisaari et al. 1999).

In Denmark by contrast, the first-admission rates of schizophrenia initially decreased and have then been increasing since the late 1980s in register based studies (Munk-Jørgensen and Mortensen 1992, Tsuchiya and Munk-Jørgensen 2002). In Finland, public health care has improved and the proportion of hospital deliveries has increased considerably since the 1960s (The Official Statistics of Finland 1972). On the other hand, patients born in the 1960s had not lived through the whole risk period for schizophrenia. The oldest patients, born 1940 to 1945, also had a lower occurrence of schizophrenia, but as the registers were computerized only in 1968 the numbers might be inaccurate. Mortality had no effect on the prevalence, as the cumulative incidence and lifetime prevalence were almost identical.

8.3. The phenotype in the isolate is similar to familial schizophrenia in the whole of Finland (Study II)

Four factors, "delusions and hallucinations", "manic", "negative", and "depressive", were detected in the genetic isolate of 190 patients with a DSM-IV diagnosis of schizophrenia.

Hence, we found that the clinical phenotype of schizophrenia in the isolate resembled that found among patients with at least two affected family members from the whole country (patients with familial schizophrenia), regardless of whether the isolate patients were the only affected individuals in their family or not. Many studies have suggested that familial schizophrenia may represent a more severe form of the disorder, with more negative (Verdoux et al. 1996, Malaspina et al. 2000, Ross et al. 2000), or disorganized (Cardno et al. 1997, Van Os et al. 1997, Wickham et al. 2001) symptoms. Thus, schizophrenia in a genetically isolated population with a high lifetime prevalence of schizophrenia represents familial schizophrenia as it manifests in pedigrees densely affected with schizophrenia. For genetic studies, four factors that are well demarcated provide a useful alternative to classical diagnostic systems. These four factors were used as phenotypic traits in a genetic study that provided further evidence that the DISC1 gene might be involved in the etiology of schizophrenia (Hennah et al. 2003).
8.4 Affective flattening and alogia associate with the familial form of schizophrenia (Study III)

Patients with at least one psychotic affected sibling, both in the isolate and nationwide samples, suffered more than singletons from severe affective flattening and alogia, such as paucity of expressive gestures, decreased spontaneous movements, unchanging facial expression, and poor eye contact. Moreover, the level of functioning (GAF) was lower and the sum of negative symptoms was significantly higher in these groups compared with the isolate patients who were the only affected individuals in their family. However, the isolate patients, regardless of their familial loading for schizophrenia, had less delusions and hallucinations than the whole country multiplex patients, which may be related to the genetic homogeneity in the isolate.

Concordant with this finding we found the negative symptoms "Paucity of expressive gestures" and "Lack of vocal inflections" to be phenotypic features in initially healthy siblings that could benefit genetic analysis in addition to clinical diagnoses (Study IV). However, SANS has not been validated or even used in a general population. So, our result that paucity of expressive gestures and lack of vocal inflections associate with psychosis in siblings is preliminary.

Our finding indicating an association between negative symptoms and familiality agrees with most previous twin, adoption, and family studies (Dworkin and Lenzenweger 1984, Burke et al. 1996, Verdoux et al. 1996, Kendler et al. 1997, Van Os et al. 1997, Wickham et al. 2001, Cardno et al. 2002b). However, this was not the outcome to emerge from analysis of the Roscommon data, which suggested that negative symptoms did not predict family characteristics (Kendler et al. 1994b), nor from the study of DeLisi and colleagues (1987) of siblings with schizophrenia or schizoaffective disorder.

We found four factors in our factor analysis of SANS and SAPS: two of the factors in SANS were "Affective flattening and alogia" and "Anhedonia and social dysfunction", as in other studies of SANS and SAPS (Table 2, Minas et al. 1994, Peralta and Cuesta 1999), and studies analyzing exclusively SANS items (Mueser et al. 1994, Peralta and Cuesta 1995, Sayers et al. 1996). Negative symptoms have repeatedly emerged as a separate factor, independent of positive symptoms, disorganization and affective symptoms. The most reliable factors within negative symptoms include diminished expression (symptoms of affective flattening and alogia) and a factor tapping anhedonia and asociality (composed of symptoms of anhedonia, diminished interest, and decreased social engagement) (Blanchard and Cohen 2005).
In our study, the two negative factors are concordant with these factors. In addition, we had a preliminary finding of negative SANS factors being associated with the diagnosis of psychosis in healthy siblings (Study IV). These results could limit the phenotypic heterogeneity of schizophrenia and might allow for the identification of a subtype for further studies.

8.5. Psychosis among initially healthy siblings of schizophrenia patients (Study IV)

Our results clearly show that nationwide health care registers cannot be used to exclude psychotic disorders in relatives of patients with schizophrenia. In 1991 7.7% of the siblings who were presumed healthy based on Hospital Discharge Register actually had psychotic symptoms. The number of false negatives would be high enough to jeopardize the results of genetic analyses, if these siblings were treated as unaffected in the analyses. Even if the initially healthy siblings were treated as unknown, as is often the case, the analyses would have compromised statistical power compared to more exact diagnoses. This finding of false negative cases was concordant with the latest Finnish studies assessing the reliability of register diagnoses (Isohanni et al. 1997, Moilanen et al. 2003, Taiminen et al. 2001). However, as Byrne and colleagues (2005) concluded in their review article, there are relatively few high quality studies addressing this issue.

The rate of emergence of new psychotic disorders among siblings during the relatively short follow-up time of this study was also high. Between 1991 and 1998, 8.7% of the siblings developed any psychotic disorder, although their mean age in 1991 was already 37 years. The high rate of new-onset psychotic disorders reflects the fact that many siblings came from multiply affected families.
9. CONCLUSIONS AND IMPLICATIONS

9.1. Conclusions

The register-based prevalence of schizophrenia in this genetic homogenous isolate was relatively high (1.5%). The prevalence of schizophrenia associated disorders was also high (1.9%), and especially so among those born 1940 to 1959 (2.4%). In addition, the prevalence of schizophrenia, based on DSM-IV consensus diagnoses and SCID interviews, was high (0.9-1.3% and 0.7-1.2%, respectively). The cumulative incidence of schizophrenia associated psychotic disorders including all deaths was 1.9%. Of those with a register diagnosis of schizophrenia associated psychotic disorders, 69% or 63% also received a record based consensus diagnosis or SCID interview diagnosis of schizophrenia. For molecular genetic research work the register diagnosis should be reassessed using either a structured interview or a best-estimate consensus diagnosis.

OCCPI phenotype analysis resulted in four factors: "Delusions and hallucinations" and "Negative" factors, and two affective ("Manic" and "Depressive") factors. Our findings suggest that the basic phenotype structure of schizophrenia in this isolated and homogeneous population is similar to that in the multiplex families representing familial schizophrenia in the whole of Finland.

Schizophrenia patients having first-degree relatives with psychotic disorder had more severe negative symptoms with affective flattening and alogia than those who were the only affected individual in the family. Moreover, the isolate patients, regardless of their familial loading for schizophrenia, had less delusions and hallucinations than the whole country multiplex patients. This finding may be related to the genetic homogeneity in the isolate.

Absence of a register diagnosis cannot be used in molecular genetic studies to confirm that siblings of patients with schizophrenia diagnosis are healthy. During a relatively short follow-up, almost one tenth (8.7%) of initially healthy siblings developed psychotic disorder. The risk of emergence of new psychotic disorders among initially healthy siblings should be taken into account in genetic analysis. This finding also encourages the use of endophenotypes in genetic analyses instead of reliance on psychiatric diagnoses only.
9.2. Clinical implication

The use of structured clinical interview allowed us to identify patients with psychotic and other mental disorders better and earlier than traditional diagnostic assessments. It also helped us to recognize the negative symptoms of schizophrenia patients. Hence, the structured diagnostic interview should be routinely used, not only in research but also in clinical practice.

In our study, almost three-quarters of initially healthy siblings of schizophrenia patients with psychotic disorders had had contact with health care professionals for mental health problems and alcohol or substance use problems, compared to one third of non-psychotic siblings. However, less than half of siblings with any lifetime diagnosis of psychotic disorder had current psychiatric treatment. This suggests that when persons who have relatives with schizophrenia or schizophrenia associated disorders seek help for any mental, alcohol or substance use problems, psychotic symptoms should always be assessed carefully using clinical interview methods.

9.3. Implications for future research

The registers in psychiatric research are excellent for identifying psychotic patients, since about 90% of patients have been hospitalized. However, there has been little systematic investigation of the validity of registers. So, register information should be cross validated with interview studies to benefit future research.

The findings from phenotype studies of negative and positive symptoms of schizophrenia patients and negative symptoms of initially healthy siblings should encourage further research. Thus, both the negative symptom factors, "Affective flattening and alogia" and "Anhedonia and social dysfunction", and also the positive symptoms factor "Delusions and hallucinations", might benefit genetic analysis in addition to clinical diagnosis.

The search for new phenotypic clusters based on signs and symptoms should be encouraged. The ultimate goal might be the division of classic schizophrenia into more specific subdivisions reflecting the possible specific genetic etiology of schizophrenia in each family.
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11. REFERENCES


Andreasen NC. The Scale of the Assessment of Negative Symptoms (SANS). Iowa City, IA: University of Iowa, 1983.


Hovatta J, Lichtermann D, Juvonen H, Suvisaari J, Terwilliger JD, Arajärvi R, Kokko-Sahi
ML, Ekelund J, Lönnqvist J, Peltonen L. Linkage analysis of putative schizophrenia gene
candidate regions on chromosomes 3p, 5q, 6p, 8p, 20p, and 22q in a population-based

Hovatta I, Varilo T, Suvisaari J, Terwilliger JD, Ollikainen V, Arajärvi R, Juvonen H,
Kokko-Sahi ML, Väissänen L, Mannila H, Lönnqvist J, Peltonen L. A Genomewide screen for
schizophrenia genes in an isolated Finnish subpopulation, suggesting multiple

Hwu HG, Yeh EK, Chang LY. Prevalence of psychiatric disorders in Taiwan defined by the

Hwu HG, Wu YC, Lee SFC, Yeh LL, Gwo SC, Hsu HC, Chang CJ, Chen WJ. Concordance of
positive and negative symptoms in coaffected sib-pairs with schizophrenia. American


Ingraham LJ, Kugelmass S, Frenkel E, Nathan M, Mirsky AF. Twenty-five-year follow-up of
the Israeli high-risk study: current and lifetime psychopathology. Schizophrenia Bulletin

Isohanni M, Mäkikyrö T, Moring J, Räsänen P, Hakko H, Partanen U, Koiranen M, Jones P. A
comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish
national birth cohort: clinical and research diagnoses of schizophrenia. Social Psychiatry
and Psychiatric Epidemiology 1997; 32:303-308.

Isohanni M, Jones PB, Moilanen K, Rantakallio P, Veijola J, Oja H, Koiranen M. Jokelainen
J, Croudace T, Järvelin MR. Early developmental milestones in adult schizophrenia and
other psychoses. A 31-year follow-up of the Northern Finland 1966 birth cohort.

Jokipii M. Folio 153 settlement. Atlas of Finland, National Board of Survey and

Johnson RA, Wichern DW. Applied multivariate statistical analysis. New Jersey:

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome Scale (PANSS) for

Kendler KS. Schizophrenia: genetics. In: Sadock BJ, Sadock VA, Editors. Kaplan and
Williams & Wilkins 2000.
Kendler KS, Gruenberg AM. An independent analysis of the Danish adoption study of schizophrenia VI. The relationship between psychiatric disorders as defined by DSM-III in the relatives and adoptees. Archives of General Psychiatry 1984; 41:555-564.


Minas IH, Klinidis S, Stuart GW, Copolov DL, Singh BS. Positive and negative symptoms in the psychoses: Principal components analysis of items from the scale for the assessment of positive symptoms and the scale for the assessment of negative symptoms. Comprehensive Psychiatry 1994; 35:135-144.


Salokangas RKR. First-contact rate for schizophrenia in community psychiatric care: Consideration of the oestrogen hypothesis. European Archives of Psychiatry and Clinical Neuroscience 1993; 242:337-346.


Torrey EF. Prevalence studies in schizophrenia. British Journal of Psychiatry 1987; 150:598-608.


Weiser M, Van Os J, Davidson M. Time for a shift in focus in schizophrenia: from narrow phenotypes to broad endophenotypes. British Journal of Psychiatry 2005b; 187:203-205.


12. APPENDIX

12.1 Appendix 1


1. Source of rating (1-6)
2. Time frame (1-4)
3. Sex code (male 0, female 1)
4. Age of onset
5. Mode of onset (1-5)
6. Single (married 0, single 1)
7. Unemployed (employed 0, Unemployed 1)
8. Duration of illness in weeks
9. Poor premorbid work adjustment (0, 1)
10. Poor premorbid social adjustment (0,1)
11. Premorbid personality disorder (0, 1)
12. Alcohol/drug abuse within one year of onset (0, 1)
13. Family history on schizophrenia (0, 1)
14. Family history of other psychiatric disorder (0, 1)
15. Coarse brain disease prior to onset (0, 1)
16. Definite psychosocial stressor prior to onset (0, 1)

APPEARANCE AND BEHAVIOR

17. Bizarre behavior (0,1)
18. Catatonia (0, 1)
19. Excessive activity (0-2)
20. Reckless activity (0-2)
21. Distractibility (0-2)
22. Reduced need for sleep (0-2)
23. Agitated activity (0-3)
24. Slowed activity (0-3)
25. Loss of energy/tiredness (0-3)
SPEECH AND FORM OF THOUGHT

26. Speech difficult to understand (0, 1)
27. Incoherent (0, 1)
28. Positive formal thought disorder (0, 1)
29. Negative formal thought disorder (0, 1)
30. Pressured speech (0-2)
31. Thought racing (0-2)

AFFECT AND ASSOCIATED FEATURES

32. Restricted affect (0,1)
33. Blunted affect (0, 1)
34. Inappropriate affect (0, 1)
35. Elevated mood (0, 1)
36. Irritable mood (0, 2)
37. Dysphoria (0-3)
38. Diurnal variation (mood worse mornings) (0, 1)
39. Loss of pleasure (0-3)
40. Diminished libido (0, 1)
41. Poor concentration (0-3)
42. Excessive self reproach (0-3)
43. Suicidal ideation (0-3)
44. Initial insomnia (0-3)
45. Middle insomnia (broken sleep) (0, 1)
46. Early morning waking (0-3)
47. Excessive sleep (0-3)
48. Poor appetite (0-3)
49. Weight loss (0-3)
50. Increased appetite (0-3)
51. Weight gain (0-3)
52. Relationship psychotic / affective symptoms (0-4)
53. Increased sociability (0-2)
ABNORMAL BELIEFS AND IDEAS

54. Persecutory delusions (0, 1)
55. Well organized delusions (0, 1)
56. Increased self esteem (0-2)
57. Grandiose delusions (0, 1)
58. Delusions of influence (0, 1)
59. Bizarre delusions (0, 1)
60. Widespread delusions (0, 1)
61. Delusions of passivity (0, 1)
62. Primary delusional perception (0, 1)
63. Other primary delusions (0, 1)
64. Delusions and hallucinations last for one week (0, 1)
65. Persecutory / jealous delusions and hallucinations (0, 1)
66. Thought insertion (0, 1)
67. Thought withdrawal (0, 1)
68. Thought broadcast (0, 1)
69. Delusions of guilt (0, 1)
70. Delusions of poverty (0, 1)
71. Nihilistic delusions (0, 1)

ABNORMAL PERCEPTIONS

72. Thought echo (0, 1)
73. Third person auditory hallucinations (0, 1)
74. Running commentary voices (0, 1)
75. Abusive / accusatory / persecutory voices (0, 1)
76. Other (non affective) auditory hallucinations (0, 1)
77. Non-affective hallucinations in any modality (0, 1)

SUBSTANCE ABUSE OR DEPENDENCE

78. Lifetime diagnosis of alcohol abuse /dependence (0, 1)
79. Lifetime diagnosis of cannabis abuse /dependence (0, 1)
80. Lifetime diagnosis of other abuse / dependence (0, 1)
81. Alcohol abuse /dependence with psychopathology (0-1)
82. Cannabis abuse / dependence with psychopathology (0-1)
83. Other abuse / dependence psychopathology (0-1)

GENERAL APPRAISAL

84. Information not credible (0, 1)
85. Lack of insight (0, 1)
86. Rapport difficult (0, 1)
87. Impairment / incapacity during disorder (0-3)
88. Deterioration from premorbid level of function (0, 1)
89. Psychotic symptoms respond to neuroleptics (0, 1)
90. Course of disorder (1-5)
12.2 Appendix 2.

SCALE FOR THE ASSESSMENT OF NEGATIVE SYMPTOMS (SANS)
(Andreasen 1983)

AFFECTIVE FLATTENING OR BLUNTING
1. Unchanging facial expression
2. Decreased spontaneous movements
3. Paucity of expressive gestures
4. Poor eye contact
5. Affective non-responsivity
6. Inappropriate affect
7. Lack of vocal inflections
8. Global rating of affective flattening

ALOGIA
9. Poverty of speech
10. Poverty of content of speech
11. Blocking
12. Increased latency of response
13. Global rating of alogia

AVOLITION - APATHY
14. Grooming and hygiene
15. Impersistance at work or school
16. Physical anergia
17. Global rating of avolition - apathy

ANHEDONIA - ASOCIALITY
18. Recreational interests and activities
19. Sexual activity
20. Ability to feel intimacy and closeness
21. Relationships with friends and peers
22. Global rating of anhedonia - asociality

ATTENTION
23. Social inattentiveness
24. Inattentiveness during mental status testing
25. Global rating of attention
12.3 Appendix 3.

SCALE FOR THE ASSESSMENT OF POSITIVE SYMPTOMS (SAPS)
(Andreasen 1984)

HALLUCINATION

1. Auditory hallucination
2. Voices commenting
3. Voices conversing
4. Somatic or tactile hallucinations
5. Olfactory hallucinations
6. Visual hallucinations
7. Global rating of hallucinations

DELUSIONS

8. Persecutory delusions
9. Delusions of jealousy
10. Delusions of guilt or sin
11. Grandiose delusions
12. Religious delusions
13. Somatic delusions
14. Delusions of reference
15. Delusions of being controlled
16. Delusions of mind reading
17. Thought broadcasting
18. Thought insertion
19. Thought withdrawal
20. Global rating of delusions

BIZARRE BEHAVIOR

21. Clothing and appearance
22. Social and sexual behavior
23. Aggressive and agitate behavior
24. Repetitive or stereotyped behavior
25. Global rating of bizarre behavior
POSITIVE FORMAL THOUGHT DISORDER

26. Derailment
27. Tangentiality
28. Incoherence
29. Illogicality
30. Circumstantiality
31. Pressure of speech
32. Distractible speech
33. Clanging
34. Global rating of positive formal thought disorder

INAPPROPRIATE AFFECT

35. Inappropriate affect