Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland,
and
Department of Psychiatry, University of Helsinki, Finland

INCIDENCE AND RISK FACTORS OF SCHIZOPHRENIA IN FINLAND

Jaana Suvisaari

ACADEMIC DISSERTATION

To be presented with the permission of the Medical Faculty of the University of Helsinki for public examination in the Auditorium of the Department of Psychiatry, on October 8, 1999, at 12 noon

Helsinki 1999

Julkaisija – Utgivare – Publisher

Kansanterveyslaitos (KTL)
Mannerheimintie 166
FIN-00300 Helsinki, Finland
puh. 09-47441
fax 09-4744 8478

Folkhälsoinstitutet
Mannerheimvägen 166
FIN-00300 Helsingfors, Finland
tel. 09-47441
fax 09-4744 8478

National Public Health Institute
Mannerheimintie 166
FIN-00300 Helsinki, Finland
tel. +358-9-47441
fax +358-9-4744 8478

Publications of National Public Health Institute
KTL A16/1999

ISBN 951-45-8713-8 (PDF version)
ISSN 0359-3584

Helsingin yliopiston verkkojulkaisut, Helsinki 1999

Supervised by:

Professor Jouko Lönnqvist, M.D., Ph.D.
Department of Mental Health and Alcohol Research
National Public Health Institute

Reviewed by:

Docent Hannu Lauerma, M.D., Ph.D.
Department of Psychiatry, University of Turku

and

Docent Pirkko Räsänen, M.D., Ph.D.
Department of Psychiatry, University of Oulu

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ABBREVIATIONS

APA	American Psychiatric Association
BZ	Bezugsziffern
CATCH-22	Acronym for the principal features of the velo-cardio-facial syndrome: Cardiac defects, Abnormal facies, Thymic hypoplasia, Cleft lip and/or palate, Hypocalcemia, and chromosome 22q11 deletion
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
GABA	Gamma-aminobutyric acid
HLA	Human leucocyte antigen
ICD	International Classification of Diseases
Lod	Logarithm of the odds
MR	Morbid risk
PSE	Present State Examination
RDC	Research Diagnostic Criteria
RNA	Ribonucleic acid
RR	Relative risk
SD	Standard deviation
STL	Seasonal and Trend decomposition using Locally weighted regression
UKKI	The Uusikaupunki-Kemijärvi Study
WHO	World Health Organization

1. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications.

Suvisaari JM, Haukka J, Tanskanen A, Lönnqvist JK. Age at onset and outcome in schizophrenia are related to the degree of familial loading. British Journal of Psychiatry 1999;173:494-500

Suvisaari J, Haukka J, Tanskanen A, Hovi T, Lönnqvist J. Association between prenatal exposure to poliovirus infection and adult schizophrenia. American Journal of Psychiatry 1999;156:1100-1102

Suvisaari JM, Haukka JK, Tanskanen AJ, Lönnqvist JK. Decline in the incidence of schizophrenia in Finnish cohorts born from 1954 to 1965. Archives of General Psychiatry 1999;56:733-740

Suvisaari JM, Haukka JK, Tanskanen AJ, Lönnqvist JK. Decreasing seasonal variation of births in schizophrenia. Psychological Medicine; in press

2. INTRODUCTION

Schizophrenia occurs worldwide and is among the most severe mental disorders. Its aetiology remains unknown, although both genetic and environmental risk factors are known to be involved. Its pathophysiology is also largely obscure, and consequently the available treatment can alleviate symptoms but not cure the disease. The enormous psychological and social distress schizophrenia causes and the limited means available for helping its sufferers means that its aetiology and pathophysiology are among the most extensively studied of the mental disorders. (Schultz & Andreasen 1999)

Schizophrenia appears to be more prevalent in Finland than in most other western countries (Torrey 1987, Lehtinen et al 1990, Hovatta et al 1997), and is a leading cause of disability retirement there, particularly among the population aged 16 to 44 years (KELA 1996). ”The Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland” project, initiated in 1988, is a collaborative venture of the Department of Mental Health and Alcohol Research and the Department of Human Molecular Genetics of the National Public Health Institute. The aim of the project is to identify genetic and environmental factors predisposing to schizophrenia. The current thesis forms part of that project.

2.1. Evolution of the diagnostic concept of schizophrenia

2.1.1. Kraepelin

The disease entity nowadays called schizophrenia was first delineated by Emil Kraepelin (1856-1926) in 1893 (Harms 1971). Kraepelin used the name dementia praecox for the disease to stress its early onset and the permanent deterioration of mental functioning it causes among the great majority of patients. He defined dementia praecox as ”a series of states, the common characteristic of which is a peculiar destruction of the internal connections of the psychic personality. The effects of this injury predominate in the emotional and volitional spheres of mental life". (Kraepelin 1919, p. 3).

Kraepelin detailed the symptoms commonly occurring in schizophrenia (Table 1), the most fundamental features of which were the weakening of volition and emotional dullness, which cause mental activities to decline, and the loss of inner unity of the activities of intellect, emotion and volition, which causes incoherence in thinking and action and inappropriate affect. However, he considered no symptom as pathognomonic for schizophrenia. (Kraepelin 1919, pp. 11-73 and 257)

Originally, Kraepelin divided dementia praecox into three clinical subtypes: hebephrenic, catatonic, and paranoid. He later elaborated this subtyping to include several other categories, while emphasizing that the subgrouping of different clinical pictures was rather artificial and of limited clinical value. (Kraepelin 1919, pp. 89-180)

Kraepelin was also the first to formulate the concept of manic-depressive insanity. In distinguishing this from dementia praecox, he did not consider any single symptom as characteristic of either disease, but stressed the importance of evaluating the whole clinical picture. The symptoms suggestive of dementia praecox in the presence of affective symptoms were lack of inner logical arrangement of mental events, early appearance of numerous auditory hallucinations, bizarre delusions, delusions of influence on will, and incoherent speech. Symptoms more suggestive of manic-depressive illness were a tendency to, and ability for, observation of self, and periodic course with complete restoration of psychic and social functioning in between. Disorders characterized by delusions and hallucinations in which disorders of emotion and volition did not exist or were minimal were referred to by Kraepelin as paraphrenias. Although these had many features in common with the paranoid form of dementia praecox, Kraepelin considered that the well-preserved mental activities and absence of disorders of volition justified the classification of paraphrenias into a separate disease entity. (Kraepelin 1919, pp. 260-328)

Table 1. Symptoms of dementia praecox according to Kraepelin

1. Hallucinations

A. Auditory hallucinations
- Unpleasant voices
- Voices that comment on the thoughts and doings of the patient
- Commanding voices
- Patient's own thoughts spoken aloud

B. Tactile hallucinations
- Somatic
- Sexual

C. Hallucinations of smell and taste

2. Delusions
- Delusions of influence
- Delusions of persecution
- Grandiose delusions
- Sexual delusions
- Ideas of reference

3. Incoherence of thought and speech
- Stereotypy of speech
- Poverty of speech
- Mutism
- Neologisms

4. Catatonic symptoms
- Automatic obedience
- Echolalia and echopraxia
- Stereotypy of movement
- Catatonic excitement
- Mannerisms
- Negativism

5. Disordered attention

6. Disordered judgement

7. Emotional dullness

8. Avolition

9. Autism

(Kraepelin 1919)

2.1.2. Bleuler

Unlike Kraepelin, Eugen Bleuler (1857-1939) did not emphasize poor outcome in diagnosing schizophrenia. It had also become more evident since Kraepelin introduced the concept of dementia praecox that the disorder did not always begin in adolescence or early adulthood. Thus, Bleuler suggested that the name of the disease be changed to ”schizophrenia” because of the characteristic disintegration of various mental functions. (Bleuler 1911, pp. 7-8)

Bleuler divided symptoms of schizophrenia into fundamental symptoms, which he considered as characteristic of schizophrenia and present in every patient and at every period of the disease, and accessory symptoms, which may dominate the clinical picture but may also be completely absent and are not pathognomonic for schizophrenia (Bleuler 1911, p. 13). The fundamental symptoms (Table 2) were disturbances of association, affectivity and attention, ambivalence, and autism. Bleuler also regarded the absence of primary disturbances of perception, orientation and memory as fundamental to schizophrenia. Some other features of the disease, such as lack of will, disturbed behaviour, and disorders in intelligence, were considered to be a consequence of these fundamental symptoms. The severity of the fundamental symptoms in individual patients may vary from ”a maximum which corresponds to complete confusion to a minimum which may be hardly noticeable”. Bleuler regarded delusions, hallucinations, and catatonic symptoms as accessory symptoms, although he admitted that it is often because of them that patients come to psychiatric treatment. (Bleuler 1911, pp. 14-226)

The diagnosis of schizophrenia was based on the presence of fundamental symptoms, though not all of them needed to be apparent in a given patient. The duration of symptoms and the outcome of the illness were not emphasized in diagnosing the disorder. Although Bleuler did not consider outcome important, he stated that ”As yet I have never released a schizophrenic in whom I could not still see distinct signs of the illness; indeed there are very few in whom one would have to search for such signs.” (Bleuler 1911, p. 256)

Bleuler divided schizophrenia into four subgroups: paranoid, catatonic, hebephrenic and simple type. Paranoid type was characterized by the presence of prominent delusions and hallucinations and included, besides paranoid forms of dementia praecox, the majority of patients Kraepelin would have diagnosed as suffering from paraphrenia. Various catatonic symptoms dominated the clinical picture in the catatonic type. Hebephrenic type consisted of all the other patients who had, at some point in their illness, exhibited acute psychotic symptoms and subsequently deteriorated but who did not present with paranoid or catatonic characteristics. Simple schizophrenia consisted of patients who gradually deteriorate affectively and intellectually without exhibiting other prominent symptoms. (Bleuler 1911, pp. 227-238)

Table 2. Fundamental symptoms of schizophrenia according to Bleuler

1. Association

- Lack of purpose or goal in the speech; poverty of ideas
- Thought condensations
- Stereotypy; echolalia
- Thought blocking
- Pressure of thoughts; clang associations

2. Affectivity

- Lack of depth to the affect; restricted affect
- Lack of consistency of affective manifestation
- Inappropriate or blunted affect

3. Attention

- Lack of selectivity of attention; impaired active attention

4. Ambivalence

- Affective ambivalence: the same concept is accompanied simultaneusly by pleasant and unpleasant feelings
- Ambivalence of will: the patient wishes and does not wish the same thing at the same time
- Intellectual ambivalence: the patient expresses contradictory thoughts in the same sentence

5. Autism

(Bleuler 1911)

2.1.3. Schneider

Kurt Schneider (1887-1967) aimed at identifying signs and symptoms that would be highly discriminating for schizophrenia and would be easily perceived by the treating physician (Carpenter et al 1973, Andreasen & Carpenter 1993). The symptoms he chose as characteristic of schizophrenia were quite different from the fundamental symptoms of Bleuler. He identified a group of delusions and hallucinations which he believed to be pathognomonic for schizophrenia and called these symptoms ”first-rank symptoms” (Table 3) (Carpenter et al 1973). Other symptoms which occurred frequently in schizophrenia but were not pathognomonic for it were called second-rank symptoms. Schneider's diagnostic concept of schizophrenia has had considerable influence on almost all diagnostic systems subsequently developed.

Table 3. First-rank symptoms of schizophrenia according to Schneider

- Audible thoughts
- Voices arguing or discussing, or both
- Commenting voices
- Somatic passivity experiences
- Thought withdrawal and other experiences of influenced thought
- Thought broadcasting
- Delusional perception
- Made impulses, thoughts, or volitional acts

(Carpenter et al 1973)

2.1.4. International Classification of Diseases, Eighth Revision

The International Classification of Diseases is a disease classification system developed by the World Health Organization to promote international comparability of health care statistics. The eighth revision of the International Classification of Diseases (ICD-8), launched in 1967, placed considerable emphasis on Schneiderian first-rank symptoms in its description of schizophrenia (WHO 1967). It included seven subtypes of schizophrenia. The simple type was characterized by oddities of conduct, difficulties in

social relationships, and decline in overall performance but without clear-cut symptoms of schizophrenia. Typical symptoms of the hebephrenic type were inappropriate affect, bizarre or catatonic behaviour, and prominent thought disorder. The catatonic type was characterized by catatonic symptoms, and the paranoid type by prominent delusions and hallucinations. In the acute schizophrenic episode, the onset of schizophrenic symptoms was acute, and a dream-like state with slight clouding of consciousness and perplexity was often present. 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 reserved for chronic residual states in which fragments of faded schizophrenic symptomatology occurred. In addition, ”other” and ”unspecified” types were reserved for patients that did not fit into other subtypes. Infantile autism was regarded as a part of schizophrenia. (WHO 1967, General Register Office 1968)

2.1.5. Diagnostic and Statistical Manual of Mental Disorders, Second Edition

The second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II), published in 1968, gave a Bleulerian definition of schizophrenia, broader than the ICD-8 definition. According to DSM-II, the mental state in schizophrenia was primarily attributable to a thought disorder, which may lead to misinterpretation of reality and sometimes to delusions and hallucinations.The subtyping of schizophrenia was similar to ICD-8, except that an eighth, childhood type, was included. (APA 1968)

2.1.6. Washington University Criteria (Feighner Criteria)

The Washington University or St. Louis or Feighner Criteria, published in 1972, represented the first diagnostic classification validated primarily by follow-up and family studies, rather than by clinical judgement and experience (Feighner et al 1972). Feighner Criteria were also the first to assign operational diagnostic criteria to each disorder they include. The diagnostic criteria for schizophrenia emphasized poor premorbid functioning, chronicity of the disorder, and absence of affective symptoms (Table 4). Subtyping was not included. Of the commonly used diagnostic criteria for schizophrenia, Feighner’s criteria are the most restrictive (Hill 1996, McGorry 1992).

Table 4. The Washington University Criteria (Feighner Criteria) for schizophrenia

For a diagnosis of schizophrenia, A through C are required:

A. Both of the following are necessary:
1. A chronic illness with at least six months of symptoms prior to the index evaluation without return to the premorbid level of psychosocial adjustment.
2. Absence of a period of depressive or manic symptoms sufficient to qualify for affective disorder or probable affective disorder.

B. The patient must have at least one of the following:
1. Delusions or hallucinations without significant perplexity or disorientation associated with them.
2. Verbal production that makes communication difficult because of a lack of logical or understandable organization. (In the presence of muteness the diagnostic decision must be deferred.)

C. At least three of the following manifestations must be present for a diagnosis of ”definite” schizophrenia, and two for a diagnosis of ”probable” schizophrenia.
1. Single
2. Poor premorbid social adjustment or work history
3. Family history of schizophrenia
4. Absence of alcoholism or drug abuse within one year of onset of psychosis
5. Onset of illness prior to age 40

(Feighner et al 1972)

Patients who fulfill the diagnostic criteria for primary affective disorder but in addition have ”a massive or peculiar alteration of perception and thinking as a major manifestation of their illness” do not have any diagnostic class in Feighner classification but are classified as having an undiagnosed psychiatric disorder.

2.1.7. Research Diagnostic Criteria

The Research Diagnostic Criteria (RDC), introduced in 1975, were modified and expanded from the Feighner Criteria. The diagnostic criteria of schizophrenia, however, changed significantly. The requirement of illness duration shortened from 6 months to 2 weeks. Schneider’s first rank symptoms were given considerable weight in the

diagnosis, while social and occupational functioning, age at onset, and family history lost their significance (Table 5). (Spitzer et al 1978)

Table 5. Research Diagnostic Criteria for schizophrenia

A. During an active phase of the illness at least two of the following are required for definite and one for probable diagnosis of schizophrenia:

1. Thought broadcasting, insertion, or withdrawal
2. Delusions of being controlled or influenced, other bizarre delusions, or multiple delusions
3. Somatic, grandiose, religious, nihilistic, or other delusions without persecutory or jealous content lasting at least one week
4. Delusions of any type if accompanied by hallucinations of any type for at least one week
5. Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behaviors or thoughts as they occur, or two or more voices converse with each other.
6. Non-affective verbal hallucinations spoken to the subject
7. Hallucinations of any type throughout the day for several days or intermittently for at least one month
8. Definite instances of marked formal thought disorder (as defined in this manual) accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganized behavior.

B. Signs of the illness have lasted at least two weeks from the onset of a noticeable change in the subject's usual condition.

C. At no time during the active period of illness being considered has the subject met the full criteria for either probable or definite manic or depressive syndrome to such a degree that it was a prominent part of the illness.

(Spitzer et al 1978)

RDC included five subtypes of schizophrenia. Prominent symptoms of each type were: delusions and/or hallucinations in the paranoid type, marked formal thought disorder and inappropriate or blunted affect or not well-organized delusions or hallucinations in the disorganized type, and catatonic symptoms in the catatonic type. The undifferentiated type was reserved for periods of illness that met the criteria for more than one subtype or none of them, and the residual type was used when psychotic symptoms were no longer prominent but residual symptoms prevailed. The mood

disorder exclusion criteria remained as strict as in the Feighner criteria. For those patients that met the criteria for a manic or depressive syndrome but in addition had at least one symptom indicative of schizophrenia, a new diagnostic class, schizoaffective disorder, emerged. Schizoaffective disorder was a broad class, including forms in which schizophrenic symptoms were of brief duration compared with the duration of affective symptoms, or vice versa. It required the presence of only one symptom suggestive of schizophrenia. This very broad definition of schizoaffective disorder was constructed to help researchers ”purify” samples of patients with schizophrenia or affective disorder by separating out those presenting mixed symptomatology. (Spitzer et al 1978)

2.1.8. International Classification of Diseases, Ninth Edition

In the ninth edition of the International Classification of Diseases, published in 1977 (WHO 1977), the description of schizophrenia had hardly changed from ICD-8. However, childhood type schizophrenia and infantile autism were removed from schizophrenic psychoses. Simple and latent schizophrenia remained in the classification, but their use was discouraged (WHO 1978).

2.1.9. Diagnostic and Statistical Manual for Mental Disorders, Third Edition

After five years of development and field trials involving over 800 clinicians, DSM-III was launched in 1980. DSM-III differed from previous internationally used diagnostic classifications such as DSM-II and ICD-9 in that operational diagnostic criteria were provided for each disorder, and from RDC and Feighner criteria in that all diagnostic classes were included. (Spitzer et al 1980)

The diagnostic criteria for schizophrenia in DSM-III were a mixture of Feighner and RDC criteria (Table 6). As in Feighner criteria, a 6-month duration of symptoms and deterioration from a premorbid level of functioning were required. However, Schneiderian first-rank symptoms were given considerable weight, as in the RDC criteria. The concept of schizophrenia was narrower than that applied in the DSM-II and ICD-9. DSM-II and ICD-9 diagnoses of simple and latent type were omitted and would

usually correspond to a severe form of schizotypal or borderline personality disorder in DSM-III. Some individuals diagnosed with schizophrenia in DSM-II and ICD-9 because of the concurrence of Schneiderian first-rank symptoms with symptoms of major affective disorder would be diagnosed as suffering from an affective disorder in DSM-III. DSM-III provided an explicit age-at-onset criterion: the onset of at least prodromal symptoms must occur before 45 years. The subtypes of schizophrenia were identical to those used in RDC: disorganized, catatonic, paranoid, undifferentiated, and residual. A diagnosis of schizophreniform disorder was given when all other diagnostic criteria for schizophrenia except the duration were fulfilled. Schizoaffective disorder was the only diagnosis in DSM-III for which diagnostic criteria were not provided, because a consensus committee found it impossible to agree on the criteria. (APA 1980, Spitzer et al 1980, Skodol & Spitzer 1982, Williams & Spitzer 1982)

2.1.10. Diagnostic and Statistical Manual for Mental Disorders, Third Edition, Revised

The diagnostic criteria for schizophrenia in the revised version of DSM-III (DSM-III-R), launched in 1987, changed in a few noteworthy ways. Most obviously, the age at onset criterion was omitted. A time duration of at least one week, or less if successfully treated, was set for the acute phase symptoms. First-rank symptoms were slightly less significant than in DSM-III. A criterion for schizophrenia in the presence of autistic disorder was added. More explicit mood and schizoaffective disorder exclusion criteria were given, because DSM-III-R included diagnostic criteria for schizoaffective disorder. The subtyping of schizophrenia remained identical to that used in DSM-III. (APA 1987)

Table 6. DSM-III criteria for schizophrenia

A. At least one of the following during a phase of the illness:

1. Bizarre delusions, such as delusions of being controlled, thought broadcasting, thought insertion, or thought withdrawal.
2. Somatic, grandiose, religious, nihilistic, or other delusions without persecutory or jealous content.
3. Delusions with persecutory or jealous content if accompanied by hallucinations of any type.
4. Auditory hallucinations in which either a voice keeps up a running commentary on the individual's behaviour or thoughts, or two or more voices converse with each other.
5. Auditory hallucinations on several occasions with content of more than one or two words, having no apparent relation to depression or elation.
6. Incoherence, marked loosening of associations, markedly illogical thinking, or marked poverty of content of speech if associated with at least one of the following:
(a) blunted, flat, or inappropriate affect
(b) delusions or hallucinations
(c) catatonic or other grossly disorganized behaviour

B. Deterioration from a previous level of functioning in such areas as work, social relations, and self-care.

C. Duration: Continuous signs of the illness for at least six months at some time during the person's life, with some signs of the illness at present. The six-month period must include an active phase during which there were symptoms from A, with or without a prodromal or residual phase.

D. The full depressive or manic syndrome, if present, developed after any psychotic symptoms, or was brief in duration relative to the duration of the psychotic symptoms in A.

E. Onset of prodromal or active phase of the illness before age 45.

F. Not due to any organic mental disorder or mental retardation.

(APA 1980)

2.1.11. International Classification of Diseases, Tenth Edition

The tenth edition of the International Classification of Diseases (ICD-10) was published in 1992. It is the first ICD edition to provide operationalized diagnostic criteria for

research purposes. It is therefore more meaningful to compare the criteria for schizophrenia (Table 7) with DSM-III-R criteria than with the previous ICD versions.

Table 7. ICD-10 Diagnostic Criteria for Research for schizophrenia

I. Either at least one of the syndromes, symptoms, and signs listed under 1. below, or at least two of the symptoms and signs listed under 2. should be present for most of the time during an episode of psychotic illness lasting for at least 1 month (or at some time during most of the days):

1. At least one of the following must be present:
a) Thought echo, thought insertion or withdrawal, or thought broadcasting
b) Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception
c) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body
d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible

2. Or at least two of the following:
a) Persistent hallucinations in any modality, when occurring every day for at least 1 month, when accompanied by delusions without clear affective content, or by persistent over-valued ideas
b) Neologisms, breaks, or interpolations in the train of thought, resulting in incoherence or irrelevant speech
c) Catatonic behaviour, such as excitement, posturing, or waxy flexibility, negativism, mutism, or stupor
d) "Negative" symptoms, such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses

II. Exclusion clauses:

1. If the patient also meets criteria for manic episode or depressive episode, the criteria listed under I(1.) and I(2.) above must have been met before the disturbance of mood developed

2. The disorder is not attributable to organic brain disease, or to alcohol- or drug-related intoxication, dependence, or withdrawal

(WHO 1993)

The required duration of symptoms is considerably shorter in ICD-10 than in DSM-III-R, one vs. six months, and ICD-10 does not require deterioration from a premorbid level of functioning. The mood disorder exclusion criterion in ICD-10 requires that the onset of psychotic symptoms must have preceded the onset of mood symptoms, while DSM-III-R 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. ICD-10 gives considerable weight to Schneiderian first-rank symptoms, but is also the first diagnostic classification to include negative symptoms. ICD-10 includes the DSM-III-R subtypes, paranoid, disorganized, catatonic, undifferentiated, and residual. In addition, simple schizophrenia is retained from ICD-9. (WHO 1993)

2.1.12. Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition

The fourth edition of the Diagnostic and Statistical Manual for Mental Disorders was published in 1994. The largest difference between DSM-III-R and DSM-IV criteria (Table 8) for schizophrenia is in the description of characteristic symptomatology. The criterion for duration of acute phase symptoms is extended from one week to one month. Hallucinations are no longer required to be prominent. DSM-IV uses the term ”disorganized speech” instead of ”incoherence or marked loosening of associations” for schizophrenic thought disorder. Besides catatonic symptoms, grossly disorganized behaviour is included as a symptom criterion. Negative symptoms are included in the criteria for the first time in the DSM system. (APA 1994)

The subtype names are identical to those used in DSM-III-R, but a hierarchy is given for them. Catatonic type is assigned whenever prominent catatonic symptoms are present regardless of other symptoms. If the criteria for catatonic type are not fulfilled, the disorganized type is assigned whenever disorganized speech and behaviour, and flat or inappropriate affect are present. If the criteria for neither catatonic nor disorganized type are present, the paranoid type is assigned whenever there is a preoccupation with delusions or frequent hallucinations. If there are prominent active-phase symptoms and the criteria for catatonic, disorganized, or paranoid type are not fulfilled, the

undifferentiated type is assigned. The residual type is used when active-phase symptoms are no longer present but there is continuing evidence for the disturbance. (APA 1994)

Table 8. DSM-IV Diagnostic Criteria for schizophrenia

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
4. Grossly disorganized or catatonic behaviour
5. Negative symptoms
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 behaviour or thoughts, or two or more voices are 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 the expected level).

C. Duration: Continuous signs of the disturbance persist for at least 6 months, of which at least one month should be of symptoms that meet Criterion A. The 6 months may include periods of prodromal and residual symptoms.

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

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance 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).

(APA 1994)

2.1.13. Summary of the evolution of the concept of schizophrenia, and concordance between diagnostic systems

During the 20th century, psychiatric nosology has evolved from ”the great professor principle” through ”the consensus of experts” to a scientific psychiatric nosology (Kendler 1990). The diagnostic concepts of schizophrenia of Kraepelin, Bleuler, and Schneider followed the great professor principle. While the detailed descriptions of symptoms in schizophrenia given by Kraepelin and Bleuler were quite similar, both men came to regard totally different aspects of the disorder as essential: while Kraepelin stressed chronicity and poor outcome, Bleuler stressed the presence of fundamental symptoms of disordered association, attention, and affectivity, plus autism and ambivalence (Kraepelin 1919, Bleuler 1911). Both described the hallucinations and delusions later termed first-rank symptoms by Schneider, but neither regarded them as essential features of schizophrenia (Kraepelin 1919, Bleuler 1911). Thus, by analogy, in trying to define the essentials of an elephant, Kraepelin chose ”trunk”, Bleuler ”ears”, and Schneider ”feet”.

DSM classifications prior to DSM-III, and ICD classifications prior to ICD-10, relied on the consensus of experts principle. In the 1960s this consensus was quite different in Europe and the United States. Thus, DSM-II adopted a broad Bleulerian definition of schizophrenia, while ICD-8 descriptions focused on Schneiderian first-rank symptoms. When comparisons of diagnostic concepts in the United Kingdom and United States were conducted in the 1960s and 1970s, it became evident that American psychiatrists diagnosed schizophrenia much more often than their British counterparts, who were more likely to diagnose affective disorders (Leff 1977). Psychiatrists in Nordic countries also applied a narrow definition of schizophrenia (Leff 1977). The large variation in diagnostic practices promoted the development of scientific nosology in psychiatry (Kendler 1990). Since Feighner’s criteria, available scientific knowledge has been used to develop diagnostic criteria. European psychiatrists have trailed behind their American colleagues in this development, ICD-10 being the first European classification to provide operational diagnostic criteria.

Scientific nosology aims at maximizing the reliability and validity of diagnostic concepts. Criteria are reliable if diagnosticians in different countries reproduce the same diagnosis from the same patients. The validity of a diagnostic concept is a much more complex matter. It is usually tested by using external validators, such as family history, biological and psychological tests, treatment response, diagnostic stability, and course of illness. However, different validators often fail to agree. For example, DSM-III criteria for schizophrenia define a patient population with a relatively poor outcome, but if family history were to be included as a validator, broader criteria for schizophrenia should be applied. A consensus of experts usually decides which validator should be given the highest priority, which has led to differences between diagnostic systems. (Kendler 1990)

The most often used diagnostic criteria in clinical practice and research nowadays are DSM-IV, ICD-10, RDC, and Feighner criteria. Although the definitions of schizophrenia in different diagnostic systems converge to a large extent, there are differences (Table 9). All except Feighner criteria give considerable weight to Schneider's first rank symptoms, although DSM-IV less so than RDC and ICD-10. The required duration of symptoms is variable, ranging from 2 weeks in RDC to 6 months in DSM -IV and Feighner criteria. The boundaries of schizophrenia, schizoaffective disorder and psychotic affective disorder are highly variable. Feighner and DSM-IV criteria follow the Kraepelinian tradition of stressing poor outcome, while such a criterion has not been included in RDC and ICD-10. The agreements between the systems in terms of clinical diagnoses are not impressive. In one study, the concordances for schizophrenia measured by kappa values (Shrout et al 1987) were 0.67 for DSM-III vs. RDC, 0.57 for DSM-III vs. Feighner criteria, and 0.44 for RDC vs. Feighner criteria (McGorry et al 1992). In another study, they were 0.64 for DSM-III-R vs. RDC, 0.59 for DSM-III-R vs. ICD-10, 0.58 for DSM-III-R vs. Feighner criteria, and 0.71 for ICD-10 vs. RDC (Hill et al 1996).

The considerable weighting of Schneider's first rank symptoms in several diagnostic systems is particularly problematic. Several studies have shown that they are not pathognomonic for schizophrenia (Carpenter et al 1973, Peralta & Cuesta, 1999).

Carpenter et al found them in 51% of patients with DSM-II schizophrenia and in 23% of patients with DSM-II affective psychoses (Carpenter et al 1973). Peralta and Cuesta found them in 69% of patients with schizophrenia, 83% with schizophreniform disorder, 65% with schizoaffective disorder, 43% with mood disorder, 52% with brief reactive psychotic disorder, and 48% of patients with psychotic disorder not otherwise specified, in a study that used DSM-III-R criteria (Peralta & Cuesta 1999). Having first-rank symptoms did not significantly increase the likelihood of having schizophrenia (Peralta & Cuesta 1999), and was not associated with duration of illness or its outcome (Carpenter et al 1973). Thus, first-rank symptoms seem to correlate poorly with all of the external validators of diagnostic criteria; they should perhaps be given less weight in future diagnostic criteria of schizophrenia and be considered as symptoms of psychosis rather than of schizophrenia (Peralta & Cuesta 1999).

Table 9. Comparison of diagnostic criteria for schizophrenia

Diagnostic system	Duration	Course	Affective symptoms	Other requirements	Weight on FRS
DSM-IV	>6 months	Deterioration from premorbid level of functioning	Affective syndrome included if relatively brief	Substance/general medical condition exclusion	+
RDC	>2 weeks	-	No prominent affective symptoms	-	++
ICD-10	>1 month	-	If present, must follow psychotic symptoms	Substance/general medical condition exclusion	++
Washington University Criteria (Feighner Criteria)	>6 months	Chronic illness without return to premorbid level of functioning	Absence of symptoms qualifying for affective disorder	At least 3 of 5: 1. Single 2. Poor premorbid social or work adjustment 3. Family history of schizophrenia 4. No substance abuse within 1 year of onset 5. Onset before 40 years	-

(Feighner et al 1972, Spitzer et al 1978, WHO 1993, APA 1994, Hill et al 1996)

However, radical changes in diagnostic criteria always cause problems in research if results from studies using the new criteria are no longer comparable with previous findings. Because of the inconvenience relating to major changes in diagnostic criteria, the DSM-IV Work Group adopted an attitude of "progressive conservatism": changes were made only if their advantages clearly outweighed their disadvantages (Andreasen 1994). It would seem likely that this reluctance to change will continue when the DSM and ICD criteria are next updated.

2.1.14. Diagnostic criteria for schizophrenia in Finland

Finland adopted the ICD-6 diagnostic classification for clinical use in 1954 (Lääkintöhallitus 1953). No separate criteria for schizophrenia were given in the classification. Schizophrenia was divided into seven subtypes: simple, hebephrenic, catatonic, paranoid, latent, and not otherwise specified, plus schizoaffective disorder and acute schizophrenic reaction.

The 1950s and 1960s saw a wealth of schizophrenia research in Finland. The diagnostic criteria used varied somewhat. The criteria used by Achté and Alanen were based on Langfeldt's primary symptoms of schizophrenia (Langfeldt 1969). Achté's criteria included ten malignant symptoms of schizophrenia: an alteration of character prior to the onset of illness in a previously healthy person, autism, schizophrenic disturbances in affectivity, schizophrenic association disorders, massive experiences of derealization, massive delusions of influence, massive experiences of depersonalization, specific schizophrenic hallucinations of conversation with voices or physical delusions, avolition, and catatonic stupor (Achté 1967, p. 317). A patient who clearly exhibited one or more of these symptoms was regarded as suffering from typical schizophrenia (Achté 1967, p. 317). The criteria used by Alanen et al were otherwise similar but did not include character alteration and avolition (Alanen et al 1966).

Between 1969 and 1986, the official diagnostic classification used in Finland was ICD-8 (Lääkintöhallitus 1968). The subtyping remained identical to ICD-6, and no diagnostic criteria were provided. However, the diagnostic concept of schizophrenia

applied by clinicians was assessed in several studies. In a study of first-contact patients with schizophrenia or schizophreniform disorder in Helsinki in 1975, only 52% of the patients who received a DSM-III diagnosis of schizophrenia or schizophreniform disorder had received a hospital discharge diagnosis of schizophrenia or schizophreniform disorder (Kuusi 1986). In another study of all first admissions to Helsinki's two mental hospitals in 1981, 35% of the patients received a diagnosis of schizophrenia (S+) or borderline psychosis (O+) as assigned by the CATEGO computer program based on a Present State Examination-interview conducted blind to clinical diagnoses, but only 19% had received a clinical diagnosis of schizophrenia or schizophreniform disorder (Pakaslahti 1987). And in an incidence study carried out between March 1 1983 and February 29 1984 covering six health care districts in Finland, Salokangas also observed that clinicians made a DSM-III diagnosis of schizophrenia less often than an independent researcher (Salokangas 1993).Thus, the diagnostic concept of schizophrenia applied by Finnish clinicians was narrow during the 1970s and 1980s.

In 1987, the general medical diagnostic classification system in Finland was updated to ICD-9. However, the diagnostic criteria for mental disorders were adopted with slight modifications from DSM-III-R (Lääkintöhallitus 1989). In this system, the first four numbers in the diagnostic codes corresponded to the ICD-9 codes, but the fifth digit was unique to the Finnish coding system and allowed for subclassification similar to that used in DSM-III-R (Kuoppasalmi et al 1989). The diagnostic criteria for schizophrenic psychoses were identical to the DSM-III-R criteria, but unlike in DSM-III-R, schizophreniform and schizoaffective disorders were classified as schizophrenic psychoses (Kuoppasalmi et al 1989). Studies comparing research and clinical DSM-III-R diagnoses conducted in the 1990s found a continuing tendency of Finnish psychiatrists to apply a narrow definition of schizophrenia. Isohanni et al compared clinical and research diagnoses in the Northern Finland 1966 birth cohort and found 71 patients fulfilling DSM-III-R criteria for schizophrenia, whereas only 37 of them had a Finnish Hospital Discharge Register diagnosis of schizophrenia (Isohanni et al 1997). In a sample of patients from one municipality, 87% with a schizophrenia diagnosis and

18% with a schizophrenia spectrum diagnosis in the register fulfilled DSM-III-R criteria for schizophrenia (Mäkikyrö et al 1998).

Since 1996, ICD-10 diagnostic codes and criteria have been used in Finland. Thus far, the effect of this change on clinical practice has not been studied.

2.2. Symptoms of schizophrenia

Schizophrenia is clinically heterogeneous. Its course and symptomatology are highly variable, which is probably one reason for the variability of results from studies on treatment, aetiology, and pathophysiology. This heterogeneity has led to a growing interest in defining specific groups of symptoms or domains of psychopathology which might be used to identify patients with a more homogenous clinical picture and, hopefully, a more homogenous aetiological background. (Rotakonda et al 1998)

The first widely used classification into symptom domains was the subdivision into positive and negative symptoms. These terms were invented by Hughlings-Jackson, who considered positive psychotic symptoms as an exaggeration of normal functioning, a release phenomenon caused by an absence of inhibitory or regulatory influences, while negative symptoms were caused by a simple loss of function. Hallucinations, delusions, disorganized speech and behaviour, and catatonic symptoms were considered as positive symptoms, while anhedonia, avolition, poverty of speech and affective blunting were classified as negative symptoms. (Andreasen 1982, Andreasen 1995)

The positive vs. negative symptom dichotomy achieved widespread use in both research and clinical work. Various rating scales for their assessment were developed (Andreasen 1982, Fenton and McGlashan 1992, Möller et al 1994). Negative symptoms were shown to be associated with poor premorbid functioning, insidious onset, intellectual impairment, and poor outcome, while the relationship between positive symptoms and outcome was less clear-cut (Crow 1985, Andreasen et al 1990, Fenton and McGlashan 1991). Negative symptoms were also associated with structural brain abnormalities and neuropsychological deficits (Andreasen et al 1990, Andreasen 1995).

Various subtypings or classifications related to positive and negative symptoms were also suggested. Andreasen and Olsen suggested a subtyping of schizophrenia into three categories - positive, negative, and mixed – based on the prominence of positive or negative symptoms, or both. They found that compared with the other two groups, patients with negative schizophrenia had significantly poorer premorbid adjustment, and poorer work and cognitive functioning. (Andreasen et al 1990, Andreasen & Olsen 1995a)

Crow suggested in 1980 that there are two syndromes in schizophrenia, each reflecting different psychopathology: Type I caused by increased number of D_2 dopamine receptors, characterised by positive symptoms, good response to neuroleptics, good outcome, and absence of intellectual impairment, and Type II caused by cell loss in temporal lobe structures, characterised by negative symptoms, cerebral ventricular enlargement, poor response to neuroleptic treatment, intellectual impairment, and abnormal involuntary movements. According to Crow, these subtypes share common aetiology, but Type I reflects the neurochemical component of schizophrenia, and Type II the structural component. (Crow 1985)

Carpenter et al (1988) emphasized the distinctions between negative symptoms and disorders in relating, and between primary and secondary negative symptoms. Disorders in relating, for example social withdrawal, may be caused by loss of social drive, but also by paranoid delusions. Thus, they should not be considered as negative symptoms. Secondary negative symptoms refer to negative symptoms that are caused by drug effects, depression, or absence of social stimulation, among others. Secondary negative symptoms should be responsive to changes in the factors with which they are associated. Primary negative symptoms are less responsive to state changes and are rarely fully remitting. Carpenter et al suggested that negative symptoms should be used as a descriptive term without implications concerning cause or duration, whereas primary negative symptoms, which are present as enduring traits, should be called ”deficit symptoms” . The syndrome associated with deficit symptoms was called ”the deficit schizophrenia”, and was associated with enduring negative symptoms, poor outcome, and a significant male excess. (Carpenter et al 1988)

The classification of symptoms as positive or negative has not always been straightforward. To solve the problem of classification, researchers applied factor-analytic techniques and consistently found that the interrelationships among the symptoms of schizophrenia are better accounted for using three dimensions: positive or psychotic, negative, and disorganized symptoms (Andreasen et al 1995a). Disorganized symptoms consist of disorganized speech, inappropriate affect, and bizarre behaviour. In a longitudinal study of the dimensions, symptoms within the three groups tended to change in unison, but the symptom groups changed independently from one another (Arndt et al 1995).

Recent studies have found that disorganized symptoms may be more familial than positive and negative symptoms: they are moderately correlated within affected sibling pairs (Cardno et al 1998, Loftus et al 1998), and are associated with an increased risk of nonaffective psychotic disorders in first-degree relatives (Cardno et al 1997, Van Os et al 1997). Negative symptoms continue to be associated with poor social outcome and poor quality of life in recent studies, while positive and disorganized symptoms do not have similar predictive value (Ho et al 1998). However, in a large follow-up study of first-episode patients with schizophrenia, only severity of positive symptoms was associated with treatment response (Robinson et al 1999), and none of the symptom dimensions was associated with relapse rate (Robinson et al 1999a).

However, the symptom dimensions of positive, negative, and disorganized symptoms are not unique to schizophrenia, being found in other psychotic disorders as well (Maziade et al 1995, Johnstone & Frith 1996, Serretti et al 1996, Rotakonda et al 1998). Moreover, associations between the symptom dimensions and clinical variables (poor premorbid functioning and negative symptoms, continuous course of illness and disorganized symptoms) have been found regardless of the diagnosis (Rotakonda et al 1998). It may be that these symptom dimensions or psychopathological domains reflect discrete pathophysiologic conditions (Rotakonda et al 1998). Consequently, it has been suggested that future aetiological research might benefit by including symptom dimensions in identifying groups to be studied (Serretti et al 1996).

2.3. Epidemiology of schizophrenia

2.3.1. Occurrence of schizophrenia

There are two types of measures of occurrence: rates and proportions. A proportion is dimensionless but rate is not, because time is retained in the unit of measurement. The most common rate-type of measure of occurrence is incidence rate or incidence density. Incidence rate quantifies the number of events occurring per unit of population per unit of time, usually the number of new cases occurring in one year per 1000 or 100 000 person years. The two most commonly used proportion-type measures of occurrence are cumulative incidence and prevalence. Cumulative incidence is calculated as the number of health outcomes occurring over a time interval divided by the size of the population at risk. Cumulative incidence is a suitable measure of occurrence in cohort studies where the loss to follow-up over the course of the study is negligible. Prevalence is the proportion of a population who have a particular health condition at a point or period (one year, lifetime) in time. The prevalence of schizophrenia is determined as the total number of cases now alive, presently or previously actively psychotic, divided by the size of the population. (Zahner et al 1995, pp. 24-25, Gottesman & Shields 1982, p. 19)

A proportion-type morbidity index commonly used in population and genetic studies is lifetime morbid risk (MR) or lifetime risk. The lifetime morbid risk is the probability that a person who survives through the period of susceptibility of manifestation will develop the disorder. If n is the total number of subjects and m is the total number of affected, the raw total rate would simply be m/n, but this would underestimate the morbidity risk since some of the well subjects who have not yet lived through the period of susceptibility may still develop the disorder. To adjust for the age of the observed sample, an age-corrected denominator called Bezugsziffern (BZ) is calculated. BZ is the sum of weights reflecting each subject's length of exposure to risk up to the age of examination. If w_i is the weight for the *i*th individual, MR is estimated by

$$MR = \frac{m}{\sum_{i=1}^{n} w_i} = \frac{m}{BZ}$$

(Faraone & Tsuang 1995, p. 115)

2.3.1.1. Prevalence

There is still a widely held view that the prevalence of schizophrenia is approximately 1% throughout the world (Schultz & Andreasen 1999). However, in a review of all prevalence studies conducted thus far, Torrey found a prevalence range exceeding 50-fold from the lowest (0.3 per 1000) to the highest (17 per 1000) reported (Torrey 1987). As he pointed out, all aetiological hypothesis, whether genetic, environmental or both, would predict significant differences in the prevalence of the disease; it would actually be surprising if no differences were found (Torrey 1987).

Recent studies using structured interviews and DSM-III-R criteria for schizophrenia have found prevalences that are considerably lower than the usually cited 1%. The National Comorbidity Survey, which was based on interviews of 8098 individuals representing a random sample of the United States population, found a 0.7% lifetime prevalence of all nonaffective psychotic disorders and a 0.15% lifetime prevalence of schizophrenia (Kendler et al, 1996). The lifetime prevalence of schizophrenia in the Irish Roscommon study was 0.54% in men and 0.26% in women (Kendler & Walsh 1995). In the British Hampstead Schizophrenia Survey, the point prevalence of DSM-III-R schizophrenia varied, depending on the age correction method used, between 0.3 and 0.48% (Jeffreys et al 1997).

In Finland, the lifetime prevalence of schizophrenia seems to be somewhat higher than elsewhere: 1.3% in the Mini-Finland Health Survey, which used the Present State Examination interview (Lehtinen et al 1990), and 1.2% in a register-based study (Hovatta et al 1997). In the UKKI (Uusikaupunki - Kemijärvi) study, the lifetime prevalence of all nonaffective psychotic disorders as defined by the Present State Examination was 2.7% in the population aged 30-80 years (Lehtinen et al 1990a).

However, these studies were based on diagnostic criteria that are broader than the DSM-III-R criteria.

2.3.1.2. Incidence

Prevalence of a disease in a population is proportional to the frequency of development of new cases only if the numbers of entries to and exits from the population are stable (Zahner et al 1995, p.26). These are dependent on birth and death rates and migration, which are rarely stable. Differences in prevalences between different countries may thus be caused by differences in migration patterns and population age structures. Therefore, incidence rates are epidemiologically more informative than prevalence (Campbell & Machin 1993, p. 117). In schizophrenia research, the use of incidence rates is preferable also because of the excess mortality among patients with schizophrenia (Brown 1997) which tends to decrease the observed prevalences.

The World Health Organization Ten Country Study has been the most systematic attempt to compare the epidemiology of schizophrenia in different countries and cultures using uniform evaluation and diagnostic criteria. The diagnostic assessment was conducted using the Present State Examination interview, and diagnoses were obtained using the CATEGO computer program. The incidence of narrowly defined schizophrenia in the ten populations aged 15-54 years varied between 0.7 and 1.4 per 10 000 person years. The differences were not statistically significant. However, the incidence of broadly defined schizophrenia varied significantly, between 1.6 and 4.2 per 10 000 person years. These findings were interpreted to suggest that the incidence of schizophrenia is similar worldwide. (Jablensky et al 1992)

Three recent studies, conducted in the Caribbean islands, applied the same methodology as the WHO Ten Country Study (Hickling et al 1995, Bhurga et al 1996, Mahy et al 1999). All found a slightly higher incidence of narrowly defined schizophrenia; 1.6 per 10 000 person years in Trinidad, 2.1 per 10 000 person years in Jamaica, and 2.8 per 10 000 person years in Barbados, while the incidence of broadly defined schizophrenia was within the limits of those observed in the WHO study (2.2, 2.4, and 3.2 per 10 000

person years, respectively) (Bhurga et al 1996, Hickling et al 1995, Mahy et al 1999). However, the incidence of schizophrenia among African-Caribbean migrants in Europe has been found to be considerably higher. In Nottingham, the incidence of ICD-10 schizophrenia was 15 per 10 000 person years among first or second generation African-Caribbean migrants when, at the same time, it was 1.7 per 10 000 person years in the rest of the host population (Harrison et al 1997). Considerably increased incidences of schizophrenia among the African-Caribbean population have also been observed in other parts of England (Castle et al 1991, Bhurga et al 1997). In The Netherlands, the risk of developing schizophrenia is approximately 4 times higher among Surinamese and Dutch Antillean immigrants than in the rest of the population (Selten et al 1997). Part of the observed increase may be caused by problems in defining the population at risk in the calculations, because not all immigrants permanently residing in a country are registered in censuses (Harrison et al 1997), and some of the hospitalized ”immigrants” may actually be transient visitors (Mortensen et al 1997). Nevertheless, the observed increase is far too large to be solely explained by such confounding factors (Harrison et al 1997).

In Finland, the incidence of DSM-III schizophrenia and schizophreniform disorder among the 15-45-year-olds was 3.6 per 10 000 person years, and the incidence of ICD-8 schizophrenia among the 15-59-year-olds 2.1 per 10 000 person years in an incidence study carried out between March 1 1983 and February 29 1984 in six health care districts. Both are higher than the incidence of narrowly defined schizophrenia in the WHO study but within the range of the incidence of broadly defined schizophrenia (Salokangas 1993). In Helsinki, the incidence of DSM-III schizophrenia and schizophreniform disorder in 1975 was 1.9 per 10 000 person years (Kuusi 1986). The definition of schizophrenia in DSM-III is almost as restrictive as the narrow schizophrenia assigned by the CATEGO program, but the rates are not comparable because the age range was 15-54 years in the WHO study and 15-45 in the Finnish studies. In the UKKI (Uusikaupunki - Kemijärvi) study, the incidence of all psychotic disorders was 18 per 10 000 person years, but this includes, besides schizophrenia, all other psychotic disorders and severe personality disorders (Lehtinen et al 1996). A recent study based on the Finnish Hospital Discharge Register found that the incidence

of DSM-III-R nonaffective psychotic disorders was 0.74 per 1000 person years in 1990 and 0.69 per 1000 person years in 1993 (Korkeila et al 1998).

2.3.1.3. Changes in the occurrence of schizophrenia

In the 19th century, the numbers of registered ”insane” increased rapidly in England, Scotland, Ireland, France, and the United States. Numerous mental hospitals had to be built, and the numbers of first admissions rose throughout the latter part of the century and until World War I. The reasons for the phenomenon were disputed. Some thought that it was merely caused by more accurate registration, by changes in legislation that made it profitable for communities to send their mentally ill residents to mental hospitals, and by reduced mortality and increased length of stay in mental hospitals. Others insisted that despite the obvious contribution of these ”nosocomial” factors, a true increase in the occurrence of insanity, particularly its more severe forms, had occurred. Edward Hare believed that it had partly been caused by a true increase in occurrence, because the rise had persisted far longer than the establishment of registration systems, it was extremely pronounced, and it had continued despite no changes in mortality in the mental hospitals. He suggested that the incidence of schizophrenia in particular had increased, because few descriptions of a disease resembling schizophrenia existed before the 19th century, and in the 18th century it was thought that young people were rarely liable to insanity. A rapid increase in the incidence of schizophrenia would also explain the rather abrupt development of interest in schizophrenia particularly during the latter part of the 19th century - although the identification of the two most important organic psychoses at that time, Korsakoff's psychosis caused by chronic alcoholism and general paresis caused by tertiary syphilis, may also have increased the interest in functional psychoses (Colp 1995). (Hare 1983, Hare 1988)

Recent research suggests that the incidence of schizophrenia may be declining. Falls in incidence (Brewin et al 1997, Balestrieri el al 1998), morbid risk (Waddington & Youssef 1994, Strömgren 1987) and first-admission rate (Munk-Jørgensen 1987, Munk-Jørgensen & Mortensen 1992, Joyce 1987, Parker et al 1985, Eagles et al 1988, Geddes

et al 1993, Takei et al 1996, Der et al 1990, de Alarcon et al 1990) have been reported from Denmark (Strömgren 1987, Munk-Jørgensen 1987, Munk-Jørgensen & Mortensen 1992), New Zealand (Joyce et al 1987), Australia (Parker et al 1985), Scotland (Eagles et al 1988, Geddes et al 1993, Takei et al 1996), England (Brewin et al 1997, Der et al 1990, de Alarcon et al 1990), Italy (Balestrieri et al 1998) and Ireland (Waddington & Youssef 1994). However, the first-admission rate has not decreased in Croatia (Folnegović 1990), in the Netherlands (Oldehinkel & Giel 1995) and parts of England (Harrison et al 1991, Castle et al 1991). These findings have prompted debate about whether the observed decline has been due to genuine changes in the incidence or to confounding factors such as changes in diagnostic criteria, treatment practice, or registration (Torrey 1989, Geddes et al 1993, Kendell et al 1993, Harrison & Mason 1993, Munk-Jørgensen 1995).

The reliability of studies that use register-based first-admission rates has been questioned, because the proportion of patients with schizophrenia who receive the diagnosis in their first admission compared with later admissions may change (Kendell et al 1993). This was controlled for in the study by Munk-Jørgensen and Mortensen, who found a significant decline in the incidence of schizophrenia in Denmark regardless of the definition of first admission used (Munk-Jørgensen & Mortensen 1992). However, Kendell et al found that misrecordings of readmissions as first admissions were common and accounted for a significant proportion of the observed decline in the incidence in Edinburgh (Kendell et al 1993). The proportion of patients treated exclusively as outpatients may also have changed, although Kendell et al found no significant increase in such patients (Kendell et al 1993), and studies including outpatients (Munk-Jørgensen & Mortensen 1992, Eagles et al 1988) have also detected a declining incidence.

Diagnostic criteria change. The narrowing clinical concept of schizophrenia, especially among young male patients, accounted for half of the decline in the study by Kendell et al (Kendell et al 1993). The decrease in the frequency of discharge diagnosis of schizophrenia in the United States has been explained as a result of the introduction of DSM-III (Loranger 1990, Stoll et al 1993). However, considerable variability in

diagnostic practice between countries used to exist (Leff 1977). Psychiatrists in Nordic countries, for example, have traditionally applied narrow diagnostic criteria of schizophrenia in their clinical practice (Pakaslahti 1987, Isohanni et al 1997, Löffler et al 1994).

Because of the methodological shortcomings of studies (Kendell et al 1993) and – perhaps – also because of the fixed belief that the incidence of schizophrenia is constant across countries and time periods (Torrey 1989), some believe that no true change in the incidence of schizophrenia has occurred, while others are convinced that it is declining (Geddes et al 1993, Kendell et al 1993, Harrison & Mason 1993, Munk-Jørgensen 1995, Crow 1995, Crow 1995a). The decline, if genuine, suggests that the frequency or intensity of risk factors of schizophrenia in the population is decreasing – or that the frequency or intensity of protective factors is increasing.

In Finland, a decline in the incidence of schizophrenia in the southern, relatively urbanized province of Uusimaa was already observed in the 1950s (Syvänne 1952): between 1929 and 1950, the incidence decreased from 0.97 to 0.47 per 1000 person years. In Helsinki, the incidence declined from 0.85 to 0.43 per 1000 person years between 1950 and 1965 (Niskanen & Achté 1972), and in Turku from 0.49 per 1000 person years in 1949-1950 to 0.40 per 1000 person years in 1969-1970 (Salokangas 1979). A recent study based on the Finnish Hospital Discharge Register found that the first admission rate of all DSM-III-R nonaffective psychotic disorders declined from 0.74 per 1000 person years in 1990 to 0.69 per 1000 person years in 1993 (Korkeila et al 1998). However, in this study the first-ever hospitalisation for psychotic disorder was defined as having no such hospitalisations during the three years preceding the index admission (Korkeila et al 1998).

2.3.1.4. Geographical variation in the occurrence of schizophrenia

Studies indicate large differences in the prevalence of schizophrenia between different countries, and smaller but significant differences in the incidence (Torrey 1987, Torrey 1989). In addition, pockets of very high and very low prevalence have been detected

(Torrey 1987). The lowest reported prevalence (0.3 per 1000, age-corrected 0.5 per 1000) has been reported among the Amish population of the United States (Torrey 1987), and the highest in a community in northern Finland (22 per 1000, age-corrected lifetime risk 3.2%) (Hovatta et al 1997). Also significant within-country variations in prevalence (Lehtinen et al 1990, Torrey & Bowler 1990, Youssef et al 1991, Hovatta et al 1997) and morbid risk (Youssef et al 1993, Hovatta et al 1997) have been observed.

The most striking differences in the occurrence of schizophrenia within countries relate to urban-rural differences. The prevalence of schizophrenia has been repeatedly observed to be higher in urban than rural areas, but previously this was assumed to be caused by social drift – patients with schizophrenia ”drift” into urban areas as a consequence of their illness or its prodromal symptoms (Freeman 1994, Torrey & Bowler 1990). However, Lewis et al showed in a Swedish conscript cohort that urban upbringing, not urban residence, was associated with increased risk of developing schizophrenia in adulthood (Lewis et al 1992). The odds ratio was highest among those who had grown up in cities (Stockholm, Göteborg, Malmö) (Lewis et al 1992). Since then, several studies have found an increased risk of schizophrenia among the urban-born, particularly those born in cities (Takei et al 1995, Marcelis et al 1998, Mortensen et al 1999). A relationship between urban birth and environmental risk factors operating prenatally or early in life has been suggested (Freeman 1994, Takei et al 1995, O’Callaghan et al 1995).

Significant geographical differences in the occurrence of schizophrenia have also been observed in Finland, but here the occurrence of schizophrenia is lower in urban areas. This was already observed in the 1960s. The rates of new disability pensions granted because of schizophrenia and other psychotic disorders were highest in eastern and lowest in southwestern Finland, and within each of the studied regions the rates were higher among those living in rural areas (Suominen 1975). In a more recent study of first-contact psychiatric patients, the incidence of all psychotic disorders among the population over 15 years varied between 0.80 per 1000 in Helsinki and 1.61 in the north Karelia (Salokangas et al 1987). The prevalence of schizophrenia in the Mini Finland Health Survey varied between 0.9% in the urbanized southern and southwestern Finland

and 2.1% in northern Finland (Lehtinen et al 1990), and even larger differences in prevalence were observed in a register-based study (Hovatta et al 1997). The most recent study, based on hospital treatments in 1993-1994, found that the first-admission rate of nonaffective psychotic disorders per 1000 person years varied between 0.56 in southwestern and 0.84 in eastern Finland, while the first-admission rate of affective disorders varied between 0.51 in northern and 0.84 in eastern Finland (Korkeila et al 1998). Thus, the incidence of psychotic disorders seems to have been higher in rural areas for decades, and this applies also to affective disorders, particularly in eastern Finland (Suominen 1975, Korkeila et al 1998a).

2.3.2. Age at onset of schizophrenia

The age at onset of schizophrenia is usually defined as the age at the onset of first psychotic symptoms (interview-based studies) or at the beginning of first hospitalization for schizophrenia (register-based studies). The age at the onset of prodromal non-psychotic symptoms has also been used in some studies. Although the age at onset may vary by several years depending on the definition used (Maurer & Häfner 1995), the times of onset of behavioural change, positive symptoms, and first hospitalization are usually correlated within individuals (DeLisi 1992).

The peak age at onset of schizophrenia occurs in early adulthood (Kraepelin 1919 p. 224, Bleuler 1911 p. 341, Sham et al 1994, Castle et al 1995). Females tend to have a later age at onset than males (Castle et al 1995) and a different age at onset distribution: that among males shows a single marked peak in the early twenties, while the distribution among females is bimodal with a second peak in the 45-54-year age group (Castle et al 1995, Sham et al 1994).

The sex difference in the age at onset has not been found in all studies (Folnegović et al 1990, Kendler & Walsh 1995), and this is notably the case in many Finnish studies (Kuusi 1986, Salokangas 1993, Hovatta et al 1997). Recent research suggests that the later age at onset in females may be confined to patients without a family history of schizophrenia, since no sex differences in the age at onset exist among patients with a

positive family history for schizophrenia (Shimizu & Kurachi 1989, Albus et al 1994, DeLisi et al 1994, Murphy et al 1994, Albus et al 1995, Gorwood et al 1995).

The ages of onset of affected siblings are correlated. The correlation coefficient for the onset ages in pairs of affected siblings has varied between 0.24 and 0.26 (DeLisi et al 1987, Kendler et al 1987, Burke et al 1996, Cardno et al 1998). A positive family history of schizophrenia is associated with an earlier age at onset (Kendler & MacLean 1990a, Maier et al 1993, Sham et al 1994, Albus et al 1994, Alda et al 1996). Early age at onset also predicts a higher risk of rehospitalization (Eaton et al 1992), poor outcome (Loebel et al 1992), and neuroleptic resistance (Meltzer et al 1997).

A family study of patients with schizophrenia (61%), delusional disorder (31%) or schizoaffective disorder (8%) with onset after the age of 60 found no increased risk of schizophrenia in the relatives of such patients, whereas the risk of major depression was significantly higher among relatives of patients than in those of matched controls (Howard et al 1997). Because of possible aetiologic heterogeneity, the authors suggest that at least a coding for late age at onset should be included in subsequent revisions of DSM and ICD (Howard & Rabins 1997).

2.3.3. Sex differences in schizophrenia

The question of whether schizophrenia is more common among males is controversial. Already in Kraepelin's material, males (57%) outnumbered females (43%) (Kraepelin 1919, p. 231). Some recent studies have replicated this observation (Kendler & Walsh 1995, Hovatta et al 1997), although the findings were mixed in the WHO Ten Country Study: males tended to have a higher incidence in the European centres, while elsewhere the disparity was often reversed (Jablensky et al 1992). The difference in the incidence or prevalence of schizophrenia between males and females diminishes or disappears when broader diagnostic criteria are applied and when other nonaffective psychotic disorders are included in the definition (Castle et al 1993, Goldstein 1997).

Besides a lower incidence and later age at onset, females tend to show better premorbid functioning, better social functioning, and a more benign course of illness (Salokangas 1983, Castle et al 1995, Goldstein 1997). Males have more negative symptoms and females more positive and affective symptoms (Castle et al 1994, Goldstein 1997). Males also have more structural brain abnormalities than females (Goldstein 1997).

The difference in the outcomes tends to diminish with advancing age (Goldstein 1997, Childers & Harding 1990). This, and the presence of a bimodal age-at-onset distribution among females, has been suggested to result from a protective effect of estrogen in females (Castle et al 1995, Goldstein 1997, Häfner et al 1998). In animal studies, estrogen has had effects on the dopaminergic, noradrenergic, serotonergic, and GABA (gamma-aminobutyric acid)-ergic systems (Castle et al 1995, Häfner et al 1998). However, direct evidence for this estrogen hypothesis is scarce; for example, no connection between the onset of schizophrenia and recent menopause has been observed (Castle et al 1995).

Although females seem to be somewhat less prone to schizophrenia and, when they do develop it, are more likely to have a benign course of the disorder, female sufferers with schizophrenia seem to have more risk factors for schizophrenia (Castle et al 1995). Several family studies have observed that the relatives of female patients show a higher morbid risk of schizophrenia and schizophrenia spectrum psychotic disorders than relatives of male patients (Castle et al 1995, Goldstein 1997), although others have failed to replicate this finding (Kendler & Walsh 1995). Some studies have reported that the increased risk of schizophrenia after second-trimester exposure to an influenza epidemic is confined to females (O'Callaghan et al 1991, Takei et al 1994). Castle and Murray have suggested that the reason for the sex differences in the incidence, symptoms, clinical course, and risk factors might be that there are subtypes of schizophrenia to which males and females are differently susceptible (Castle et al 1994, Castle et al 1995).

2.3.4. Seasonal variation of births in schizophrenia

Schizophrenic patients worldwide have a 5-8% excess of births during the winter and spring months compared with the general population (Torrey et al 1997). The peak months of schizophrenic births have been between January and April in the Northern hemisphere, and between July and September in the Southern Hemisphere. However, the winter-spring excess is smaller and less consistent in the Southern Hemisphere (McGrath & Welham 1999). Within countries, the seasonal variation in some studies has been more pronounced among the urban-born than the rural-born (O'Callaghan et al 1995), while others have not detected such an association (Mortensen et al 1999). Studies of sex differences have given contradictory results, some finding more pronounced seasonality among females, others among males. Shifts in the peak of seasonal variation over time have also been observed. (Torrey et al 1997)

The cause of the seasonal variation of births in schizophrenia is unknown. A statistical artifact caused by age incidence has been suggested (Lewis 1989), and refuted (Dalén 1990, Pulver et al 1990, Torrey & Bowler 1990a, Watson 1990). It has also been suggested that parents of patients with schizophrenia have a seasonal conception pattern that is slightly different from that of the general population. This so-called procreational habits hypothesis predicts that siblings of patients should also have a winter-spring excess in their births. This has not been supported by studies conducted on the siblings of patients with schizophrenia, but the sample sizes have been relatively small. (Torrey et al 1997)

Several theories have linked seasonality of births to genetic factors, pregnancy and birth complications, nutritional deficiencies, weather effects, and to seasonal variation in light, external toxins, or hormonal levels. Studies that have investigated the association between pregnancy and birth complications and seasonal variation of births have obtained contradictory results, some finding more complications among the winter-born, others among the summer-born (Torrey et al 1997). However, sample sizes have been small. Several researchers have suggested that the winter-spring excess of births in schizophrenia may be caused by variations in maternal hormonal levels brought about

by seasonal variations in light (Torrey et al 1997). The hypothesis is indirectly supported by findings of a latitude gradient in the magnitude of the seasonal variation (Torrey et al 1977). Hypotheses that link seasonal variation of births in schizophrenia to nutritional deficiencies and exposures to industrial chemicals have not been tested (Torrey et al 1997).

Several studies have investigated the association between outdoor temperature during gestation and seasonal variation of births. Asssociations between both exceptionally high and low temperatures during gestation and the magnitude of the seasonal variation have been reported, but several studies have also failed to detect any association between seasonal variation of births in schizophrenia and outdoor temperature (Torrey et al 1997). Somewhat more encouraging results have been obtained from studies searching for associations between infectious epidemics during gestation and seasonality of births in schizophrenia. However, these findings have concerned a variety of infections (Watson et al 1984, Torrey et al 1988, Takei et al 1996, Torrey et al 1997).

2.4. Genetic epidemiology of schizophrenia

Classic epidemiology was interested in finding environmental risk factors for diseases, while classic genetics focused on finding genes causing or predisposing to illnesses. Genetic epidemiology is interested in both genetic and environmental causes of diseases. The basic terminology of genetic epidemiology is presented in Table 10. (Faraone & Tsuang 1995, p. 81)

Table 10. Basic terminology of genetic epidemiology

Concept	Significance
Allele	A different form of the same gene
Anticipation	Exacerbation in the disease (earlier onset and/or more severe form) from parent to child
Association studies	Assess the association of a disease and genetic markers in unrelated patients and controls
Autosome	Non-sex chromosome
Concordance	Proportion of twin pairs who are similarly affected
Dominant allele	An allele that is expressed if either of the pairs of a chromosome has it
Gene-environment interaction	Different effect of a genotype on disease risk in persons with different environmental exposures
Genetic heterogeneity	Different genes cause the same disorder
Genetic marker	A DNA sequence with a known chromosomal location
Genotype	Genetic constitution
Haplotype	A group of closely located alleles which are inherited together as a unit
Heritability	Measures the degree to which genetic factors influence variability in the phenotype: if phenotypic variability (V_p) is divided into statistically independent genetic (V_g) and environmental variability (V_c), heritability (h^2) can be calculated as the ratio of genetic and phenotypic variances ($h^2 = V_g / V_p$). Specific to the population and time period studied.
Heterozygosity	Different alleles are present at a given locus on the pairs of a chromosome
Homozygosity	The same allele is present at a given locus on both pairs of a chromosome
Incomplete penetrance	All individuals possessing a disease gene do not manifest the disease
Liability	Predisposition to develop a disorder
Linkage	Close proximity of loci on a chromosome
Linkage analysis	Assesses the association of disease and a genetic marker within families
Locus	The site of a specific gene on a chromosome
Lod score	Logarithm of the odds, a statistical term that incidates whether two loci are linked. A lod score of 3 or higher is commonly accepted as showing linkage.
Pairwise concordance	Method of calculating concordance in which every pair of twins is counted only once
Penetrance	Frequency with which a particular genotype is expressed by the individuals possessing it
Phenocopy	Case of a particular disease caused entirely by environmental factors
Phenotype	The observable characteristics of an individual, determined by genetic and environmental factors
Proband	Name used for cases and controls in genetic studies
Pleiotropy	Same gene may express more than one phenotype
Probandwise concordance	Method of calculating concordance in which twin pairs in which both members are ascertained indepently are counted twice. Only probandwise rates can be compared directly with the general population occurrence estimates.
Recessive allele	An allele that is expressed only if both pairs of a chromosome have it
Vulnerability indicator	Any genetic, biological, psychological, or behavioural trait that may reflect liability to develop a disorder

(Gottesman & Shields 1982, Kremen et al 1992, Kendler & Diehl 1993, Faraone & Tsuang 1995, Ottman 1996, Owen & Craddock 1996, Plomin et al 1997, Skuse 1997, Pekkarinen 1998)

Faraone and Tsuang have introduced the term ”chain of genetic epidemiologic research” to describe the logical progression of questions in genetic epidemiologic research. The first question, ”Is the disorder familial”, is answered using a research design known as the family study method. The best designs for answering the second question, ”What are the relative contributions of genes and environment”, are twin and adoption studies. The answer to the third question, ”What is the mode of transmission”, may be found using segregation analysis. The answer to the fourth question, ”Where is the gene(s) located”, is, with luck, found with linkage or association studies. (Faraone & Tsuang 1995, p. 82)

Table 11. Morbid risk of schizophrenia in relatives of probands with schizophrenia

Relationship	Morbid Risk	Relationship	Morbid Risk
General population	1 %	**Uncles / aunts**	2 %
Parents	6 %	**Nephews / nieces**	4 %
Siblings	9 %	**Grandchildren**	5 %
Children	13 %	**Half-siblings**	6 %
Dizygotic twins	17 %	**First cousins**	2 %
Monozygotic twins	48 %	**Spouses of patients**	2 %

(Gottesman 1994)

2.4.1. Is schizophrenia familial? Family studies

Numerous family studies conducted between 1920 and 1987 have confirmed that relatives of probands with schizophrenia have an increased risk of developing schizophrenia. The risk decreases rapidly from close to more distant relatives (Table 11) (Gottesman 1994). First-degree relatives of schizophrenia probands have an approximately ten-fold risk of developing schizophrenia compared to relatives of control probands (Kendler & Diehl 1993). The relatives of probands with schizophrenia also have an increased risk of other disorders known as the schizophrenia spectrum disorders: schizotypal and paranoid personality disorder, and other nonaffective psychotic disorders (Kendler & Diehl 1993).

The results of the most recent epidemiologic family study, the Irish Roscommon Family Study, are of special interest because of the use of the most sophisticated methodology and systematic case ascertainment of all the family studies conducted thus far. The study included three proband groups: schizophrenic, affective, and control. Probands and all available first-degree relatives were interviewed and rediagnosed according to DSM-III-R diagnostic criteria. For the deceased and those who could not be traced or refused to be interviewed, the diagnosis was based on case note information and family history interview. After diagnostic evaluation, probands were classified into 7 groups: schizophrenia, schizoaffective disorder, schizotypal personality disorder, other nonaffective psychosis, psychotic affective illness, nonpsychotic affective illness, and controls. (Kendler et al 1993a)

The morbid risks of schizophrenia and schizophrenia spectrum disorders and affective illnesses are presented in Table 12. The numbers are based on morbid risks among relatives who were personally interviewed. The study confirmed the higher risk of schizophrenia among relatives of probands with schizophrenia, schizoaffective disorder, schizotypal personality disorder and other nonaffective psychosis, compared with relatives of controls. The risk of schizophrenia was also higher among relatives of probands with psychotic affective illness. Among relatives, the risk of schizophrenia was significantly higher in siblings than in parents. (Kendler et al 1993a)

The morbid risk of schizoaffective disorder was, compared with relatives of controls, significantly higher only among relatives of probands with psychotic affective illness. When schizoaffective disorder and other nonaffective psychosis were merged into a single diagnostic group, the relatives of probands from all groups except nonpsychotic affective illness had a significantly higher risk of these combined nonaffective psychotic disorders than relatives of controls. (Kendler et al 1993b)

Table 12. Morbid risks of schizophrenia, schizophrenia spectrum disorders, and affective illnesses among first-degree relatives of probands with schizophrenia, schizophrenia spectrum disorder, or affective illness in the Roscommon Family Study

Proband's DSM-III-R Diagnosis	Relatives' Morbid Risk					
	Schizo-phrenia	SAD	ONAP	SPD+ PPD	AI	BAI
Schizophrenia	6.5	2.3	1.2	8.2	24.9	1.2
SAD	6.7	1.8	2.3	5.6	49.7	4.8
SPD	6.9	3.9	5.5	5.0	10.7	0
ONAP	5.1	0	2.1	3.9	26.6	2.2
PAI	2.8	5.8	2.3	3.6	28.8	8.6
NPAI	0.6	2.5	0.6	2.9	31.1	6.6
Control	0.5	0.7	0.7	1.7	22.8	1.4

SAD = schizoaffective disorder
SPD = schizotypal personality disorder
ONAP = other nonaffective psychosis
PAI = psychotic affective illness
NPAI = nonpsychotic affective illness
PPD = paranoid personality disorder
AI = all affective illnesses
BAI = bipolar affective illness
(Kendler et al 1993a-d)

The morbid risk of schizotypal or paranoid personality disorder was significantly higher among relatives of probands with schizophrenia and schizoaffective disorder, and almost significantly higher among relatives of probands with schizotypal personality disorder, other nonaffective psychotic disorder, and nonpsychotic affective disorder than among relatives of controls. In the relatives of schizophrenic, schizoaffective, and schizotypal probands, the prevalence of schizotypal or paranoid personality disorder was more than twice as large in parents as in siblings. (Kendler et al 1993c)

The morbid risk of all affective illnesses was significantly higher only among relatives of probands with schizoaffective illness compared with relatives of controls. The risk of bipolar affective illness was significantly higher among relatives of probands with psychotic affective illness and almost significantly higher among relatives of probands with schizoaffective illness than among relatives of controls. However, a substantially higher proportion of affectively ill relatives of schizophrenic vs. control probands had psychotic, especially mood-incongruent psychotic, symptoms. (Kendler et al 1993d)

The findings from another large family study using modern diagnostic criteria are mainly consistent with the Roscommon findings, but some differences emerged. The Iowa Study was a follow-up and family study of 510 consecutive cases with a discharge diagnosis of schizophrenia admitted to the Iowa Psychopathic Hospitals from 1934 to 1944, which used structured interviews and DSM-III diagnostic criteria (Kendler et al 1985). As with the Roscommon Study findings, the risk of schizophrenia was increased not only among relatives of probands with schizophrenia or a schizophrenic spectrum disorder but also among those of probands with psychotic affective illness (Kendler et al 1985, Kendler et al 1986). Another family study also found an increased morbid risk of schizophrenia in the relatives of probands with major depressive disorder with mood-incongruent psychotic features, although this was not statistically significant due to the small sample size (Maj et al 1991). The relatives of probands with schizoaffective disorder had as a high risk of schizophrenia as relatives of probands with schizophrenia, but only the risk of bipolar affective illness was higher among relatives of probands with schizoaffective disorder than among relatives of controls, while the risk of unipolar affective disorder was similar to that in the relatives of controls in the Iowa Study (Kendler et al 1986). In the smaller family study, the risk for major affective disorders was not increased in the relatives of probands with DSM-III-R schizoaffective disorder, depressive type (Maj et al 1991).

Family studies have thus consistently shown that schizophrenia is familial, a predisposition that is not limited to schizophrenia, but to a spectrum of related disorders. This so-called schizophrenia spectrum includes schizoaffective disorder, schizophreniform disorder, schizotypal personality disorder, paranoid personality

disorder, and delusional disorder. The findings of increased risk of schizophrenia among relatives of probands with psychotic affective illness and the frequent occurrence of psychotic symptoms among affectively ill relatives of schizophrenic probands certainly present a challenge to the decision about which disorders to include in the schizophrenia spectrum, and also to the delineation of the diagnostic boundaries of schizophrenia, schizoaffective disorder, and psychotic affective illness.

2.4.2. What are the relative contributions of genes and environment?

2.4.2.1. Twin studies

Twin studies offer a powerful method of disentangling the effects of genetic and environmental factors. Monozygotic twins have almost identical genomes, while dizygotic twins share only approximately half of their genes. Both usually share the same rearing environment. Thus, if environmental factors entirely explain the familial clustering, there should be no differences in the concordances between monozygotic and dizygotic twins. Conversely, if genetic factors are important, the concordance should be considerably higher among monozygotic than dizygotic twins. If genetic factors alone were sufficient determinants, there should be a 100% concordance among monozygotic twins. The comparison of discordant monozygotic twins helps to identify environmental factors predisposing to or protecting from schizophrenia. Also, the variability of abnormality in monozygotic twins helps to identify less severe variants of the same underlying vulnerability. (Gottesman & Shields, pp. 72-73)

Twin studies have shown that the heritability of schizophrenia in different populations is high (Kendler & Diehl 1993, Cannon et al 1998, Cardno et al 1999). In a Finnish national twin cohort, the heritability of schizophrenia was 83%; the remaining 17% of the variance in liability was due to unique environmental factors, while common environmental factors seemed to have no influence on the liability (Cannon et al 1998). The probandwise concordance was 46% among monozygotic twins, and 9% among dizygotic twins (Cannon et al 1998). The results from a British study were almost identical: the heritability was 83%, the rest of the liability being best explained by

unique environmental factors (Cardno et al 1999). The concordance was 41% among monozygotic and 5% among dizygotic twins (Cardno et al 1999).

The importance of genetic factors also emerged in two studies that investigated the risk of schizophrenia and schizophrenia spectrum disorders among offspring of identical twins discordant for schizophrenia (Gottesman & Bertelsen 1989, Kringlen & Cramer 1989). In the Danish twin study, there was no significant difference in the morbid risk of schizophrenia between offspring of affected twins (10%) and unaffected co-twins (17%) (Gottesman & Bertelsen 1989). However, sample sizes were quite small: three schizophrenic probands had a total of 14 offspring, 1 of whom was affected, while 6 unaffected cotwins had 24 offspring, 4 of whom were affected (Gottesman & Bertelsen 1989). The sample size in the Norwegian twin study was larger (Kringlen & Cramer 1989). Of the 28 offspring of schizophrenic twins, five (18%) had a schizophrenia spectrum disorder, whereas 2 of the 45 offspring of unaffected co-twins had a schizophrenia spectrum disorder (4%) (Kringlen & Cramer 1989). These differences were not statistically significant (Kringlen & Cramer 1989). Although both of these studies lacked statistical power, they suggest that unaffected monozygotic cotwins tend to carry the genotype predisposing to schizophrenia, but that it remains unexpressed in them – for example, because they have not been exposed to environmental risk factors (Gottesman & Bertelsen 1989).

The studies of discordant monozygotic twins have also given clues about environmental risk factors. The findings of higher concordance rates among monochorionic (twins sharing the same placenta and chorion) than dichorionic monozygotic twins (Davis & Phelps 1995), greater intrapair differences in finger ridge count among monozygotic twins discordant for schizophrenia than among normal monozygotic twins (Bracha et al 1992), and higher frequency of serious perinatal complications in the affected co-twin (Torrey et al 1994) suggest the involvement of prenatal environmental factors.

Twin studies, in summary, suggest that genetic factors are the most important risk factors for schizophrenia. However, environmental factors are also important: less than

half of individuals with an identical genome – identical twins – are concordant for schizophrenia.

2.4.2.2. Adoption studies

Adoption studies compare the effects of different rearing environments among groups that are assumed to be similar in their genetic predisposition, and the effects of different genetic predisposition among groups that are assumed to have similar rearing environments.

In the *adoptees' families design*, the probands are adoptees who have developed schizophrenia in adulthood and unaffected control adoptees. The psychiatric status of the biological and adoptive relatives is investigated. If genetic factors are important, the rate of schizophrenia should be higher among the biological than adoptive relatives of an affected adoptee. If the rearing environment is important, more abnormalities should be observed among the adoptive families of affected than unaffected adoptees. (Gottesman & Shields 1982, pp. 76-77)

The largest study to use the adoptees' families design was the Danish Adoption Study of Schizophrenia (Kety et al 1994). This found significantly increased risks of DSM-III schizophrenia, schizoaffective disorder, and schizotypal personality disorder among biological relatives of probands with the same disorders than among relatives of control probands, but no increased risk among adoptive relatives of affected vs. control probands (Kety et al 1994, Kendler et al 1994).

In the *adoptees method*, the parent with schizophrenia is the proband. The identification of probands can follow two paths. One starts with patients with schizophrenia who have children, and locates those children who have been adopted. The alternative path identifies all adoptees and selects those whose biological parent or parents have schizophrenia. After the probands have been identified, the rate of occurrence of schizophrenia among their adopted children is compared with the rate among adoptees with unaffected biological parents. If genetic factors are important in the aetiology of

schizophrenia, the rate of schizophrenia should be higher among those with an affected biological parent. (Gottesman & Shields, pp. 75-76)

The largest and most recent study to use the adoptees method was the Finnish Adoptive Study of Schizophrenia (Tienari et al 1994, Wahlberg et al 1997). The findings confirm the genetic contribution in schizophrenia: 8.4% of the adopted offspring of probands with schizophrenia developed a non-affective psychotic disorder compared with only 0.5% of the the adopted offspring of control probands (Tienari et al 1994). However, a gene-environment interaction also emerged in the study (Wahlberg et al 1997). When the adoptees were tested for schizophrenic thought disorder at the mean age of 21, only those adoptees whose biological mother had had schizophrenia and whose adoptive parents showed a high level of communication deviance displayed schizophrenic thought disorder (Wahlberg et al 1997). This was not observed among adoptees who only had a biological mother with schizophrenia or adoptive parents with a high level of communication deviance (Wahlberg et al 1997).

Adoption studies confirm the importance of genetic factors in the aetiology of schizophrenia. The Finnish Adoptive Study has provided evidence for gene-environment interaction in the development of schizophrenia.

2.4.2.3. High-risk studies

The third method used to separate the contribution of genetic and environmental factors in the aetiology of schizophrenia is the high-risk method, which is also feasible for identifying early indicators of an emerging schizophrenia (Cornblatt & Obuchowski 1997). In high-risk studies, individuals who have a higher risk of developing schizophrenia than those in the general population are identified in childhood and followed up through the risk period for developing schizophrenia. Typically, high-risk samples consist of offspring of schizophrenic parents. The best-known high-risk studies of schizophrenia are the Copenhagen High Risk Project (Cannon & Mednick 1993), the New York High-Risk Project (Erlenmeyer-Kimling et al 1997), and the Israeli High-Risk Study (Ingraham et al 1995).

The largest of the high-risk studies is the Copenhagen High Risk Project, which has followed up 207 children born to mothers with chronic schizophrenia and 104 controls with healthy parents for more than 30 years (Cannon & Mednick 1993). Their findings again support the strong effect of genetic factors in the development of schizophrenia: the prevalences among offspring of schizophrenic mothers vs. controls were 16.2% vs. 1.9% for DSM-III-R schizophrenia, 4.6% vs. 0.9% for DSM-III-R other nonaffective psychotic disorders, and 21.3% vs. 5% for schizotypal, schizoid, and paranoid personality disorders (Parnas et al 1993). However, they also found that offspring of schizophrenic mothers who later developed schizophrenia had had significantly more birth complications than high-risk subjects who remained unaffected (Parnas et al 1982). Offspring of schizophrenic mothers who had a schizophrenia spectrum personality disorder had had less birth complications than those who had developed schizophrenia and those who remained unaffected (Parnas et al 1982). Birth complications interacted with genetic risk in determining cerebral ventricular enlargement in high-risk subjects (Cannon et al 1993a). Severe instability in the early rearing environment was another risk factor for schizophrenia among the high-risk subjects (Cannon & Mednick 1993).

The New York High Risk Study includes, besides offspring of schizophrenic parents and controls, a third group consisting of offspring of parents with a severe affective disorder. The findings are of interest in relation to the diagnostic boundaries of the schizophrenia spectrum. While schizophrenia and other nonaffective psychotic disorders except schizoaffective disorder occurred only among offspring of schizophrenic parents, RDC schizoaffective disorder, mainly schizophrenic type, was more common and RDC schizoaffective disorder, mainly affective type, less common among the offspring of parents with affective disorder than among those of schizophrenic parents. Affective psychoses were equally common among both high-risk groups. Otherwise, the New York High Risk Project has focused more on detecting early biological and behavioural markers of schizophrenia than on identifying environmental risk factors for schizophrenia. (Rosenberg et al 1997, Erlenmeyer-Kimling et al 1997, Freedman et al 1998)

The Israeli High-Risk Study consists of 50 offspring of schizophrenic parents, half of whom were raised in a kibbutz, the other half by their biological parents, and 50 control offspring of healthy parents similarly raised either in a kibbutz or by their biological parents. Schizophrenia occurred only among high-risk subjects and equally among those reared in a kibbutz or by their biological parents. (Ingraham et al 1995)

In Finland, Gunnel Wrede began a high-risk study of schizophrenia in the 1970s. Cases had been born in Helsinki between 1960 and 1964 to schizophrenic mothers. The mothers had been born between 1916 and 1948 and treated in Hesperia hospital for a psychotic disorder. The children have not yet been followed up in adulthood, but they did experience more pre- and perinatal complications than controls born in the same hospitals (Wrede et al 1980). In adolescence, the children born to mothers with paranoid schizophrenia were significantly better functioning socially than their peers from the same class, while the social functioning of other high-risk subjects was slightly worse than their peers. (Wrede 1984)

Results from high-risk studies provide strong support for the importance of genetic factors in the development of schizophrenia, but they also emphasise the existence of environmental risk factors and gene-environment interactions.

2.4.3. What is the mode of transmission?

The three simple Mendelian modes of inheritance are autosomal recessive, autosomal dominant, and X-linked. In autosomal recessive inheritance, only probands who are homozygotic for the disease allele are affected. Both parents of the affected probands are usually unaffected but 25% of their siblings are affected. The proband’s children and more distant relatives are rarely affected. In autosomal dominant inheritance, probands who are heterozygotic for the disease allele are also affected. One of the proband's parents is always affected, as well as 50% of siblings and children, and there is usually a long family history of the disorder. The third mode is X-chromosome linked inheritance, which is usually recessive; the X-linked dominant mode of inheritance is extremely rare. A female with one X-linked recessive allele will not show the disease,

but half of her sons will be affected, while half of her daughters will be unaffected carriers. A male with an X-linked recessive allele can only have received the allele from his mother. He cannot transmit the disease to his sons, but half of his daughters will be unaffected carriers. (Gottesman & Shields 1982, pp. 60-62)

A new mutation class - the so-called dynamic mutations caused by unstable DNA - identified in the beginning of the 1990s may obscure the otherwise Mendelian pattern of inheritance. Unstable DNA consists of pathologically expanding DNA nucleotide triplets. These DNA sequences display a marked tendency to amplify when transmitted from parent to child. The person will remain asymptomatic until a certain number of triplet repeats, after which symptoms start to emerge with increasing severity depending on the number of repeats. Huntington's disease and Fragile X syndrome are examples of triplet repeat diseases. Typical of these diseases is a phenomenon called anticipation, a tendency of symptoms to get worse and age at onset to become earlier from one generation to the next. (Petronis & Kennedy 1995, O'Donovan & Owen 1996)

Besides single gene mendelian transmission, there are three other types of transmission models: single major gene, oligogenic, and multifactorial polygenic. Single major gene models suggest that there is one major gene which accounts for most of the genetic transmission of a disorder, but other genes and environmental conditions may also have some minor effect. Oligogenic models assume that there are several genes whose combined action causes the illness. The action of the genes may be additive or interactive (epistatic, meaning that the combined effect of the genes is more or less than the sum of their separate effects). (Faraone & Tsuang 1995, p. 95)

Multifactorial polygenic inheritance means that a large number of genes of small effect occur simultaneously and combine with environmental effects to determine the outcome. The difference between oligogenic and multifactorial polygenic models is one of degree: there are several, but perhaps less than ten, genes in the oligogenic model, while there may be even hundreds of genes in the multifactorial polygenic model. Polygenic inheritance is characterized by a clinical range of outcomes from borderline to severely affected, by severely ill probands having more affected relatives than mildly

ill probands, by the increasing risk to relatives with greater numbers of affected family members, by a sharply decreasing risk from close to more distant relatives, and by a distribution of cases on both maternal and paternal sides of a family. Multifactorial polygenic models assume that the liability to develop a disorder is normally distributed, and that individuals above a certain threshold manifest the disorder. There may be different thresholds for mild and more severe forms of the disorder. (Gottesman & Shields 1982 p. 63, Faraone & Tsuang 1995 pp. 95-96)

Analyses that assess the mode of transmission are called segregation analyses. Unfortunately, they have not been successful in identifying the mode of transmission of schizophrenia, and almost all modes of transmission have their supporters (Crow 1995, Crow 1995a, Tsuang & Faraone 1995, Owen & Craddock 1996).

2.4.4. Where are the genes located? Molecular genetic studies

The search for genes conferring vulnerability to schizophrenia started in the 1980s with linkage analysis studies of large, densely affected families (Kendler & Diehl 1993). Initially, there were some promising findings in individual studies, but replication studies failed to support the observed linkages (Kendler & Diehl 1993).

Developing methodology in the 1990s has made genomewide scans feasible, and a number of genomewide scans have been conducted in recent years. The results, summarized in Table 13, have been somewhat disappointing. Findings suggesting linkage have been made in nearly all human chromosomes, but replications have been rare. The most promising areas remain more or less a matter of opinion. Worldwide, they might be located on the short arms of chromosomes 2, 6, 8, and 10. (Crow & DeLisi 1998, DeLisi 1999, DeLisi & Crow 1999a)

As a part of The Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland project, one genome scan and one study focusing on previously identified linkages have recently been completed.

Table 13. Positive findings on genome scans of schizophrenia

Chromosome	Worldwide	Finland	Chromosome	Worldwide	Finland
1q		+	**10p**	+	
2p	+		**10q**	+	
2q	+		**12p**	+	
4p	+		**12q**	+	
4q	+	+	**13q**	+	
5p	+		**14q**	+	
5q	+		**15p**	+	
6p	+		**16q**	+	
6q	+		**18p**	+	
7q	+		**18q**	+	
8p	+		**20q**	+	
8q	+		**22q**	+	
9q	+		**Xp**	+	+

+ means lod>2 or P<0.01
(Crow & DeLisi 1998, DeLisi & Crow 1999, Hovatta et al, in press)

In the genome scan conducted in pedigrees originating from a genetically isolated community in Finland, the strongest evidence for linkage was obtained from chromosome 1q (Hovatta et al 1999). Although none of the previous genomewide scans have found evidence for linkage in this area, a balanced translocation strongly associated with schizophrenia and other psychotic disorders has been found close to this area in a Scottish pedigree (Devon et al 1998). The next promising area was on chromosome 4q, where some evidence of linkage has been observed in previous genomewide scans, although in an area somewhat proximal to this finding (DeLisi 1999). The third region with a lod score over two was located on Xp, where previously weak evidence for linkage has again been observed (Hovatta et al 1999). In a study that investigated candidate regions on chromosomes 3p, 5q, 6p, 20p, and 22q on an independent sample of large Finnish pedigrees, some evidence for linkage was found on chromosomes 5p, 6p, 8p, and 20p, although the maximum lod score did not exceed 2 in any of the regions (Hovatta et al 1998).

Genomewide scans are one strategy for identifying genes predisposing to schizophrenia. Another widely used strategy is to study candidate genes. The problem with such studies is that because the pathogenetic mechanism of schizophrenia is obscure, the possibly defective biochemical pathways are not known. (DeLisi 1999)

Dopamine receptor genes have been widely studied. Except for increased homozygosity of the D3 receptor among patients with schizophrenia, the findings have been negative. Findings concerning N-methyl-D-aspartate receptors, catechol-O-methyltransferase and apolipoprotein E4 have equally been negative. Controversial, weak positive findings exist on the serotonin 2A receptor, α-7 nicotinic acetylcholine receptor, some HLA-alleles, and a gene coding for an aspect of the potassium channel. Overall, candidate gene studies conducted thus far have failed to identify any genes related to schizophrenia. (DeLisi 1999)

Some rare chromosomal translocations and other chromosomal aberrations have been linked with schizophrenia. A microdeletion on chromosome 22q11 causing the velo-cardio-facial syndrome has repeatedly been associated with schizophrenia (Murphy & Owen 1996, DeLisi 1999). Patients with the velo-cardio-facial syndrome or CATCH-22 have a 10-30% risk of developing nonaffective psychotic disorder (Murphy & Owen 1996). A few studies have detected balanced translocations or other chromosomal aberrations in single pedigrees (Tsuang & Faraone 1995, DeLisi 1999). Some evidence of the involvement of dynamic mutations in schizophrenia has also been obtained (DeLisi 1999).

Overall, the findings from genetic studies are modest compared with the efforts invested. There are, however, several reasons why this should be so. The uncertainty of the correct phenotypic definition of schizophrenia or schizophrenia spectrum disorders, incomplete penetrance, and genetic heterogeneity make schizophrenia even more complex than most other complex disorders (Kendler & Diehl 1993). It may be that there are no genes of major effect involved in the aetiology of schizophrenia (Owen & Craddock 1996), and large family studies may not be the correct method to search for genes of minor effect. Besides, densely affected pedigrees may actually be more likely

to have multiple disease genes segregating than smaller ones (Owen & Craddock 1996). Association studies and those focusing on genetic isolates have been offered as one solution (Owen & Craddock 1996). It has also been suggested that hypothesis-driven research should be emphasised more than the current approach of trying first to find the gene and only after that the cause (DeLisi 1999).

2.5. Environmental risk factors of schizophrenia

2.5.1. Infections

There was already speculation about infections being involved in the aetiology of schizophrenia back in Kraepelin's and Bleuler's times (Kraepelin 1919 pp. 240-241, Bleuler 1911 pp. 343-344): the spirochete causing neurosyphilis had been identified, and it seemed that the involvement of infections in the aetiology of schizophrenia at least could not be ruled out. Psychotic symptoms associated with influenza infections during the pandemic of 1918-1919 fuelled these speculations. The infectious aetiology theory was then forgotten until findings of abnormalities in the immune system among patients with schizophrenia, and observations that viruses were capable of causing new symptoms decades after the primary infection, revived interest in the early 1970s. (Yolken & Torrey 1995)

There are several hypotheses on how an infection could cause schizophrenia. It could be a direct result of an active infection which disrupts cellular and molecular functioning. Or a viral infection might act in a more subtle way, for example by mimicking CNS transmitters or receptors. Schizophrenia could also be caused by a latent virus that is periodically reactivated, or by retroviral genomic material integrated into host-cell DNA. Finally, it has been suggested that it is the immune response, rather than an initial infection, that is responsible for the development of schizophrenia. The suggested timing of the infection varies from the prenatal period to the onset of schizophrenia. (Kirch 1993)

Indirect evidence for an involvement of infections comes from findings suggesting a dysfunction of the immune system and from ecological studies. Abnormalities in the immune system reported in patients with schizophrenia include alterations in peripheral lymphocyte populations (Nikkilä et al 1995), an increased number of atypical peripheral lymphocytes (Yolken & Torrey 1995), protein and immunoglobulin abnormalities in the cerebrospinal fluid (CSF) (Ahokas et al 1985, Yolken & Torrey 1995), increased frequency of antinuclear and other autoantibodies (Yolken & Torrey 1995, Spivak et al 1995), and various abnormalities in cytokine concentrations (Yolken & Torrey 1995, Naudin et al 1997, Rothermundt et al 1998).

Ecological or population correlation studies compare cross-sectional population data for both exposure and disease occurrence. In schizophrenia epidemiology, ecological studies have been used to investigate whether infectious epidemics or other insults during the prenatal development are associated with an increased risk of the later development of schizophrenia. Ecological studies cannot prove a causal relationship but they are particularly useful for hypothesis generation. (Breslow & Day 1987, p.4)

Several ecological studies have investigated the association between prenatal exposure to influenza epidemics and later development of schizophrenia. Most (Mednick et al 1988, Barr et al 1990, Takei et al 1996a, O'Callaghan et al 1991, Kunungi et al 1995, McGrath et al 1994, Takei et al 1995a), but not all (Torrey 1988, Susser et al 1992, Erlenmeyer-Kimling et al 1994) have found an association between second-trimester exposure to an influenza epidemic, especially the worldwide 1957 epidemic, and later development of schizophrenia. The original finding was reported from Helsinki (Mednick et al 1988), and the authors were able to locate prenatal clinic records from a sample of mothers of patients who later developed schizophrenia. The mothers who had been exposed to the influenza epidemic during the second trimester had reported influenza-like infection significantly more often (87%, 13/15) than mothers who had been exposed during the first or third trimester (20%, 2/10) (Mednick et al 1994). Others have also observed that mothers of patients with schizophrenia who had had influenza during gestation had had it significantly more often in the second than in the first or third trimester (Wright et al 1995). It has been suggested that a proportion of the

genetic predisposition for schizophrenia might be mediated by genes controlling the maternal immune response to gestational influenza (Wright et al 1995). However, the findings concerning the association between prenatal influenza and schizophrenia have not been consistent; notably, the findings from the two cohort studies were negative (Crow & Done 1992, Cannon et al 1996). Other infections have been investigated less frequently, and replicated associations have generally not been found (Watson et al 1984, Torrey et al 1988, O'Callaghan et al 1994).

Direct evidence of an infection has been sought by studies on antibodies, antigens, and the viral genomes. Studies on peripheral and CSF viral antibodies have sometimes reported elevated concentrations of various antibodies, but consistent elevations against a specific causal agent have not been detected (Ahokas et al 1987, Yolken & Torrey 1995). Findings concerning viral antigens and the viral genome have also usually been negative (Yolken & Torrey 1995), recent results on Borna disease virus being an exception.

Borna disease virus infects a broad range of warmblooded animals (Lipkin et al 1997). It has a predilection for neurons of the limbic system, and it causes a variety of neurological symptoms in affected animals but may also run a life-long latent course (Bode et al 1988, Lipkin et al 1997). Increased prevalences of Borna disease-specific antibodies have been found in psychiatric patients, both among those with affective disorders (Bode et al 1988) and those with schizophrenia (Waltrip et al 1995, Iwahashi et al 1997). Borna disease virus proteins have been detected in the CSF of patients with major depression (Deuschle et al 1998), and Borna disease virus genome transcripts from the postmortem brain samples of patients with schizophrenia and bipolar disorder (Salvatore et al 1997). Although positive findings are limited to a small minority of patients (2-10%), they are intriguing and certainly encourage study of the role of Borna disease virus in the aetiology of schizophrenia and other mental disorders.

Enteroviruses belong to the picornaviruses, small RNA-viruses, and consist of polio viruses, coxsackie viruses, echo viruses, and other enteroviruses (Hovi 1998). Enteroviruses are good candidate agents for involvement in the aetiology of

schizophrenia, because 1) they cause CNS infections: they are the most common cause of viral aseptic meningitis and also cause encephalitis (Muir & van Loon 1997), 2) acute infections may be accompanied by psychotic symptoms (Wang et al 1996), 3) they may cause fetal infections leading to cerebral ventriculomegaly (Dommergues et al 1994), 4) they may persist in the body for years (Hovi 1998), and 5) they may cause new symptoms decades after the primary infection (Bruno et al 1994).

A contribution of a prenatal polio virus infection to the development of schizophrenia has been suggested, because a decline in the incidence of schizophrenia occured in many countries after the introduction of polio vaccination (Eagles 1992, Squires 1997). It has been suggested that the winter-early spring excess of schizophrenic births is caused by an infection during the second trimester of fetal development (Huttunen et al 1994). If so, polio virus epidemics, which peak in late summer and early autumn (Nathanson & Martin 1979), are a better candidate to explain the seasonality than the winter and spring infections usually suggested (Eagles 1992). There is also a similar geographical variation in the seasonality of poliomyelitis epidemics (Nathanson & Martin 1979) and schizophrenic births (Torrey et al 1977). Environmental survival of polio viruses is very sensitive to both humidity and temperature (Nathanson & Martin 1979). In areas with high relative humidity and low variation in temperature, the annual variation in the incidence of poliomyelitis was low, while it was very high in areas with large temperature and humidity variations. In the United States, the seasonal variation in the incidence of poliomyelitis was highest in the New England states and lowest in the West South Central states (Texas, Louisiana, Arkansas, Oklahoma). Similarly, the seasonal variation of births in schizophrenia was most pronounced in New England and least pronounced in the southern United States (Torrey et al 1977). Further support for the hypothesis comes from the latency of the effect of poliovirus. Decades after the primary infection, new symptoms – the so-called post-polio syndrome - can emerge (Bruno et al 1994, Dalakas 1995). Acute polio infection of the central nervous system affects, besides motor neurons and motor cortex, the hypothalamus, thalamus, cerebellum, and reticular formation in the brain stem, areas that partially correlate with those in which brain lesions have been observed in schizophrenia (Bruno et al 1994, Dalakas 1995a, Heckers 1997).

Thus far, few studies have investigated the possible role of enteroviruses in the aetiology of schizophrenia. Two previous studies have compared the incidence of paralytic poliomyelitis and the number of schizophrenic births (Watson et al 1984, Torrey et al 1988). The first detected no association (Watson et al 1984), while the second found a significant coherence between schizophrenic births and poliomyelitis - a finding difficult to explain because poliomyelitis preceded the schizophrenic births by 18 months (Torrey et al 1988). In neither of these studies was the place of birth of the patients known. A third study found no relationship between the number of deaths caused by poliomyelitis and schizophrenic births (O'Callaghan et al 1994) - however, death is a rare outcome of polio virus infection. Rantakallio et al found that neonatal meningitis caused by Coxsackie B5, another enterovirus, was associated with an increased risk of adult schizophrenia (Rantakallio et al 1997).

2.5.2. Obstetric complications

The association between pre- and perinatal complications and later development of schizophrenia has been convincingly demonstrated. Birth cohort studies, in which a general population birth cohort born in a certain area in a limited time period has been followed up from prenatal period until adulthood, have consistently found an association between pre- and perinatal complications and later development of schizophrenia (Sacker et al 1995, Hollister et al 1996, Jones et al 1998), although only on a trend level in the American study (Buka et al 1993). In the Northern Finland 1966 Birth Cohort Study, low birth weight (<2500g), short gestation and low Apgar scores after birth were associated with an increased risk of later development of schizophrenia. Low birth weight was also found to be a risk factor in the British Perinatal Mortality Survey (Sacker et al 1995). In the Danish Perinatal Cohort, Rhesus incompatibility (mother Rhesus D-negative, child Rhesus D-positive) was a risk factor for schizophrenia (Hollister et al 1996). The British Perinatal Mortality Survey also observed that mothers of children who developed schizophrenia were more often Rhesus negative than the mothers of other members of the cohort (Sacker et al 1995). In a meta-analysis of all case-control studies conducted thus far, the pooled odds ratio for

exposure to obstetric complications and subsequent development of schizophrenia was 2.0 (Geddes & Lawrie 1995).

Prenatal insult is also suggested by the excess of minor physical anomalies observed among patients with schizophrenia, although these are at least partially determined by genetic factors (O'Callaghan et al 1991a, Murphy & Owen 1996a, Ismail et al 1998). A study of monozygotic twins discordant for schizophrenia found that they had greater intrapair differences in finger ridges than normal control twins (Bracha et al 1992). This is consistent with a second trimester insult affecting the two twins differently, because differences in finger ridges mainly reflect differences in fetal size during the second trimester (Bracha et al 1992). Extreme maternal stress (caused by loss of a spouse or sudden outbreak of a war) during the second trimester of pregnancy has also been associated with an increased risk of later development of schizophrenia (Huttunen & Niskanen 1978, Van Os & Selten 1998).

The British Perinatal Mortality Survey also observed that the physique, mental health and lifestyle of the mothers of children who later developed schizophrenia was significantly different from that of other mothers (Sacker et al 1995). They were more likely to have low weight before pregnancy, more often suffered from mental health problems, more often smoked during pregnancy, made fewer visits to antenatal clinics, and their average parity was greater (Sacker et al 1995). Mothers who have schizophrenia have more pregnancy and birth complications than control mothers, and the children of schizophrenic mothers more often have low birthweight and poor neonatal condition (Wrede et al 1980, Sacker et al 1996). Therefore, the association between obstetric complications and later development of schizophrenia might also partially reflect characteristics of the mother instead of being a true risk factor for schizophrenia (Sacker et al 1995).

2.5.3. Malnutrition

The effect of prenatal nutrition on the risk of later developing schizophrenia has been investigated in the Dutch Famine Study (Susser et al 1998). This study has investigated

the occurrence of various neurodevelopmental disorders among a cohort of children who were exposed to severe famine while in utero during the winter of 1944-1945. The German blockade in The Netherlands caused a severe famine that lasted from October 1944 to May 1945. Individuals who had been conceived during the height of the famine between February and April 1945 and had thus been exposed to famine during the first trimester showed a twofold increase in the risk of schizophrenia (Susser et al 1996) and also an increased risk of schizoid personality disorder (Hoek et al 1996). Individuals exposed to the famine during the second trimester of fetal development had an increased risk of later developing affective psychosis, which was statistically significant in males but not in females (Brown et al 1995).

2.5.4. Childhood rearing environment

Psychodynamic theories have considered disturbed early interaction between parents and child to be an important factor in the development of schizophrenia (Alanen et al 1966, Alanen 1990). However, as a result of vast biological research the family environment has been seen as less and less important; Weinberger stated in his 1995 Lancet review of the aetiology and pathophysiology of schizophrenia that ”decades of scientifically unfounded psychological and social theories that blamed families and society have given way to increasingly compelling scientific evidence that schizophrenia is a brain disorder” (Weinberger 1995). Does the childhood rearing environment, then, have any effect on the risk of developing schizophrenia? Several recent studies suggest that the early rearing environment might indeed have such an impact. In the 1946 British Birth Cohort Study, mothers of children who later developed schizophrenia had worse than average general understanding and management of their children, although none of them was known to be mentally ill (Jones et al 1994). In the Northern Finland 1966 Birth Cohort, being a child from an unwanted pregnancy was significantly associated with the later development of schizophrenia (Myhrman et al 1996). However, being from a single-parent family was not associated with the risk of developing schizophrenia or other psychotic disorders (Mäkikyrö et al 1998a), neither was maternal depression during pregnancy (Veijola et al 1998). In the Finnish Adoption Study, schizophrenic thought disorder was observed only among those children whose

biological mother had schizophrenia and whose adoptive parents showed high communication deviance (Wahlberg et al 1997), a finding suggested in a previous high-risk study (Miklowitz 1994). In the Copenhagen High-Risk Study, severe instability in the early rearing environment was associated with an increased risk of adult schizophrenia (Cannon & Mednick 1993). Thus, the possibility that the childhood rearing environment might be a risk factor for – or a protective factor against – the later development of schizophrenia should not be discarded.

2.6. Aetiological models of schizophrenia

It has been convincingly demonstrated that both genetic and environmental factors are important in the aetiology of schizophrenia, but how do their effects combine to produce the disorder? This problem of mechanism of action and interactions of genetic and environmental risk factors is common to all aetiologic research on complex diseases (Ottman 1996).

Kremen et al (1992) and Tsuang et al (1990) have presented alternative aetiological models of schizophrenia and research strategies with which to test them. The strategies to study vulnerability indicators of schizophrenia, such as birth complications or cerebral ventricular enlargement, based on different aetiological models are the high-risk method, the family study method, and the familial-sporadic strategy (Lewis et al 1987). In the latter, patients are divided into familial cases who have a positive family history of schizophrenia or schizophrenia spectrum disorders, and sporadic cases, who have no family history of schizophrenia spectrum disorders (Lewis et al 1987).

Aetiological models of schizophrenia fall into two broad categories: unitary models and discrete subtype models. Unitary models can further be divided into multifactorial and latent trait models. Multifactorial unitary models assume that schizophrenia is a multifactorial disorder determined by a single set of aetiological factors that initiate the same basic pathogenic processes. Phenotypic heterogeneity reflects quantitative differences along a single continuum of severity. Latent trait models assume a common factor underlying the single disease process, and observed variations in the phenotype

are caused by pleiotropy. In contrast, discrete subtype models suggest that schizophrenia can be subdivided into distinct disorders at the level of aetiology or pathophysiology. (Kremen et al 1992)

The multifactorial polygenic model assumes that liability to schizophrenia is composed of genetic and environmental risk factors that act in an additive fashion. If we are studying an indicator that is thought to be environmental, for example birth complications, the model suggests that familial probands will manifest less severity on the indicator than sporadic probands, familial probands will manifest greater severity than their relatives with milder schizophrenia spectrum disorders, and unaffected relatives of familial probands will have the lowest severity. If the indicator is thought to reflect genetic liability, the group with the greatest amount of genetic vulnerability will manifest the greatest severity. Thus, familial probands should show greater severity on the indicator than sporadic probands, relatives with schizophrenia spectrum disorders should show less severity than familial probands but greater severity than the unaffected relatives of familial probands, and unaffected relatives of familial probands should show greater severity on the indicator than the unaffected relatives of sporadic probands. (Kremen et al 1992)

The latent trait model is a single major locus model in which the pathogenic gene can cause schizophrenia, or increased severity on the indicator, or both. The indicator is a marker of the presence of the same genotype as the disorder itself. A strict single-gene model has been proposed by Crow, who suggests that one human gene, that causing cerebral asymmetry, contributes substantially to the predisposition to psychosis (Crow 1995, 1995a). This gene, according to Crow, is crucial to the development of language and is associated with significant variation, which explains the variation in the phenotype (Crow 1995a). The model excludes any environmental risk factors (Crow et al 1995a). The model by Crow, although elegant, is not supported by the majority of research findings (Tsuang & Faraone 1995, DeLisi 1999).

Kremen et al (1992) modified the latent trait model by suggesting that sporadic probands are phenocopies and do not, therefore, have the genotype that produces the

indicator. This modified model predicts that familial probands will manifest greater indicator severity than sporadic probands, unaffected relatives of familial probands will show greater severity on the indicator than unaffected relatives of sporadic probands, and relatives with schizophrenia spectrum disorders will manifest equal indicator severity to the familial probands themselves (Kremen et al 1992).

The interactive model suggests that some combination of pathogenic genes and environmental risk factors is necessary for schizophrenia to develop. One variant of the model is a multifactorial version, which suggests that if a threshold number of genes with small additive effects is not passed, no amount of environmental liability is sufficient for schizophrenia to develop. Another variant assumes that there is a single pathogenic gene which alone causes mild schizophrenia spectrum disorder, and schizophrenia develops only with enough additional environmental liability. Both of the models predict the same findings. If it is assumed that the indicator is environmentally caused, the familial probands will manifest the greatest severity on the indicator, relatives of familial probands with schizophrenia spectrum disorders will manifest the least indicator severity, and unaffected relatives of familial probands will show intermediate indicator severity. The model does not allow for genetic differences between familial and sporadic probands and no specific predictions can be made with respect to sporadic probands. (Kremen et al 1992)

The discrete subtype model assumes that schizophrenia may be caused by either genetic or environmental factors. If the indicator reflects some alternate, nongenetic cause of schizophrenia, the model predicts that sporadic probands will manifest greater severity on the indicator than familial probands, and no differences with respect to the indicator among any of the groups of relatives because none of them has been subject to the environmental factor associated with the indicator. (Kremen et al 1992)

There is also the possibility that the indicator is caused by the underlying pathophysiological process of schizophrenia, in which case there should be no difference in the severity of the indicator between familial and sporadic probands, schizophrenia spectrum relatives of familial probands should show intermediate severity

of the indicator between probands and unaffected relatives, and unaffected relatives of both familial and sporadic probands should manifest minimal severity. If the indicator is a result of being treated, only those probands, whether familial or sporadic, who have been treated will have the indicator. (Kremen et al 1992)

How do findings from studies conducted thus far fit into these models? It seems likely that none of the models will fit all cases with schizophrenia. For example, some rare cases of schizophrenia seem to be caused by gross abnormalities in chromosomes (Tsuang & Faraone 1995). Several different models are supported by the research. Cerebral ventricular enlargement has been shown to be more prevalent among sporadic than familial cases, especially among males (DeQuadro et al 1996, Murray & Jones 1995), supporting, in the absence of information on relatives, both the multifactorial polygenic model with an environmental indicator and the discrete subtypes model. The Copenhagen high-risk study found greater ventricular enlargement in high-risk subjects with schizophrenia than high-risk and low-risk subjects with schizophrenia spectrum disorders or no disorder (Cannon et al 1994). However, they also observed that among the high-risk subjects, those who later developed schizophrenia experienced the greatest number of obstetric complications, while those who later developed schizophrenia spectrum disorders experienced the least, supporting the interactive model in the effect of obstetric complications (Parnas et al 1982). In the determination of ventricular enlargement, they found a linear increase in cerebral ventricles with increasing level of genetic risk for schizophrenia, and an interaction between obstetric complications and genetic risk: the effect of obstetric complications was largest among persons with two affected parents (Cannon et al 1993a).

Different aetiological models may thus account for different aspects of the disorder, and the extreme homogeneity model, which assumes that schizophrenia is caused by exactly the same pattern of genetic and environmental factors, can be rejected (Tsuang & Faraone 1995). Gottesman and Shields proposed a combined model, in which the majority of cases would be caused by the combined effect of genetic and environmental factors (Gottesman & Shields 1982, pp. 220-222). The genetic effect would mostly be polygenic, but there might also be cases caused by a single major gene plus polygenic

background. Besides these cases, there would be rare cases caused by single rare genes or chromosomal abnormalities, and rare phenocopies caused entirely by environmental factors (Gottesman & Shields 1982, pp. 220-222). This kind of model, which lets many flowers blossom, would seem wise until proved otherwise.

2.7. Summary

Schizophrenia is a global disorder, but there is controversy over whether it also occurs at similar frequency worldwide (Torrey 1989). The peak age at onset is early adulthood (Sham et al 1994). It tends to occur more frequently – or at least at an earlier age – among males than females (Castle et al 1995). Recent studies have suggested that the incidence of schizophrenia is declining (Munk-Jørgensen 1995). These studies have divided the opinion of researchers: some regard the findings as unreliable, caused entirely by the operation of confounding factors such as narrowing diagnostic criteria, while others believe that a genuine decline in the incidence has occurred (Geddes et al 1993, Kendell et al 1993, Harrison & Mason 1993, Munk-Jørgensen 1995). If the decline is genuine, new information on the risk or protective factors of schizophrenia may be gained by investigating what was happening when the incidence declined, or when the cohorts whose incidence declined were born.

Both genetic and environmental factors have been shown to be important in the aetiology of schizophrenia. Although the heritability of schizophrenia in different populations has been high, no genes predisposing to schizophrenia have so far been identified. Obstetric complications are the best supported environmental risk factor for schizophrenia, but they are probably not themselves sufficient to cause it (Geddes et al 1995). Infections may also be involved in the aetiology of schizophrenia (Yolken & Torrey 1995). Patients with schizophrenia have a seasonal variation of births that differs from that of the general population (Torrey et al 1997), and persons born in urban areas with high population density seem to have an increased risk of developing schizophrenia (Mortensen et al 1999). The cause of both these phenomena is unknown, but environmental risk factors has been suggested.

In Finland, many aspects of the epidemiology of schizophrenia have not been previously studied; these include possible changes in incidence, and seasonal variation of births in schizophrenia. However, we have a long tradition of aetiologic research on schizophrenia (Alanen et al 1966, Mednick et al 1988, Tienari et al 1994), and research on the genetic epidemiology of schizophrenia has advanced in recent years (Hovatta et al 1997, Cannon et al 1998). Finland's stable, relatively isolated population and excellent health-care registers are unique assets for epidemiologic research. Thus, this study was set out to investigate epidemiological features and some risk factors of schizophrenia in the Finnish population. The study focused on changes in the incidence of schizophrenia, time trends in the seasonal variation of births in schizophrenia, the association between prenatal exposure to poliomyelitis epidemics and later development of schizophrenia, and the association between familial loading for psychotic disorders and age at onset and outcome of schizophrenia.

3. AIMS OF THE STUDY

The aim of this study was to investigate epidemiological features and some risk factors of schizophrenia in a nationwide, register-based sample of Finnish patients with schizophrenia. The study consisted of four original publications, the aims of which were:

(I) To investigate the impact of high or low familial loading of schizophrenia or all psychotic disorders on the age at onset of schizophrenia, duration of hospitalisations, probability of receiving a disability pension because of schizophrenia, and mortality, with a special interest on the modifying effect of sex.

(II) To investigate whether prenatal exposure to polio virus epidemics is associated with an increased risk for later development of schizophrenia and whether the effect is limited to a specific time during gestation.

(III) To investigate whether the incidence of schizophrenia has declined and if so, whether the decline was caused by period-related confounding factors or by a true cohort effect or both, and whether there were any sex differences in the decline.

(IV) To study whether there is seasonality of births among patients with schizophrenia in Finland, and if so, whether there are any time trends in the magnitude of the seasonality, and whether there is any association between seasonality and urban birth, sex, and age at onset of schizophrenia.

4. METHODS

4.1. The Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland project

This study forms part of the collaborative project "The Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland" run by the Department of Mental Health and Alcohol Research and the Department of Human Molecular Genetics at the National Public Health Institute. The project was initiated in 1988, and its principal investigators are professors Jouko Lönnqvist and Leena Peltonen-Palotie. The aims of the project are to characterize the epidemiology of schizophrenia in Finland, especially genetic epidemiology, to investigate genetic and environmental risk factors of schizophrenia and their interactions, and to identify ultimately at least one gene predisposing to schizophrenia. The project was approved by the Ethics Committee of the National Public Health Institute (25 May 1994, 7 October 1998) and by the Ministry of Social Affairs and Health (2140/69/88, 105/07/98).

4.2. Subjects and registers

Three nationwide health care registers were used to identify all persons born between 1940 and 1969 who had developed schizophrenia before 1992: the Finnish Hospital Discharge Register, and two registers of the Social Insurance Institution, the Pension Register and the Free Medicine Register. Parents and siblings of these probands were identified from the National Population Register. Information on the relatives was linked back to the health care registers to obtain data on their hospital admissions, pensions, and free medications.

The National Population Register records information on place of birth, place of current residence, marital status, and first-degree relatives of each Finnish citizen. For persons who have died since the establishment of the register the date of death is also registered. The Finnish Hospital Discharge Register covers all public and private hospitals in

Finland. For each inpatient stay, data on beginning and ending dates, primary and up to three subsidiary diagnoses, and hospital identification code are listed. Also listed are the type of referral and of follow-up treatment, whether the admission was voluntary and, if not, the duration of non-voluntary treatment. The Pension Register indexes the beginning and ending dates and the primary diagnoses for disability pensions. The Free Medicine Register contains data on the diagnoses of persons receiving free outpatient medication. The data in these registers were linked using the personal identification number, which codes the date of birth and sex and is unique for each person.

Register information for this study was obtained for the years 1969-1991. ICD-8 diagnostic criteria and codes were used in all the registers before 1987. Between 1987 and 1991, psychiatric diagnoses were coded according to ICD-9, applying DSM-III-R diagnostic criteria. The Social Insurance Institution registers only the first three digits of diagnostic codes. Therefore, we accepted all probands having a 295 diagnosis according to the ICD-8 and ICD-9 codes. Besides core schizophrenia, this includes patients with schizophreniform and schizoaffective disorders, and also patients with simple and latent schizophrenia treated before 1987.

These registers allowed us to identify 30 339 patients with schizophrenia born between 1940 and 1969, 27 098 of whom (89%) had at least one hospitalization with a diagnosis of schizophrenia. The real proportion of patients with at least one hospitalisation is higher, because information from the Finnish Hospital Discharge Register was obtained from 1969 onwards, when patients from the oldest cohort were already 29 years old. There were 16 926 males (56%) and 13 413 females.

Family information was found for 24 657 patients, whereas it could not be located for 5682 patients. Of the patients without family information, 4728 had been born between 1940 and 1949, 883 between 1950 and 1959, and 71 between 1960 and 1969. Of the 95 719 identified first-degree relatives, 41 692 were parents, 53 586 siblings, and the remaining 441 other relatives, usually grandparents.

In this study, only subjects born between 1950 and 1969 were investigated. Subjects born in the 1940s were excluded because the first hospitalisation, and therefore the age at onset, could not be reliably determined and because of the large amount of missing family information. There were 16 687 patients with schizophrenia born between 1950 and 1969. Of them, 15 398 (92%) had had at least one hospitalisation with a diagnosis of schizophrenia. Disability pension because of schizophrenia had been granted to 9394 (56%) of the patients, and free antipsychotic medication for schizophrenia before 1987 to 8848 (53%) of them. Between 1987 and 1991, 4017 (24%) additional patients had received free antipsychotic medication, but the exact diagnosis was no longer registered. Family information was found for 15 733 patients (94%).

Of the 1289 patients with no hospitalisation for schizophrenia, 611 had free antipsychotic medication and disability pension, 202 only had disability pension because of schizophrenia and 470 only had free antipsychotic medication because of schizophrenia; 403 (31%) had had at least one hospitalisation because of another psychotic disorder.

Age at onset was defined as the age at the beginning of first hospitalisation for schizophrenia or age at the beginning of first hospitalisation for any psychotic disorder. The latter was considered to be a closer approximation of the true age at onset. In one of the publications, the age when the person had started to receive the pension minus one year was used to approximate the age at onset among patients who had had no hospitalizations but received disability pension because of schizophrenia.

4.3. General population information

The Population Register Centre provided sex-specific, monthly numbers of births in each Finnish municipality from 1940 to 1969 as multidimensional tables, with sex and year, month and place of birth as marginals. A large number of birth cohorts was thus formed, each consisting of males or females born in the same municipality during one month of a particular year. From each of these the number of deaths up to 1969 and the annual number of deaths from 1970 to 1991 were obtained.

4.4. Data on infectious diseases

We obtained the monthly Reports on Infectious Diseases originally kept by the National Board of Health, stored in the archives of the National Research and Development Centre for Welfare and Health. These were based on the reports delivered by every Finnish physician to the National Board of Health. Each physician was required to report the cases of infectious diseases they had treated (Lääkintöhallitus YK 1163). A separate, detailed report on each case was required for some diseases, including poliomyelitis, while the weekly number of treated cases was enough for others, for example influenza. The reports were obtained for the years 1950-1969, and included the monthly numbers of infections separately for each province and for the three largest towns (Helsinki, Tampere, Turku) in Finland. In this study, we used the monthly numbers of new cases of paralytic poliomyelitis.

4.5. Statistical methods

4.5.1. Familial loading, age at onset and outcome

We set out to study the effect of familial loading for schizophrenia on the age at onset and outcome by comparing two extreme groups with each other, one with an extremely high and another with an extremely low familial loading, along with a third group representing the majority of patients with schizophrenia. The study population consisted of all patients with schizophrenia born between 1950 and 1969 with available family information (*n*=15 733). The study used the familial / sporadic distinction as a research strategy (Lewis et al 1987), but the definitions of both familiality and sporadicity were more stringent than in previous studies (Roy & Crowe 1994).

To estimate the familial loading of the patients we used the familial loading score designed by Pak Sham (Verdoux et al 1996), which takes account of family size and age structure. Familial loading score was based on the following assumptions: the lifetime risk of schizophrenia in a first-degree relative is 10 per cent for familial probands and 0.5 per cent for sporadic probands. The age range at risk is 15 to 50 years, during which

period the risk increases linearly from zero to the lifetime risk. The likelihood ratio of a proband being familial or sporadic, given that a relative of age x is affected, is:

$$\frac{0.1 \cdot \left(\frac{x-15}{50-15} \right)}{0.005 \cdot \left(\frac{x-15}{50-15} \right)} = 20$$

The likelihood ratio if a relative of age x is unaffected is:

$$\frac{1 - 0.1 \cdot \left(\frac{x-15}{50-15} \right)}{1 - 0.005 \cdot \left(\frac{x-15}{50-15} \right)}$$

Thus, the likelihood ratio for affected relatives is independent of the relative's age but for unaffected relatives it depends on age at the end of the follow-up period, which in this study was 31 December 1991 or the date of death. The likelihood ratio was calculated for each relative, and an overall likelihood ratio for whether the proband was familial or sporadic was obtained by multiplying together the individual likelihood ratios. Finally, the familial loading score was obtained by taking the logarithm of the product. The natural logarithm was used in this study, while Verdoux et al used the common logarithm. A negative score means that the proband has no affected first-degree relatives. (Verdoux et al 1996)

For each patient, a familial loading score was calculated for schizophrenia (ICD 8 295) and for all psychotic disorders (ICD 8 291-299). The ICD 291-299 categories are alcoholic psychoses, drug psychoses, transient organic psychotic disorders, other organic psychotic conditions, schizophrenic psychoses, affective psychoses, paranoid states, other nonorganic psychoses, and psychoses with origins specific to childhood (WHO 1967). The range of the familial loading scores was -1.0 to 23.8 for all psychotic disorders and -1.0 to 20.7 for schizophrenia. Of the 15 733 patients with available family information, 3427 (22%) had a positive loading score for schizophrenia, i.e., at least one first-degree relative with schizophrenia, and 5489 (35%) had a positive

loading score for all psychotic disorders, i.e., at least one first-degree relative with any psychotic disorder.

The patient population was divided into three groups based on their familial loading. Patients from families with at least three first-degree relatives with schizophrenia were classified as having high familial loading for schizophrenia (loading score for schizophrenia >4.0), and patients with the lowest loading score for all psychotic disorders as having low familial loading for psychosis (loading score for psychoses <-0.5). All the other patients were classified as having intermediate familial loading. Hereafter, the group with high familial loading will be called the familial group, the group with low familial loading the sporadic group, and the group with intermediate familial loading the intermediate group.

The familial group consisted of 761 patients, the sporadic group of 725 patients, and the intermediate group of 14 247 patients. The proportion of males and females in each group did not differ significantly (χ^2 =5.48, d.f.=2, *P*=0.065). The mean number of siblings of patients was 5.7 in the familial group, 7.4 in the sporadic group, and 3.5 in the intermediate group. The proportion of patients born in the 1960s was smallest in the sporadic group and largest in the intermediate group (χ^2 =99.8, d.f.= 2, *P*<0.001) and because of this, year of birth was adjusted for in the analyses. The cases in the familial group came from families with an average of 3.3 affected first-degree relatives.

Outcome was measured by the annual duration of hospitalisation, risk of receiving a disability retirement pension, and mortality. We calculated the annual duration of hospitalisation by dividing the number of days spent in hospital during the follow-up period by the number of follow-up years.

The age at onset and the duration of hospitalisation were modelled with linear mixed models, where sex, category of familial loading, and an indicator variable for being the first to develop schizophrenia in the family were used as fixed explanatory variables, and family was used as a random effect to account for the correlation between siblings (Laird & Ware 1982). The variable "first to develop schizophrenia in the family" was

included to control for the possibility that patients already having an affected family member might have a shorter interval between the occurrence of psychotic symptoms and first hospitalisation.Year of birth was controlled for in the analyses. Because early onset is associated with higher risk of rehospitalisation (Eaton et al 1992), age at onset was used as an explanatory variable in the model for the duration of hospitalisation. Interaction between sex and familial loading was included when significant.

The risk of receiving a disability retirement pension, and mortality were modelled with the Cox proportional hazard model (Cox & Oakes 1994). Follow-up was from the onset of the disease until the event in question, the censoring date of these analyses being the end of 1991. In these models age at onset, sex, and category of familial loading were used as explanatory variables.

The level of significance in the models was determined by the Wald χ^2 -test.

4.5.2. Prenatal exposure to polio epidemics

When studying the association between prenatal exposure to polio epidemics and subsequent schizophrenia, the study population was limited to births between 1951 and 1969, because the polio epidemics data was from 1950 to 1969.

It was assumed that the monthly number of births of individuals who later developed schizophrenia in each province followed the Poisson probability model. This model assumes that the number of new cases of schizophrenia (c) occurring in a particular age-time-exposure cell takes on the values k=0, 1, 2, ... with probabilities

$$P(c = k) = e^{-\lambda n} \frac{(\lambda n)^k}{k!}$$

where λ denotes the unknown rate and *n* the person-years. The numbers of new cases occurring in different cells are regarded as statistically independent. (Breslow & Day 1987, p. 131)

To analyse the possible association between prenatal exposure to polio virus epidemics and later development of schizophrenia, we used a Poisson regression model with the number of schizophrenic births as a response variable, and geographical area, birth cohort, age, sex, month of birth, and incidence of paralytic poliomyelitis as explanatory variables. Circular transformation (Batschelet 1981) was applied to the month of birth to analyze seasonal variation. The population size in each cell was used as weight to obtain correct estimates.

The high variability in monthly incidence of poliomyelitis by province caused by small numbers in most cells was smoothed using a moving average with a three month window. The incidence of poliomyelitis was then dichotomized to an indicator variable (0= no cases of poliomyelitis, 1=any cases of poliomyelitis). To test whether the effect of polio epidemics increased along with the severity of the exposure, the incidence of poliomyelitis was also divided into deciles; the first six deciles, in which the incidence was zero, were pooled.

The incidence of schizophrenic births was modelled with and without the incidence of polio. The improvement in model fit was tested using a χ^2 likelihood ratio test.

4.5.3. Time trends in the incidence

We limited the study of time trends in the incidence of schizophrenia to persons born between 1954 and 1965 to permit us to reliably identify the age at onset and to allow identical follow-up times for each cohort. Each person was followed from the 16th through 26th birthday. Those born outside Finland or of unknown birthplace were excluded. Patients had to have received the first diagnosis of schizophrenia between their 16th and 26th birthday. However, age at onset was defined as age at the beginning of the first hospitalisation for any psychotic disorder excluding psychotic disorders caused by alcohol or substance abuse, because it is a closer approximation of the time of emergence of first psychotic symptoms than the age at the beginning of first hospitalisation for schizophrenia. In addition, patients for whom disability pension because of schizophrenia had been granted somewhere between their 16th and 26th

birthday and who were hospitalized for any psychotic disorder at that age were also included. Their age at onset was also defined as age at the beginning of the first hospitalisation for any psychotic disorder. Persons who received the first diagnosis of schizophrenia after the 26th or before the 16th birthday were not included in the sample because the available follow-up time was not identical for all cohorts. These patients were identified from the registers and their numbers in each cohort compared to estimate whether their exclusion caused any bias. We also excluded patients with no hospitalizations, because a meaningful age at onset could not be defined. Their numbers allowed us to estimate the proportion of patients treated as outpatients in each cohort.

Age-specific incidences in each cohort and period were first calculated using exact person-years at risk for each cohort. Period refers to the year of onset, and cohort to the year of birth. Age, period, and cohort were each divided into 2-year intervals.

4.5.3.1. Age-period-cohort analysis

Time trends in the incidence of a disease may provide important clues to its aetiology. The three time factors of interest are age, period (date of diagnosis), and cohort (date of birth), and the analysis method by which the effects of these three factors on incidence is estimated is called age-period-cohort analysis, and is widely used in cancer epidemiology (Holford 1991, McNally et al 1997, Robertson & Boyle 1998). In psychiatric research it has been used to study time trends in the incidence of major depression (Klerman 1988, Wickramaratne 1989) and in suicide rates (Moens et al 1987, Granizo et al 1996), while only one previous study has used the method to assess time trends in the incidence of schizophrenia (Takei et al 1996).

The problem with this method arises because age, period, and cohort are linearly dependent: knowing any two of them, the third can be calculated. For example, if we are currently living in 1999 and we meet a 30-year-old man, we know that he has been born in either 1968 or 1969. This linear dependence means that the linear effects of age, period, and cohort cannot be separated, because there is no unique set of regression parameters. Different methods to overcome this nonidentifiability problem have been

suggested. The only ones that avoid using arbitrary constraints or making strong assumptions about the effects of age or cohort are those that do not attempt to separate the effects of cohort and period on the linear component of the change but only estimate deviations from linearity. We have used one of these methods, that of Clayton and Schifflers. (Clayton & Schifflers 1987, Holford 1991, Robertson & Boyle 1998)

Clayton and Schifflers avoid the nonidentifiability problem by estimating solely the curvature effects of period and cohort, which can be reliably estimated. They introduced the term "drift" to describe the sum of linear cohort and period effects. Drift cannot be partitioned into linear cohort and linear period effects and is therefore not usually reported. After fitting the drift term, the curvature effects of age, cohort and period can be reliably estimated. The underlying model used is the Poisson regression model with standard Poisson assumptions (see 4.5.2.). The effects of age, period, and cohort are assumed to be multiplicative. (Clayton & Schifflers 1987)

Curvature or "non-drift" effects operate in such a way that the relative risks between adjacent cohorts (or periods) are not identical. They are calculated as contrasts between relative risks in adjacent periods or cohorts:

$$\frac{\left(\frac{e^{\beta_{i+1}}}{e^{\beta_i}}\right)}{\left(\frac{e^{\beta_i}}{e^{\beta_{i-1}}}\right)}$$

where β_i denotes the Poisson regression parameter estimates and i the distinct periods (or cohorts). On the logarithmic scale, these contrasts are second derivatives, β_{i+1}-2 β_i+ β_{i-1}. Although there are also other methods to calculate the curvature effects, these second derivatives have the advantage that their value is affected only by neighbouring data. (Clayton & Schifflers 1987)

Besides age, period, and cohort, the Poisson regression model used in this study included as explanatory variables sex and seasonal variation of births. Seasonal variation of monthly number of births was modelled using the method of Jones et al,

which allows an arbitrary shape for the seasonal effect by representing the data as a short Fourier series (Jones et al 1988). Only the first harmonic was found significant, and was entered into the main model as "seasonality". The model included all main effects and all two-variable interactions involving sex. The significance of each explanatory variable, after adjusting for the effect of other variables, was assessed by comparing the full age-period model with one including all other variables except that whose significance was tested. The goodness of fit of the models was compared using χ^2 likelihood ratio tests.

4.5.4. Time trends in the seasonal variation of births in schizophrenia

The life table data used in the analyses of seasonality of births among patients with schizophrenia were constructed using month of birth, sex, place of birth (urban or rural), age at onset, and birth cohort as marginals. The study population was individuals born between 1950 and 1969.

Age at onset was defined as age at the beginning of the first hospitalisation for any psychotic disorder (ICD-8 and ICD-9 295-299). If a person had no hospitalizations but received disability pension because of schizophrenia, the age when he or she started to receive the pension minus one year was used to approximate the age at onset. The one-year subtraction was made because disability pension can be granted only after a one-year period of sickness allowance. For the regression analyses, age at onset was grouped into five categories: 16-20, 21-25, 26-30, 31-35, and 36-41. The birth cohort was grouped into four categories: 1950-1954, 1955-1959, 1960-1964, and 1965-1969. Place of birth was categorized as urban or rural; urban meant being born in Helsinki, Tampere or Turku, the only towns in Finland with populations exceeding 50 000 throughout the study period.

The life table data used in the analyses were constructed using month of birth, sex, place of birth (urban/rural), age at onset, and birth cohort as marginals. Unadjusted risk ratios for the incidence of schizophrenia were first calculated separately for each of these explanatory variables.

We then used the Poisson regression model to analyse the seasonal variation further. The main model without seasonal variation was fitted using sex, age group, birth cohort, and place of birth as explanatory variables. A linear time trend and all its significant two-variable interactions with sex, age, cohort, and place of birth were then added.

After this, the seasonal variation was added by fitting a short Fourier series to the model (Jones et al 1988). The first harmonic was fitted first, and higher harmonics were then added when significant. The time interval 0 to T was divided into k intervals, where t_0=0 and t_k=T. In this study, the birth cohorts span 20 years. T was therefore 240 months and k 240. The fundamental period of the seasonality model (P) was 12 months. The intensity, $\lambda(t)$, of the Poisson process that is a time trend and a simple harmonic curve was for group i:

$$\lambda_i(t) = a_i\left[1 + b_i\left(t - \frac{T}{2}\right) + c_i \cos\left(\frac{2\pi t}{P} + \Phi_i\right)\right]$$

where a_i was a parameter that allows the size of each group to be arbitary, $b_i(t-T/2)$ was the trend which was centered for computational reasons, c_i was the amplitude of the cyclic curve, and Φ_i was the phase angle. The formula for the cosine of the two angles, $2\pi t/P$ and Φ_i , was for computational reasons rewritten as:

$$c_i \cos\left(\frac{2\pi t}{P} + \Phi_i\right) = \alpha_i \cos\left(\frac{2\pi t}{P}\right) + \beta_i \sin\left(\frac{2\pi t}{P}\right)$$

where $\alpha_i = c_i \cos(\Phi_i)$ and $\beta_i = -c_i \sin(\Phi_i)$. When higher harmonics were added, the intensity function became

$$\lambda_i(t) = a_i\left\{1 + b_i\left(t - \frac{T}{2}\right) + \sum_{h=1}^{p}\left[\alpha_{ih} \cos\left(\frac{2\pi ht}{P}\right) + \beta_{ih} \sin\left(\frac{2\pi ht}{P}\right)\right]\right\}$$

where h denotes the ordinal number of the harmonic (first, second, etc.)

The first harmonic and its two-variable interactions with sex, age, cohort, place of birth, and trend were first fitted and their significance tested. The adding of higher harmonics and their interactions with background variables was then continued until no significant

increase in the model fit was observed. The significances of variables and interaction terms were tested using log likelihood ratio tests with χ^2 distribution.

The STL method, Seasonal and Trend decomposition using Loess (locally weighted regression), was used to visualize year-to-year fluctuation in the seasonal variation of births in schizophrenia. The STL procedure decomposes an incidence time series into three components: trend, seasonal, and remainder. Trend is the linear change in the incidence. After trend has been removed, seasonal variation and changes in its amplitude are more easily discernible. The remainder consists of residuals from the model, which describe other than seasonal or linear trend variation in the incidence. Ideally, residuals consist solely of random variation, but they may also reveal other systematic variation. The STL is quite robust in detecting both trends and seasonal variation. (Cleveland et al 1990)

All statistical analyses were performed with the statistical software S-PLUS, version 3.4 (MathSoft, 1996).

5. RESULTS

5.1. The effect of familial loading on the age at onset and outcome

Characteristics of the groups are presented in Table 14. The mean ages at onset of psychosis were 23.2 (standard deviation (SD) 4.9) years in the familial group, 23.7 (SD 5.1) years in the intermediate group, and 25.2 (SD 5.3) years in the sporadic group. The corresponding mean ages at onset of schizophrenia were 23.7 (SD 5.2), 24.3 (SD 5.4) and 25.8 (SD 5.7) years.

Table 14. Characteristics of the familial, intermediate, and sporadic groups

	Familial group		Intermediate group		Sporadic group	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**
Number of probands	307	454	6012	8235	334	391
Year of birth:						
1950-1954	142 (46%)	217 (48%)	2381 (40%)	3320 (40%)	173 (52%)	210 (54%)
1955-1959	94 (31%)	146 (32%)	1849 (31%)	2488 (30%)	113 (34%)	126 (32%)
1960-1964	56 (18%)	69 (15%)	1142 (20%)	1597 (19%)	43 (13%)	44 (11%)
1965-1969	15 (5%)	22 (5%)	640 (11%)	830 (10%)	5 (2%)	11 (3%)
Age at onset[1]:						
Schizophrenia	23.1 (SD 5.1)	24.1 (SD 5.3)	24.4 (SD 5.5)	24.2 (SD 5.3)	25.8 (SD 6.0)	25.8 (SD 5.4)
Psychosis	22.6 (SD 4.7)	23.7 (SD 5.0)	23.7 (SD 5.2)	23.7 (SD 5.0)	25.1 (SD 5.6)	25.3 (SD 5.2)
Annual duration of hospitalisations[2]	73 (SD 82)	65 (SD 76)	59 (SD 74)	65 (SD 77)	50 (SD 66)	51 (SD 69)
Retired	219 (71%)	325 (72%)	3548 (59%)	5213 (63%)	200 (60%)	254 (65%)
Deaths	34 (11%)	82 (18%)	820 (14%)	1452 (18%)	52 (16%)	66 (17%)

[1]years

[2]days

There was no sex difference in the mean age at onset of schizophrenia (males 24.2 (SD 5.3) years, females 24.4 (SD 5.5) years) or of psychosis (males 23.7 (SD 5.0) years, females 23.8 (SD 5.3) years). However, the age at onset of schizophrenia distributions did show sex differences. Among males, the distributions were unimodal and similar in shape among all the groups, but the peak was earliest in the familial and latest in the sporadic group. Among females, the first peak occured at approximately the same age in the early twenties in all the groups, but was considerably sharper and declined rapidly in the familial group. The age at onset distribution in the sporadic group was bimodal, with a second peak in the late twenties.

In the linear mixed model, being first to develop schizophrenia in the family predicted an earlier onset. When adjusted for the year of birth, order of developing schizophrenia, and sex, the age at onset was, compared with the sporadic group, one year earlier in the intermediate group and 3.3 years earlier in the familial group. The intraclass correlation of the age at onset among siblings was 0.28 ($P<0.001$).

To assess whether this effect of familial loading on the age at onset is continuous, we divided the sample into deciles based on the familial loading score. When familial loading score for schizophrenia was used, the first seven deciles consisted of patients with no affected relatives, among whom the effect of familial loading was not continuous: a significant difference was observed only between the first and the other deciles. Deciles 8 to 10 consisted of patients with at least one affected relative, and in these groups the age at onset decreased significantly with increasing familial loading score. The results were similar when the familial loading score for psychosis was used.

We also explored the relationship between age at onset and number of affected siblings in the family. The results show that the age at onset decreased with rising number of affected siblings (Table 15).

Table 15. Number of affected siblings in the family and patient's age at onset of schizophrenia

Number of affected siblings	Mean age at onset	Number of patients	Patients with no hospitalisations
1	24.4 (SD 5.4)	12308	1023
2	24.1 (SD 5.2)	1811	144
3	23.7 (SD 5.3)	297	35
4	23.6 (SD 5.4)	77	4
5	22.7 (SD 3.7)	16	2
6	21.1 (SD 3.5)	10	0
8	22.2 (SD 3.9)	6	0

Trend-tested F=12.6, P<0.001

The mean annual duration of hospitalisation after the onset was 68 (SD 78) days in the familial group, 62 (SD 76) days in the intermediate group, and 51 (SD 68) days in the sporadic group. The mean annual duration of hospitalisation was 59 (SD 74) days for females and 64 (SD 77) days for males. The linear mixed model detected no interaction between sex and familial loading, although the annual duration of hospitalisation in the familial group was longer among females than males (Table 14). Being first to develop schizophrenia in the family was not associated with the duration of hospitalisation. Later age at onset and female sex predicted shorter hospitalisation. Compared with the sporadic group, belonging to the intermediate and familial groups predicted significantly longer hospitalisation, and belonging to the familial group predicted significantly longer hospitalisation than in the intermediate group. When the age at onset was excluded from the model, the effect of familial loading was similar but the differences between the groups became more significant. The intraclass correlation of duration of hospitalisation in siblings from the same family was 0.76 (P<0.001).

The risk of receiving a disablity retirement pension was highest in the familial group. Females had a significantly lower relative risk of retirement. Not being first to develop schizophrenia in the family was associated with lower risk of retirement. No interaction

between sex and familiality was detected. Mortality was significantly lower among females (relative risk (RR) 0.74, 95% confidence interval (CI) 0.67-0.80), and later age at onset was associated with higher mortality (RR 1.10, 95% CI 1.09-1.11). However, the degree of familial loading was not related to mortality.

5.2. Prenatal exposure to polio epidemics

The incidence of paralytic poliomyelitis showed very high variability, because even during epidemics there were few cases in one province. The high variability was first reduced by dichotomizing the incidence to an indicator variable (0= no cases of poliomyelitis, 1=any cases of poliomyelitis). In another analysis, a moving average with a three-month window was used before dichotomization. To investigate whether the effect would increase with the severity of exposure, the incidence of poliomyelitis was also divided into deciles; the first six deciles, in which the incidence was zero, were pooled.

In the first regression model, in which the incidence of poliomyelitis was dichotomized but not smoothed, exposure to poliomyelitis epidemics 5-6 months before birth was associated with a significantly increased risk of later developing of schizophrenia (RR 1.06, 95% CI 1.01-1.11). When seasonality was omitted from the model, the relative risk increased slightly (RR 1.07, 95% CI 1.02-1.12).

When a smoothed incidence of poliomyelitis was used, exposure to a polio epidemic 5 months before birth was associated with an increased risk of later developing schizophrenia (RR 1.05, 95% CI 1.00-1.11). When seasonality was omitted from the model, the effect became significant throughout the second trimester (RR 1.06-1.08 4-6 months before birth).

The effect did not, however, increase with the severity of exposure. The relative risk of developing schizophrenia compared with the first six deciles with no exposure was 1.13 in the seventh, 1.05 in the eight, 0.98 in the ninth, and 1.05 in the tenth decile.

5.3. Changes in the incidence

The incidence of schizophrenia peaked in the 20-21-year age group in both sexes, and no sex differences in the onset age were found. Males had 31% higher incidence than females. Incidence declined significantly in successive cohorts, from 0.79 per 1000 person years among males and 0.58 per 1000 person years among females in the 1954-1955 cohort to 0.53 and 0.41 per 1000 person years, respectively, in the 1964-1965 cohort. There were differences in the pattern of decline in individual age groups, and in some age groups the incidence actually rose before it started to decline, but the overall decline in each age group was of the same magnitude among both sexes. (Table 16)

Table 16. Age-specific incidences of schizophrenia per 1000 person years in cohorts born in 1954-1965

	Age groups					
Cohort	**16-17**	**18-19**	**20-21**	**22-23**	**24-25**	**All**
Males						
1954-1955	0.34	0.92	0.91	0.99	0.77	**0.79**
1956-1957	0.32	0.77	0.86	0.91	0.82	**0.74**
1958-1959	0.25	0.53	0.74	0.81	0.99	**0.66**
1960-1961	0.25	0.65	0.90	0.74	0.62	**0.63**
1962-1963	0.19	0.50	0.82	0.61	0.63	**0.55**
1964-1965	0.19	0.55	0.62	0.71	0.57	**0.53**
All Cohorts	0.26	0.66	0.81	0.80	0.74	
Females						
1954-1955	0.33	0.64	0.63	0.63	0.69	**0.58**
1956-1957	0.35	0.61	0.67	0.65	0.56	**0.57**
1958-1959	0.16	0.39	0.73	0.74	0.56	**0.51**
1960-1961	0.20	0.38	0.63	0.50	0.53	**0.45**
1962-1963	0.22	0.40	0.55	0.60	0.37	**0.43**
1964-1965	0.19	0.44	0.55	0.44	0.44	**0.41**
All Cohorts	0.24	0.48	0.63	0.60	0.53	

Table 17. Age-specific incidences of schizophrenia per 1000 person years among cohorts born in 1954-1965 according to age and period of first diagnosis

	Age groups					
Period	**16-17**	**18-19**	**20-21**	**22-23**	**24-25**	**All**
Males						
1970-1971	0.26	-	-	-	-	0.26
1972-1973	0.32	0.89	-	-	-	0.57
1974-1975	0.32	0.86	0.96	-	-	0.70
1976-1977	0.26	0.52	0.84	0.96	-	0.64
1978-1979	0.21	0.63	0.77	0.98	0.73	0.67
1980-1981	0.19	0.59	0.86	0.79	0.85	0.66
1982-1983	0.23	0.52	0.83	0.80	1.0	0.76
1984-1985	-	0.58	0.67	0.64	0.63	0.64
1986-1987	-	-	0.63	0.66	0.62	0.64
1988-1989	-	-	-	0.66	0.60	0.64
1990-1991	-	-	-	-	0.53	0.53
Females						
1970-1971	0.29	-	-	-	-	0.29
1972-1973	0.36	0.66	-	-	-	0.49
1974-1975	0.23	0.55	0.66	-	-	0.47
1976-1977	0.18	0.53	0.63	0.65	-	0.49
1978-1979	0.22	0.36	0.71	0.57	0.67	0.50
1980-1981	0.18	0.41	0.61	0.79	0.61	0.52
1982-1983	0.27	0.40	0.64	0.51	0.58	0.52
1984-1985	-	0.51	0.52	0.62	0.49	0.54
1986-1987	-	-	0.62	0.49	0.43	0.48
1988-1989	-	-	-	0.38	0.45	0.43
1990-1991	-	-	-	-	0.35	0.35

Because the data were cohort-based, the age groups were not equally represented in each period. Only the periods from 1978 to 1983 included all age groups, those aged 16-19 years represented by cohorts born in the 1960s and those aged 22-25 years by cohorts born in the 1950s. In these periods, the incidences were quite low among the 16-19-year-olds but still high among the 22-25-year-olds, thus not supporting a strong period effect. (Table 17)

Table 18. Patients excluded from the analyses because of onset before 16 years or lacking age at onset

Cohort	Excluded		
	Age at onset <16 years[1] (No.)	Disability pension, no hospitalization[2] (No.)	Free medication, no hospitalization[3] (No.)
1954-1955	46	113	60
1956-1957	51	88	29
1958-1959	35	63	36
1960-1961	40	64	24
1962-1963	44	51	20
1964-1965	44	51	12

[1]First diagnosis of schizophrenia before 16th birthday

[2]Disability pension because of schizophrenia granted before 26th birthday, no hospitalizations

[3]Free medication but no hospitalizations nor disability pension because of schizophrenia

The number of patients who had received disability pension because of schizophrenia before their 26th birthday but had no hospitalisations decreased in successive cohorts, as did the number of patients with free medication because of schizophrenia but without hospitalizations or disability pension. The number of patients with childhood-onset schizophrenia was stable, but we lacked information concerning the youngest age groups from the cohorts born in the 1950s. (Table 18)

The proportion of patients diagnosed with schizophrenia in their first admission decreased from 77% in the first to 70% in the last cohort. The incidence of other nonaffective psychotic disorders rose from 0.13 to 0.19 per 1000 between the first and last cohorts.

5.4. Time trends in the seasonal variation of births in schizophrenia

Of the 16 687 patients with schizophrenia born between 1950-1969, 15 398 had at least one hospital treatment because of schizophrenia, and 872 received disability pension but

had no hospitalizations because of schizophrenia. There were 417 patients excluded because they only had free medication but no hospitalization or disability pension for schizophrenia. In addition, 378 patients had to be excluded because of missing values for some of the variables. Thus, the final sample consisted of 15 892 patients.

Table 19. Incidence and relative risk of schizophrenia according to month and place of birth in Finnish birth cohorts born in 1950-1969

Variable		Incidence per 1 000	Relative risk	95% CI	χ^2	d.f.	P
Month of Birth	**January**	0.48	1.00	-	22.2	11	0.02
	February	0.47	0.99	0.92-1.07			
	March	0.43	0.91	0.84-0.98			
	April	0.46	0.96	0.90-1.04			
	May	0.44	0.93	0.86-1.00			
	June	0.44	0.93	0.86-1.00			
	July	0.45	0.94	0.87-1.01			
	August	0.42	0.88	0.81-0.95			
	September	0.43	0.89	0.83-0.96			
	October	0.44	0.92	0.85-0.99			
	November	0.43	0.91	0.84-0.98			
	December	0.45	0.95	0.88-1.02			
Place of Birth	**Rural**	0.45	1.00	-	29.2	1	<0.001
	Urban	0.40	0.89	0.85-0.93			

In the unadjusted analysis, incidence was highest among those born in January, February, April, and December, and higher among the rural-born than the urban-born (Table 19). In the Poisson regression analysis, the main effects of sex, age at onset, place of birth, birth cohort, and trend were all significant. A significant interaction was observed between trend and place of birth: the incidence of schizophrenia declined more slowly among the urban than the rural born. The main effect of the first harmonic of the seasonal variation was almost significant, and highly significant two-variable

interactions between the first harmonic and the birth cohort and the age at onset were observed. The higher harmonics and their interactions were not significant.

To analyse the interactions further, the unadjusted analysis and the Poisson regression analysis including the first harmonic of the seasonal variation were conducted separately for each cohort and age group. Among the birth cohort 1950-1954, the peak relative incidences were observed between November and January. Compared with January, December showed a relative incidence of 1.04, and the other months relative incidences between 0.92 and 0.98. Seasonal variation of births in the 1955-1959 birth cohort was considerable. The relative incidence was, compared with January, highest in February, 1.01. The relative incidences in all the other months varied between 0.74 and 0.85, being lowest between August and November. The cohorts born between 1960 and 1964 also showed a seasonal variation of births, although this was less consistent than in the cohorts born in the 1950s. The most consistent elevations in relative incidence were observed between February and June. In the birth cohort born between 1965 and 1969, the peak relative incidences were observed in April and October, and the largest deficit in November. The most consistent seasonal variation was the late summer deficit.

Among patients with age at onset between 16 and 20 years and 26 and 30 years, there was a marked winter-spring excess of births, January being the peak month. Among those with onset between 21 and 25 years, January was a deficit month but otherwise there was also a winter-spring excess of births. Although January was the peak month among those with onset between 31 and 35 years, they otherwise showed an autumn excess and spring deficit of births, as did patients with age at onset over 35 years.

In the STL decomposition, there was an overall declining trend in the incidence of schizophrenia. The amplitude of the seasonal variation increased from the beginning of the 1950s, and a marked seasonal variation was observed in the middle to late 1950s, followed by a rapid decrease. In the 1960s, the amplitude of the seasonal variation was smaller than at the beginning of the 1950s. The residuals from the model were still rather large, suggesting that other sources of variation in the incidence besides trend and seasonal variation also existed.

6. DISCUSSION

This study was based on a nationwide population of nearly all treated patients with schizophrenia born in the 1950s and 1960s, and their first-degree relatives. Patients were ascertained from three independent registers. Our main findings were that the incidence of schizophrenia declined in birth cohorts born from 1954 to 1965, and this decline was caused by both cohort- and period related factors. The incidence was higher among the rural-born, but it decreased more rapidly than among the urban-born. Concurrently, the magnitude of the seasonal variation of births among future patients with schizophrenia decreased. One candidate that might explain part of the observed decline in incidence and decrease in magnitude of the seasonal variation was the elimination of the polio virus from Finland: second-trimester exposure to polio virus epidemics was found to be associated with an increased risk of the later development of schizophrenia. We also observed that high familial loading for schizophrenia was associated with early onset and poor outcome of schizophrenia, but not with increased mortality. In the following, methodological issues and the findings in each of the publications are discussed in detail.

6.1. Methods and methodological limitations

During the last three decades, case registers have become an invaluable tool in psychiatric epidemiology, increasingly being used in Finnish research, too (Aro et al 1995, Hovatta et al 1997, Isohanni et al 1997, Korkeila et al 1998, Korkeila et al 1998a, Cannon et al 1998, Cannon et al 1999). The use of registers in obtaining data for cohort- and case-control studies offers several advantages. Firstly, it is possible to obtain much larger data sets than by any other method. For many rare events such as the occurrence of cancer among patients with schizophrenia, register epidemiology offers the only possibility for meaningful research. Registers are also the best method for choosing representative samples for studies, whereas those based on the patient population in a given hospital at a given moment, for example, are usually biased toward more chronically ill patients. Registers can also be used to select representative samples of

patients for more detailed studies, for example, multiply-affected families for genetic studies. (Mortensen 1992)

The use of registers is not without limitations, however. The first concern relates to the accuracy of the data – is every hospital treatment reported to the register, and are the data from hospital case notes transferred accurately into the register? The accuracy of data on psychiatric diagnoses in the Finnish Hospital Discharge Register was studied in 1986 and found to be excellent; when entries in the register were compared with data on hospital case notes, the primary diagnosis in the register and hospital case notes was identical in 99% for schizophrenia and in 98% for all mental disorders, and the dates of admission and discharge were identical in 96% of the cases (Keskimäki & Aro 1991). The information in the Pension and Free Medicine Registers is accurate because payment of these benefits is based on the registers.

The second concern in the study was the reliability of the register diagnoses of schizophrenia, which are inevitably of variable quality. The reliability of schizophrenia diagnosis in the Hospital Discharge Register has been assessed in several studies. In a study of first-contact patients with schizophrenia or schizophreniform disorder in Helsinki in 1975, only 52% of the patients who received a DSM-III diagnosis of schizophrenia or schizophreniform disorder had received a hospital discharge diagnosis of schizophrenia or schizophreniform disorder (Kuusi 1986). In another study of all first admissions to the two mental hospitals in Helsinki in 1981, 35% of the patients received a diagnosis of schizophrenia (S+) or borderline psychosis (O+) as assigned by the CATEGO computer program based on a Present State Examination interview, but only 19% had received a clinical diagnosis of schizophrenia or schizophreniform disorder (Pakaslahti 1987). Salokangas also observed in an incidence study covering six health care districts in Finland that clinicians made a DSM-III diagnosis of schizophrenia less often than an independent researcher (Salokangas 1993). Isohanni et al compared clinical and research DSM-III-R diagnoses of schizophrenia in the Northern Finland 1966 birth cohort and found 71 patients fulfilling DSM-III-R criteria for schizophrenia; only 37 of them had a register diagnosis of schizophrenia (Isohanni et al 1997). In a sample of patients from one municipality, 87% of patients with a schizophrenia

diagnosis and 18% of patients with a schizophrenia spectrum diagnosis in the register fulfilled DSM-III-R criteria for schizophrenia (Mäkikyrö et al 1998). Cannon et al found 92% agreement (κ=0.84) between the register diagnosis of schizophrenia and an interviewer's DSM-III-R diagnosis in 72 randomly selected probands and 43 of their siblings born in Helsinki from 1950 to 1958 (Cannon et al 1998). These studies indicate that Finnish psychiatrists tend to apply a narrow definition of schizophrenia in their clinical practice and that the register diagnosis of schizophrenia can be considered reasonably reliable, although our results concerning the incidence of other nonaffective psychotic disorders suggest that slight narrowing in the clinical concept of schizophrenia has occurred.

Our incidence calculations were based on the number of persons alive in each of the birth cohorts defined by sex and year, month, and place of birth at the end of 1969, and the yearly number of deaths between 1970 and 1991. This method did not allow us to correct for all the effects of migration. While the Finnish population during the 1950s and 1960s was considerably more stable than in most other countries, with negligible immigration, emigration from Finland was much more common. Before World War Two, most emigration was to the United States and Canada. Interestingly, all the US states favoured by Finns (Michigan, Minnesota, New York, Massachusetts, Washington, California and Wisconsin) (Korkiasaari 1989) had a high prevalence of insanity at that time (Torrey & Bowler 1990). After the war, emigration shifted toward Sweden; between 1954 and 1991, 440 000 Finns moved to Sweden, while emigration to other countries was negligible (Institute of Migration 1999). During the same years, however, 250 000 persons moved from Sweden to Finland, and almost all were returning Finns (Institute of Migration 1999). More than half of the immigrants living in Sweden were still Finnish citizens (Korkiasaari 1989) and remained in Finnish registers. It was thus impossible to correct for all the effects of migration, although we excluded persons born outside Finland from the study, and those born in Finland who have moved abroad permanently are not included in any of the registers. To our knowledge, no studies of the incidence of schizophrenia among Finnish immigrants in Sweden have been published. However, the rate of suicide among them is higher than that in Finland (Ferrada-Noli et al 1995). Immigrants from these cohorts may have had more

psychiatric morbidity than those who stayed in Finland, but most of those who remained Finnish citizens were returned to Finland if longer periods of psychiatric treatment were needed. Therefore, we believe that migration was not a major confounder in the study.

As the true age at onset was not known, it was approximated by using the age at the onset of first hospitalisation for schizophrenia or for any psychotic disorder. "Any psychotic disorder" included in the first publication alcohol- and substance-induced psychotic disorders, which may have resulted in defining the age at onset of those cases whose first hospitalisation was caused by such disorders too early. In the majority of the cases, both definitions overestimate the true age at onset.

In the fourth publications, one of the variables of interest was urban vs. rural birth. Urban birth was defined as having been born in Helsinki, Tampere, and Turku, which were the only towns in Finland with more than 50 000 inhabitants at the beginning of the 1950s, and all already had over 100 000 inhabitants. The definition is comparable to “city birth” in other studies (Lewis et al 1992, Mortensen et al 1999). There clearly were other urban areas in Finland in the 1950s and 1960s. However, urbanization was rapid between 1950 and 1969, and the population in many towns increased severalfold. By 1969 there were eleven towns with more than 50 000 inhabitants. Population density in each area in each year would have been more informative than the simple dichotomization used, but unfortunately such information was not available. However, the effect of urbanization has been shown to be strongest in highly densely populated areas (Verdoux et al 1997, Marcelis et al 1998, Mortensen et al 1999). Few areas other than Helsinki, Tampere, and Turku would have been thus classified in Finland.

The statistical methods used in the study have been extensively used and validated. The only method yet to be established was the familial loading score, used to quantify familial loading. One of the major problems in using the familial / sporadic distinction is the misclassification problem. If families are small and relatives young, a proband may be mistakenly classified as sporadic because of lack of sufficient follow-up information from the family (Roy & Crowe 1994). Familial loading score was designed to be “a simple extension of the family history positive-negative dichotomy to take

account of family size and age structure" (Verdoux et al 1996). It has been used in a number of recent studies (Verdoux et al 1996, Van Os et al 1997, Cannon et al 1999). However, we found its use as a continuous variable problematic: it cannot solve the problem of misclassification in small families. It is still impossible to classify a proband who is an only child as familial or sporadic; the same applies in families with one affected and 1-3 unaffected siblings. However, we found the familial loading score a useful method to identify families with the smallest familial loading. For example, if a proband aged 18 is the oldest child in family with 12 children, we still know nothing about his familial risk, but if he is the youngest, we know considerably more. In such families, the familial loading score works as it is meant to: it places the families in correct order according to their size and age structure, and is thus a feasible method for identifying the most and least familial probands.

The strengths of this register-based study were the nationwide, representative patient population, the identification of patients from three independent registers, the availability of family information, and the availablity of population information enabling the calculation of exact person-years at risk.

With these methodological assets and limitations in mind, findings from each of the publications are discussed further in the following.

6.2. The effect of familial loading on the age at onset and outcome

We used the familial vs. sporadic, or high vs. low familial loading, research strategy to investigate whether the degree of familial loading has any effect on the age at onset and outcome of schizophrenia. The study was motivated by the controversies provoked by previous research findings. While studies conducted before 1994 found no differences in the age at onset in familial and sporadic schizophrenia (Roy & Crowe 1994), two recent investigations have observed an earlier onset in familial schizophrenia (Albus et al 1994, Alda et al 1996). Consistently with this, relatives of early-onset probands have had a higher risk of schizophrenia in several studies (Kendler & MacLean 1990a, Maier et al 1993, Sham et al 1994). In addition, several others have found that the later onset

among females is confined to sporadic schizophrenia, while no sex differences exist in familial schizophrenia (Shimizu & Kurachi 1989, Albus et al 1994, Murphy et al 1994, Gorwood et al 1995). Previous studies found no association between outcome and familiality, but Verdoux et al noted high familial loading to associate with poor outcome (Verdoux et al 1996). We hypothesised that this discrepancy was caused by too broad definitions of familiality and sporadicity and too small sample sizes in the earlier studies. Our study benefitted from strict definitions of high and low familial loading and a large, nationwide, representative sample. Our aim was to discover whether by using the familial / sporadic distinction it is possible to separate patient groups that differ in their clinical characteristics.

The intermediate group in our sample consisted of a large spectrum of patients, some of whom even had a first-degree relative with schizophrenia, while others had quite large families with no relatives with psychotic disorders. The intermediate group could thus be regarded to represent schizophrenia in general. The familial group consisted of patients with at least two first-degree relatives with schizophrenia, making it reasonable to assume that their disease was more genetic than in the majority of patients. The sporadic group consisted of patients from very large families with no other first-degree relatives suffering from schizophrenia, who thus probably had a less genetic form of the disorder than those in the other groups.

As in other recent research, we found that familial schizophrenia is associated with early age at onset and sporadic with later. We found no sex differences in age at onset in the whole sample, which is consistent with previous Finnish research (Kuusi 1986, Salokangas 1993, Hovatta et al 1997). Both females and males with sporadic schizophrenia had a later age at onset, while in most previous studies only females with sporadic schizophrenia had a later age at onset (Shimizu & Kurachi 1989, Albus et al 1994, Murphy et al 1994, Gorwood et al 1995). However, females with sporadic schizophrenia seemed to consist of two separate groups, one with similar age at onset to females in the intermediate group, and another with later age at onset. This latter group would be especially interesting to study further, because it might reveal aetiologic heterogeneity.

Females with familial schizophrenia had a slightly earlier onset than males. Some previous studies have observed that relatives of female early-onset patients have an increased risk of schizophrenia compared with relatives of later-onset females or early- or later-onset males (Sham et al 1994a); our findings support this. It may also be that high familial loading decreases the age at onset only among females. This would lead to the disappearance of the age-at-onset difference between males and females in countries where females usually have a later age at onset, and an earlier onset in familial females in our sample where no sex difference existed in the age at onset in the first place. However, the age-at-onset difference between males and females in the familial group was very small - only one year.

The correlation of age at onset between affected siblings was remarkably similar to that found in previous studies (0.28 vs. 0.24-0.26) (DeLisi et al 1987, Kendler et al 1987, Burke et al 1996, Cardno et al 1998). The correlation between siblings suggests that age at onset is partly under genetic control, making it one possible phenotypic marker to be used in genetic studies (Cardno et al 1998a). Genetic loci contributing to the variation in the age at onset of schizophrenia were searched for in a recent genome scan and tentative evidence for linkage was found on chromosome 17q (Cardno et al 1998).

Familial schizophrenia was associated with longer and sporadic schizophrenia with shorter annual duration of hospitalisation. Familial schizophrenia was also associated with a higher risk of receiving a disability retirement pension. The findings are in accordance with those of Verdoux et al, who found an association between poor outcome and high familial loading (Verdoux et al 1996).

This study suggests that by using very stringent criteria of familiality and sporadicity it is possible to ascertain groups of patients that differ in the severity of schizophrenia. However, this would also be suggested by the multifactorial polygenic model, which predicts that the more predisposing genes an individual has, the more severe is the illness (Gottesman & Shields 1982, p. 224). Whether there is any difference in the underlying aetiological mechanisms remains for future studies to reveal.

No association between familial loading and mortality was found. Mortality was significantly lower among females, and later age at onset was associated with higher mortality. Overall mortality in this group of relatively young patients was high: 13.6% among females and 17.6% among males. In a Danish study, the mortality after the first five years of the first diagnosis of schizophrenia was 11.1% among females and 11.9% among males (Munk-Jørgensen & Mortensen 1992), which is comparable to our finding because the follow-up time among the majority of patients in our study was considerably longer than 5 years, although they were younger. Munk-Jørgensen and Mortensen found that mortality increased from the 1970s to 1980s. While the causes of death were not analysed in the present study, our results clearly indicate the need for further studies of the mortality of patients with schizophrenia in Finland, especially the proportion of deaths due to suicide and possible time trends.

6.3. Prenatal exposure to polio epidemics

We observed that second-trimester exposure to polio epidemics increased the risk of the later development of schizophrenia modestly but significantly. The relatively small effect of the exposure is unsurprising given that genetic factors are most important in the etiology of schizophrenia and that several other possible environmental risk factors have already been identified. It may also be that we lacked statistical power. The timing accords with previous findings of a neurodevelopmental insult in schizophrenia during the second trimester of fetal life (Huttunen et al 1994).

That the effect did not increase with the severity of exposure might be because we restricted ourselves to the incidence of paralytic poliomyelitis. Paralytic symptoms develop in less than 1% of those infected with the polio virus and only after an incubation period of up to one month (Nathanson & Martin 1979). In addition, the case:infection ratio depends on age, level of immunity in the population, and the type of poliovirus (Nathanson & Martin 1979). There are three virus types of polio virus, type 1 being the most virulent and type 2 the least (Nathanson & Martin 1979).

The first field trial of a polio vaccine in Finland was conducted during a large poliomyelitis epidemic in 1954. A large number of 6-12-year-old children were recruited, half of whom were vaccinated while the other half served as controls. Their antibody status was measured before the vaccination, and again after the termination of the epidemic. At the baseline, 61% of children had antibodies against Type 1 virus, 44% against Type 2 virus, and 62% against Type 3 virus. The epidemic was caused by a Type 1 virus, against which the vaccine did not protect. After the epidemic, 25% of the originally seronegative subjects had developed antibodies against the Type 1 virus, regardless of whether they had received the vaccination or not. During the epidemic, the incidence of paralysis among those acquiring the infection increased from 1 per 250 to 1 per 110. Serologic results were available from 65 cases with paralytic poliomyelitis: 64 cases were caused by Type 1 virus, one by Type 2 virus. (Penttinen & Pätiälä 1961)

According to the findings of Penttinen and Pätiälä, the susceptible population in the 1954 epidemic was considerable, although more than half of the 6-12-year-old children already had antibodies against Type 1 and Type 3 strains. The seroconversion rate among the susceptible population was also high: the epidemic was widespread. It seems reasonable to assume that during an epidemic like this, a significant proportion of pregnant women (although clearly less than half) belonged to the susceptible population and a significant proportion of those belonging to the susceptible population also got the infection. The findings also suggest that the virulence of the virus may change even during one epidemic.

The association between prenatal exposure to polio virus and adult schizophrenia might be limited to one of the serotypes. Or it might be confined to one exceptionally virulent form of one of the serotypes. Thus, it would have been interesting to study the association according to the type of virus that had caused the epidemic in each of the years, but unfortunately the information was not available.

We are left with many unanswered questions. An ecological study cannot prove causal association. For this, a follow-up study of pregnant women who actually had polio virus infection during the 1950s would be needed. The type of polio virus which caused the

infection should also be known. While such a study might be almost impossible to conduct, our results encourage research on other enteroviruses, which in many respects are similar to polio viruses and have become the most common viral agents causing aseptic meningitis (Muir & van Loon 1997).

6.4. Changes in the incidence

The incidence of schizophrenia in the 16-25 year age groups was higher than in the WHO Ten Country Study, where incidences of the same magnitude among the 15-24-year-olds were observed only in a few areas and using broadly defined schizophrenia (Jablensky et al 1992). However, previous Finnish studies have obtained similar results: the cumulative incidence of DSM-III-R schizophrenia up to 28 years was 0.69% in the northern Finland 1966 cohort (Jones et al 1998), and the incidence of all psychotic disorders in a study conducted in the 1980s varied between 0.49 and 0.88 per 1000 person years among the 15-24-year-olds (Salokangas et al 1987).

Our method differed from other studies, except that from south Verona (Balestrieri et al 1997), because we examined birth cohorts, while others investigated patients admitted for the first time in a defined period. The results suggest that the incidence of schizophrenia has declined. We found no sex differences, while others have found a greater decline in women (Strömgren 1987, Geddes et al 1993, Waddington & Youssef 1994, Takei et al 1996) or in men (De Alarcon et al 1990, Munk-Jørgensen & Mortensen 1992, Balestrieri et al 1997). The decline was of the same magnitude as that observed in previous European studies (Strömgren 1987, Munk-Jørgensen 1987, Eagles et al 1988, Der et al 1990, De Alarcon et al 1990, Munk-Jørgensen & Mortensen 1992, Geddes et al 1993, Waddington & Youssef 1994, Takei et al 1996, Brewin et al 1997, Balestrieri et al 1997). A recent Finnish study based on first admissions of all nonaffective psychotic disorders in 1990 and 1993 also found a decline in the first-admission rate (Korkeila et al 1998); however, this was actually not the true rate, because first admission was defined as having no hospitalisation during the three previous years (Korkeila et al 1998).

In accordance with the Scottish age-period-cohort analysis (Takei et al 1996), we found that the effects of period and cohort on the decline were both significant.

6.4.1. Cohort-related factors

The significant birth cohort effect suggests that the frequency or intensity of one or more risk factors involved in the etiology of schizophrenia, probably operating early in life, has decreased – or that the intensity or frequency of some protective factors has increased. Both genetic and environmental risk factors may change over time.

The Finnish population was relatively isolated for centuries. Genetic isolation may be the reason for pockets of exceptionally high prevalence of schizophrenia (3-4%) in rural eastern and northern Finland (Hovatta et al 1997). Migration from rural to urban regions increased rapidly after World War II, and marriage between persons from different parts of Finland became more common. In our sample, the proportion of patients with parents born in the same municipality fell from 30% in 1954 to 23% in 1965. This may have caused the incidence to decline, if genes predisposing to schizophrenia had become enriched in some areas of Finland. It has also been suggested that schizophrenia could be associated with decreased developmental stability caused by genetic homogeneity (Markow 1992). If so, increasing genetic heterogeneity caused by migration inside Finland could have resulted in a decline of the incidence of schizophrenia. However, when the hypothesis suggesting that decreasing isolation might cause the rare autosomal recessive diseases of the Finnish Disease Heritage to disappear was tested using the incidence of congenital nephrotic symptoms, no evidence for decline in the incidence was observed (Laakso et al 1992).

Public health care in Finland improved substantially from 1954 to 1965, reflected in a dramatic decrease in infant and maternal mortality and an increase in hospital deliveries from 75 to 99 per cent (Official Statistics of Finland 1972). Because obstetric complications are a risk factor for schizophrenia (Geddes & Lawrie 1995), these improvements may have affected the incidence of schizophrenia.

Infections are also a possible explanation for the observed cohort effect. Polio virus was eliminated from Finland in the beginning of the 1960s (Nathanson & Martin 1979), but large epidemics occurred in the 1950s, and as we have shown, second trimester exposure to polio epidemics may increase the risk of developing schizophrenia. Another possibility is influenza: three large influenza epidemics occurred in 1953, 1955, and 1957. The decreasing seasonal variation of births after very pronounced seasonality in the mid 1950s suggests that a reduced intensity of some seasonally varying environmental risk factor might be involved in the decline of incidence.

6.4.2. Period-related factors

The effect of period on the incidence of schizophrenia was significant. Period effects reflect the impact of risk factors operating in adult life which affect several or all age groups simultaneously. For example, suicide rates in England declined in all age groups during World War II, and also in the 1960s after the detoxification of domestic gases (Murphy et al 1986). In schizophrenia, period-related risk factors are not known and it seems more likely that the significant period effect found in the present study reflects artifacts caused by period-related confounding factors.

Register information reliability may change over time. Registers not using personal identification numbers usually have a code for first admissions, which has been used in several previous register-based studies and found to be rather unreliable (Kendell et al 1993). We avoided this problem. The incidence of schizophrenia may also appear to change if the proportion of persons with schizophrenia who never seek treatment changes. However, the proportion of schizophrenic patients who never receive psychiatric treatment in Finland is small: in a health survey based on a nationally representative sample of 8000 persons carried out in 1978-1980, 99% of persons with a psychotic disorder had received psychiatric treatment (Lehtinen et al 1991).

The proportion of schizophrenic patients treated exclusively as outpatients may change (Kendell et al 1993). The Finnish psychiatric health care system has undergone considerable changes. The number of beds in psychiatric hospitals peaked at the

beginning of the 1970s (Salokangas 1994), and since 1982 the number of beds has been decreasing rapidly (Korkeila et al 1998). Although a shift toward outpatient treatment could have occurred at the same time, the numbers of patients on disability pension or free medication for schizophrenia but never hospitalized did not indicate any rise in the proportion treated solely as outpatients. The situation would probably have been different in the 1990s: acute psychosis teams, which treat psychotic patients with intensive outpatient treatment and aim at avoiding inpatient treatments unless necessary, have been established in nearly all health care districts (Tuori et al 1998). The decrease in the number of beds in psychiatric hospitals was also rapid in the beginning of the 1990s (Korkeila et al 1998). However, the overall rate of patient admissions in psychiatric hospitals remained the same in 1990 and 1993, although there were 4540 fewer beds available in 1993 (Korkeila et al 1998). Thus, the use of hospital care is not determined solely by the availability of hospital beds (Korkeila et al 1998).

Narrowing of the diagnostic concept of schizophrenia explained a significant proportion of the decline in the incidence of schizophrenia in Edinburgh (Kendell et al 1993). Although Finnish psychiatrists tend to apply a narrow definition of schizophrenia in their clinical practice (Pakaslahti 1987, Salokangas 1993, Isohanni et al 1997, Cannon et al 1998), with more tendency to false negative than false positive diagnoses, diagnostic criteria changed in Finland in 1987 when DSM-III-R criteria were adopted for clinical use. We observed a subsequent significant increase in the incidence of other nonaffective psychotic disorders. Although the numbers were small, a diagnostic shift from schizophrenia to these diagnoses could explain some of the observed decline in schizophrenia incidence. The rise in the incidence of other nonaffective psychotic disorders also reflected the increased diagnostic delay, partly caused by shorter hospital admissions (Tuori et al 1998) in the 1980s: the proportion of schizophrenic patients who were so diagnosed in their first admission decreased from 77% in the first to 70% in the last cohort. Thus, a narrowing clinical concept of schizophrenia at least partially explains the observed period effect.

If the age at onset or the time lag between the onset of first symptoms and the beginning of first hospitalisation changes, age-specific incidences may alter without any change in

the overall incidence (Kendell et al 1993). No increase in the age at onset was observed in this study; on the contrary, the peak of highest incidence shifted toward an earlier age. The time lag between the onset of first symptoms and first hospitalization has been assessed in studies of first-admission patients conducted quinquennially in the Helsinki area (Achté et al 1986). Although the lag has varied somewhat over the years, being longest in the 1965 and 1970 cohorts, no major changes that could explain the observed decline in the incidence have occurred (Achté et al 1986).

6.4.3. Age-period-cohort analysis

The age-period-cohort analysis method we used is widely accepted and produces reliable estimates (Holford 1991, McNally et al 1997, Robertson & Boyle 1998). However, it assesses only deviations from linearity, i.e., curvature effects, while the effects of period and cohort in any steady, linear changes remain unexplained. Because of this, the effects of period and cohort we observed should not be interpreted as the total effects of cohort and period on the incidence. Nevertheless, curvature effects provide valuable information, because many changes in cohort-related factors, e.g. infections, and period-related factors, e.g. changes in diagnostic criteria, are abrupt in nature and should cause deviations from a linear trend. Another possibility would have been to use some constraint to ensure identifiability of the linear component of the effects. However, the use of such constraints is acceptable only if they are based on sound theoretical grounds, which is usually not the case (Robertson & Boyle 1998). The effect of using such constraints is marked, and usually the results obtained are not considered reliable (McNally et al 1997, Robertson & Boyle 1998). Therefore, we felt it was safer to a use method that produces reliable, albeit conservative, estimates (McNally et al 1997).

Based on the results of our study it seems reasonable to conclude that the age-specific incidence of schizophrenia among persons aged 16 to 25 years in Finland has decreased. A significant cohort effect was observed, suggesting that some risk factors for schizophrenia, probably operating early in life, have diminished in intensity. The effect of period was also significant and probably reflects changes in diagnostic criteria. The

findings from this cohort-based study accord with those of several period-based studies, thus strengthening evidence of a worldwide decline in the incidence of schizophrenia. More detailed studies on cohorts born in the 1950s and 1960s that focus on risk factors of schizophrenia may reveal causes of the decline. Such studies are currently being conducted in Helsinki (the Helsinki 1951-1960 Birth Cohort) (Cannon et al 1999) and in Oulu (the Northern Finland 1966 Birth Cohort) (Isohanni et al 1996).

6.5. Time trends in the seasonal variation of births in schizophrenia

We observed that seasonal variation in schizophrenic births in the 1950s was prominent, but it decreased considerably in the 1960s. We failed to detect any interaction between place of birth and seasonality, implying that urban birth is not associated with season of birth in Finland. However, we did observe an interaction between place of birth and trend: the incidence of schizophrenia declined more slowly among the urban born population. In line with most previous studies (Torrey et al 1997), no interaction between sex and season of birth was observed. The decline in the incidence of schizophrenia coincided with the decrease of seasonality in schizophrenic births. It may be, as suggested by Procopio and Marriott, that some of the decline in the incidence was caused by a disappearance or diminishment of a seasonal aetiological agent (Procopio and Marriott 1998). The factor might be an infection, as discussed earlier.

The availability of detailed and reliable register information allowed us to construct historical birth cohorts and to use accurate person-years to calculate the incidence of schizophrenia. We were thus able to control for the association between season of birth and mortality in the general population. Postneonatal deaths, especially those caused by infections and sudden infant death syndrome, show a marked seasonality with a peak during winter (Peterson et al 1979, Hare et al 1981, Apostolidou et al 1994). Previously, perinatal mortality has also shown similar seasonal variation (Timonen et al 1968, Rantakallio 1971, Hare et al 1981). The seasonal variation of perinatal deaths diminished in England and disappeared completely by 1965 (Hare et al 1981), but still existed in the Northern Finland 1966 Birth Cohort (Rantakallio 1971).

Our finding of declining seasonal variation contradicts the findings of two recent studies which found either no change (Procopio & Marriott 1998) or an increase (Eagles et al 1995) in the seasonality of births. However, we avoided some possible sources of bias by using entire birth cohorts as the study population. The study in England and Wales was based on all hospital treatments during one year and included patients born between 1938 and 1977 (Procopio & Marriott 1998). The probability of admission in a given year may not be unrelated to the season of birth, because mortality in the general population may be associated with season of birth and because seasonal variation of births in schizophrenia may be associated with the severity of the illness (Torrey et al 1997). In the Scottish study, the study sample was selected from first contacts between 1962 and 1987 and included patients born between 1900 and 1969 (Eagles et al 1995). Thus, only very late-onset cases could have been identified from the earliest cohorts. Relatives of patients with very late-onset schizophrenia do not have an increased risk of schizophrenia, suggesting that very late-onset and earlier-onset schizophrenia may not be genetically linked (Howard et al 1997). Cases from the oldest cohorts might not then be suffering from exactly the same disorder as the others. Another limitation in the Scottish study was that population information was not available. In Finland, the seasonal variation of general births shifted during the 20th century from a summer peak before World War II (Lagerqvist & Niemineva 1949) to a spring peak since the 1950s. If a similar shift occurred in Scotland, this might have caused the observed increase in the odds ratio for winter/spring births.

Another puzzling finding was the considerable seasonal variation between 1955 and 1959. The overall variation in the relative incidence was almost 30%, the incidence of schizophrenia was higher in each of the months between December and April than in any other, and the relative incidence was quite low, 0.74-0.79, between July and November. This variation was much more marked than the usually cited 5-8% winter-spring excess (Torrey et al 1997). Unfortunately, few previous studies covering the 1950s and 1960s reported the amplitude of the seasonal variation separately for different birth cohorts. Eagles et al found an increased ratio of births between December and May compared with June and November in the 1950s, but the increase was confined to males and was even more pronounced in the 1960s (Eagles et al 1995). However, a recent

Japanese study of seasonal variation of births among patients born between 1955 and 1960, excluding those born between June 1957 and May 1958, found an 10% excess of births in the winter, and a 14% deficit of births in the summer (Kunungi et al 1997), which is almost comparable to our findings.

Influenza and polio epidemics together might at least partly explain the observed pattern of seasonal variation. Two of the largest epidemics of poliomyelitis in Finland occurred in 1954 and 1956, and the incidence of paralytic poliomyelitis was also high in 1955, 1959, and 1960. The highest numbers of influenza cases during the 1950s were reported in 1957, 1953, and 1955 - more in each of these epidemics than in any that occurred during the 1960s. Other possible explanations for the decreasing seasonal variation might be decreased exposure to cold temperature during pregnancy because of improved living conditions. Also the seasonal variation of obstetric complications observed in the 1950s birth cohorts (Timonen et al 1965) might have decreased because of the improving obstetric care, and this might have caused the seasonal variation of births in schizophrenia to decrease. However, neither of these hypothesis explain the observed increase in the seasonal variation in the 1950s.

An interaction between age at onset and seasonal variation was observed: autumn birth was more common among those aged over 30 years at onset of schizophrenia. Interestingly, these patients all belonged to cohorts born in the 1950s who otherwise showed marked winter/spring excesses. Age of onset groups 16-20 years and 26-30 years showed the most prominent winter-spring excesses of births. However, the 1950-1954 cohort was underrepresented in the age group 16-20 years, and the 1965-1969 cohort in the age group 26-30 years. The study population did not include patients with onset after 41 years. Although our results suggest an association between early onset and winter-spring excess of births, far reaching conclusions should not be drawn from the observation because of the limitations mentioned.

We observed no interaction between seasonal effect and place of birth, which suggests that the agent causing the seasonality was equally prevalent in the three largest towns and in other parts of Finland. However, the incidence of schizophrenia was higher in

rural than urban areas, which accords with findings of higher incidence and prevalence of schizophrenia in rural eastern and central Finland (Salminen 1975, Salokangas et al 1987, Lehtinen et al 1990, Hovatta et al 1997, Korkeila et al 1998). In the WHO Ten Country Study, the incidence of schizophrenia was higher in a rural than an urban area of India (Jablensky et al 1992). In Western countries, the incidence of schizophrenia has been higher in urban than in rural areas (Freeman 1994), and higher among those born or brought up in urban than in rural areas (Lewis et al 1992, Verdoux et al 1997, Marcelis et al 1998, Mortensen et al 1999). It has been suggested that the higher incidence in urban areas is caused by more crowded living conditions which predispose to infections during pregancy and childhood (Mortensen et al 1999). It may be that living conditions in Finland were actually more crowded in rural areas, which could be one reason for the higher incidence of schizophrenia in rural areas. Another reason could be genetic isolation (Hovatta et al 1997).

An interesting interaction was observed between overall trend in the incidence of schizophrenia and place of birth: incidence declined more slowly among the urban than rural born. Marcelis et al recently found that urban birth increased the risk of developing schizophrenia more in birth cohorts born in the 1960s and 1970s than in older cohorts (Marcelis et al 1998). Urbanization began in Finland only after World War II and has been very rapid. Our findings suggest that the factors in urban living that confer increased risk of developing schizophrenia may not have existed in Finland until the 1960s, or that the intensity of the factors is increasing. Alternatively, the frequency or intensity of risk factors of schizophrenia may have been decreasing in rural areas.

6.6. Implications for further studies

This study is a part of an ongoing research project on the epidemiology and aetiology of schizophrenia. The aim of the study was to use register data to identify research methods, candidate risk factors, and time periods in which risk factors for schizophrenia may have changed quantitatively or qualitatively. This information can be used in the planning of more targeted research.

The aim of the first publication was methodological. The familial / sporadic schizophrenia distinction was originally proposed as a research strategy to separate patients with more genetically caused (familial) or more environmentally caused (sporadic) disease (Lewis et al 1987). The method has attracted much criticism, partly due to the misunderstanding that a sporadic case is equal to a phenocopy (McGuffin et al 1987, Roy & Crowe 1994). The method also has its supporters, however, who consider it a useful strategy together with family, adoption, and twin studies in the identification of genetic and environmental risk factors for schizophrenia (Kremen et al 1992). In 1994, Roy and Crowe reviewed all studies using the distinction. They found no evidence of differences in any clinical features between the familial and sporadic groups, and only a few differences in vulnerability indicators. However, they concluded that "the scarcity of studies with adequate methodology precludes any definite judgement about the validity of the familial-sporadic distinction" (Roy and Crowe 1994). Roy and Crowe set criteria for future studies using the distinction, and they stressed two aspects: stringent definitions of familiality and sporadicity, and adequate sample size. This study used stringent definitions of both familiality and sporadicity, and the sample size was over 10 times larger than in any of the previous studies. We have shown that using stringent definitions it is possible to identify familial and sporadic groups that differ in their age at onset and outcome. Interesting sex differences also emerged. In the future, these patients should be personally contacted to study vulnerability indicators in these groups and their relatives. Another implication for future research is that age at onset of schizophrenia can be used as one method to classify phenotype in genetic studies.

We found an association between second trimester exposure to polio virus epidemics and adult schizophrenia. Our findings add to the existing evidence that adverse events during the second trimester of fetal life increase the risk of developing schizophrenia (Huttunen et al 1994). An ecological study cannot, however, prove a causal association. In the future, a cohort of mothers who have had polio virus infection during pregnancy should be traced and followed up, but it is uncertain whether such cohorts exist. It should also be further clarified whether the association is specific, limited to one serotype of polio viruses, or more general, extending perhaps to other types of

enteroviruses as well. Another Finnish study has found an association between neonatal Coxsackie B5 meningitis and adult schizophrenia. There is strong evidence for enteroviruses being involved in the aetiology of acute myocarditis and dilated cardiomyopathy, and one of the suggested mechanisms has been that enteroviruses may trigger an exaggerated immune response not only to the viral antigens but to the host tissue (Baboonian & Treasure 1997). There is also evidence that they are involved in the aetiology of insulin-dependent diabetes mellitus (Hovi 1998), another disease with known autoimmune background. Compared with these two diseases, the evidence suggesting that enteroviruses are involved in the aetiology of schizophrenia is scarce, and further studies are needed. It may be impossible to retrospectively locate cohorts of persons whose mothers had enteroviral infection during pregnancy. Another, more feasible alternative is to locate persons who have had an enteroviral CNS infection during childhood and study the incidence of psychotic disorders among them. If enteroviruses are shown to be involved in the aetiology of schizophrenia along with insulin-dependent diabetes mellitus and some heart diseases, there will be an urgency to develop vaccination against all of them.

The apparent time trends in both the incidence and the seasonality of births imply that some change in the frequency or intensity of risk factors for schizophrenia occurred between the 1950s and 1960s. Changes in both genetic and environmental risk factors could be involved in the decline of the incidence of schizophrenia. However, the decrease in the seasonality of births might be accounted for more by changes in environmental than genetic risk factors. These findings imply that cohorts born during the 1950s and 1960s should be better characterized according to the environmental risk factors they have experienced. Further studies should attempt to locate cohorts with reliable exposure information on infections and on pre- and perinatal events. More detailed studies on geographical variation in the incidence of schizophrenia in Finland, and on time trends in different regions of the country, are needed to further delineate areas with large changes in incidence. Such areas, along with those with persistent high incidence, would be of special interest.

7. SUMMARY

This study forms a part of the collaborative project "The Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland" of the Departments of Mental Health and Alcohol Research, and of Human Molecular Genetics at the National Public Health Institute. The aim of the study was to investigate epidemiological features and some risk factors of schizophrenia among individuals born between 1950 and 1969 who developed schizophrenia before 1992 (n=16 687). Patients with schizophrenia were identified using the Finnish Hospital Discharge Register, the Pension Register, and the Free Medicine Register. Their parents and siblings were identified using the National Population Register. Schizophrenia was defined as having a 295 diagnosis according to the 8th and 9th revision notation of the International Classification of Diseases.

Changes in the incidence of schizophrenia were studied among birth cohorts born between 1954 and 1965. The incidence declined from 0.69 to 0.47 per 1000 person years. The decline was equal among both sexes and was not caused by changes in the onset age. The effects of period and cohort on the change were both significant. While the effect of period reflects the operation of period-related confounding factors such as the change in diagnostic criteria that occurred in 1987, the cohort effect suggests that the intensity or frequency of one or more risk factors for schizophrenia has decreased.

Seasonal variation with a significant excess of births during the winter months was observed among patients with schizophrenia born in the early 1950s. The amplitude of the seasonal variation increased considerably among patients born between 1955 and 1959 but decreased in the 1960s to a lower level than in the early 1950s. Seasonal variation of births was not associated with sex and place of birth (urban/rural). A significant interaction between seasonal variation and age at onset of schizophrenia was observed: autumn birth was more common among patients aged over 30 years at onset. The incidence of schizophrenia was higher among the rural-born than the urban-born, but declined more slowly among the urban-born.

An association between prenatal exposure to polio virus epidemics and later development of schizophrenia was observed. Exposure to polio epidemics 5 months before birth was associated with an increased risk of developing schizophrenia (RR 1.05, 95% CI 1.00-1.11). When seasonality was omitted from the regression model, the effect of polioepidemics became significant throughout the second trimester, relative risks varying between 1.06 and 1.08 4-6 months before birth.

Familial schizophrenia was associated with early age at onset and sporadic with later. No sex differences in the onset age were found in the whole sample, but females with sporadic schizophrenia seemed to consist of two groups, one with similar onset age to females in the intermediate group, and another with later onset. The correlation of age at onset between affected siblings was 0.28. Familial schizophrenia was associated with longer annual duration of hospitalisation and sporadic schizophrenia with shorter. Familial schizophrenia was also associated with a higher risk of receiving a disability retirement pension. The degree of familial loading was not associated with mortality.

Both the decline observed in the incidence of schizophrenia and the decrease in the seasonal variation of births among patients with schizophrenia suggest that the intensity or frequency of one or several risk factors for schizophrenia decreased from the 1950s to the 1960s. While the risk factors involved could be genetic or environmental, or both, environmental risk factors seem more likely to explain the decreasing seasonal variation. The significant association observed between prenatal exposure to poliovirus epidemics and later development of schizophrenia suggests that the elimination of polio virus is one possible explanation for the observed changes in the incidence and in the pattern of seasonal variation. Familial / sporadic distinction may be one useful strategy in the search for environmental risk factors for schizophrenia. While we showed that familial and sporadic schizophrenia differ in their clinical picture, further studies should demonstrate whether they also differ in aetiology.

The results encourage more detailed studies on the early risk factors for schizophrenia in birth cohorts born in the 1950s. Attention should focus on environmental risk factors, especially infectious diseases, and on the family history of psychiatric disorders.

8. ACKNOWLEDGEMENTS

This study was carried out at the Department of Mental Health and Alcohol Research of the National Public Health Institute. I wish to express my gratitude to the Director General of the National Public Health Institute, Professor Jussi Huttunen, M.D., Ph.D., for the facilities to perform this study.

I am most grateful to my supervisor, Professor Jouko Lönnqvist, for introducing me to psychiatric research. Without his guidance, support and vast scientific knowledge, this study would not have been possible. Despite his tight schedule, he always found time for my problems and has always been able to solve them efficiently. Perhaps the most important thing throughout these years, however, has been his unflagging confidence in my ability to do scientifically meaningful research and to work independently, which has been a most important source of encouragement.

I am deeply indebted to Jari Haukka, Ph.D., whose expertise in epidemiology and statistics was essential during all the phases of the study and who conducted all the statistical analyses. I appreciate our numerous discussions, which greatly expanded my understanding of statistical methodology. Antti Tanskanen, B.Sc. performed an enormous task with the register information, without which the study would not have been possible, and also gave important practical advice in every phase of the study. Professor Tapani Hovi, M.D., Ph.D., provided his vast knowledge on enteroviruses and research methods, as well as a persistently friendly and encouraging attitude.

I am very grateful to the official reviewers of the dissertation, Docent Pirkko Räsänen, M.D., Ph.D. and Docent Hannu Lauerma, M.D., Ph.D. for their encouraging comments and constructive critisism.

I am very thankful to the whole research team of the Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland project. My warmest thanks to Hannu Juvonen, M.D. for sharing the ups and downs of scientific work, for our numerous discussions, and for reading and commenting on this manuscript. My sincere thanks to Maija Norilo: all my practical problems disappeared the day she started to work in our

project. Ritva Arajärvi, M.D., Timo Partonen, M.D., Ph.D., Annamari Tuulio-Henriksson, M.Sc., and Marjut Schreck, M.Sc. have been enjoyable companions and excellent collaborators in studies yet to be published. I wish to thank Jesper Ekelund, M.D. for valuable comments on this dissertation and for our co-operation throughout the years. I am also grateful to Iiris Hovatta, Ph.D. for our years of collaboration, along with Tiina Paunio, M.D., Ph.D. and Teppo Varilo, M.D. I enjoyed the special atmosphere of the Department of Human Molecular Genetics and my glimpse of the hectic life in the laboratory there.

Tuula Kieseppä, M.D. has been a close companion whose opinions in scientific issues as well as other aspects of life I appreciate very much. I've greatly enjoyed our daily discussions and travelling together to congresses.

I am very thankful to Richard Burton, B.Sc., for his invaluable linguistic assistance during the whole work. I also wish to thank Tiina Hara, Sirkka Laakso, and Olli Kiviruusu for their friendly help in all practical issues, and the excellent librarians of the National Public Health Institute whose help has been extremely important throughout the years.

I am grateful for the financial support for the study given by The Academy of Finland, The Jalmari and Rauha Ahokas Foundation, The Foundation for Psychiatric Research in Finland, The Maud Kuistila Foundation, The Finnish Medical Foundation, and The Sigrid Juselius Foundation.

Finally, I wish to thank my husband Janne. In so many ways he has given me what is best in my life, but he has also been of invaluable help in this work. By sharing his enormous knowledge on medical sciences, he showed me that research could be fun and encouraged me to begin this work. Our discussions during the years have been decisively important, as has been his reading and commenting on all the original publications and this dissertation. His practical help with computers also proved invaluable. I am deeply grateful for the patience he has shown in the face of my sometimes overly enthusiastic approach to work.

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