

*Erika Lauronen*

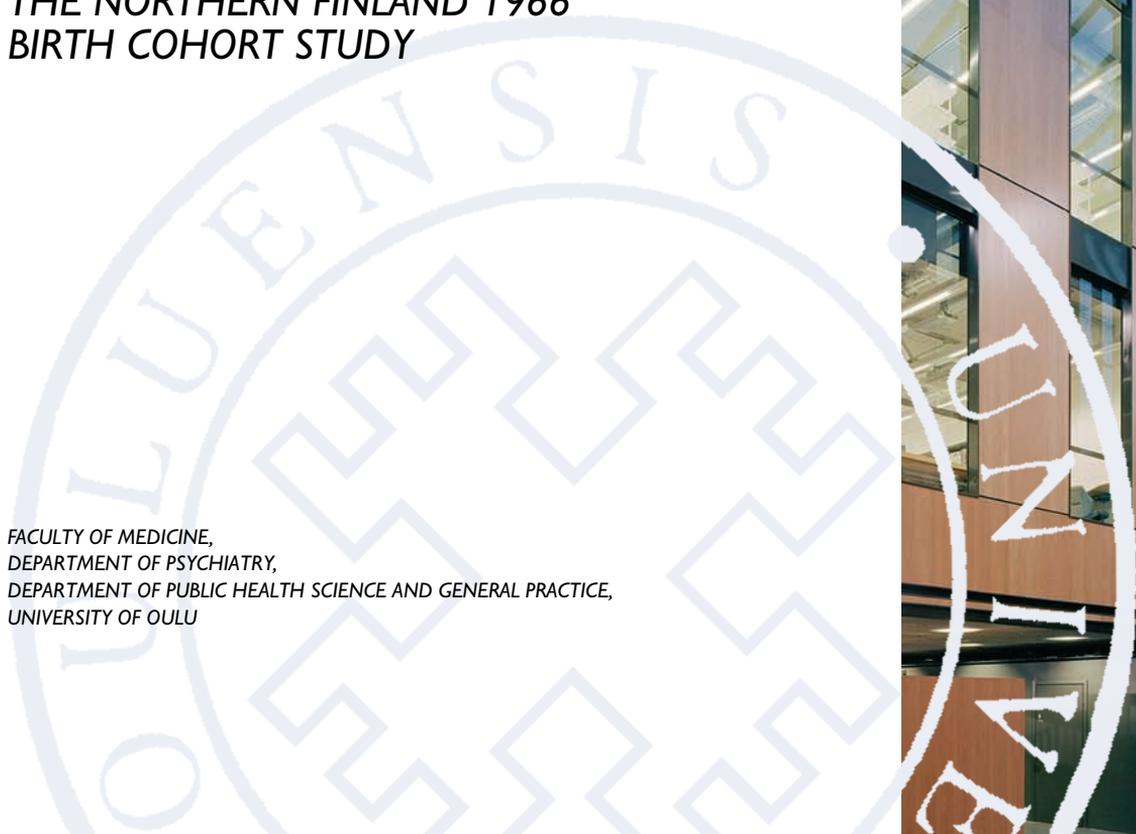
COURSE OF ILLNESS,  
OUTCOME AND  
THEIR PREDICTORS  
IN SCHIZOPHRENIA

THE NORTHERN FINLAND 1966  
BIRTH COHORT STUDY

FACULTY OF MEDICINE,  
DEPARTMENT OF PSYCHIATRY,  
DEPARTMENT OF PUBLIC HEALTH SCIENCE AND GENERAL PRACTICE,  
UNIVERSITY OF OULU

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*ERIKA LAURONEN*

**COURSE OF ILLNESS, OUTCOME  
AND THEIR PREDICTORS  
IN SCHIZOPHRENIA**

The Northern Finland 1966 Birth Cohort study

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Supervised by  
Professor Matti Isohanni  
Docent Juha Veijola

Reviewed by  
Docent Jyrki Korkeila  
Professor Kristian Wahlbeck

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**Lauronen, Erika, Course of illness, outcome and their predictors in schizophrenia. The Northern Finland 1966 Birth Cohort study**

Faculty of Medicine, Department of Psychiatry, Department of Public Health Science and General Practice, University of Oulu, P.O.Box 5000, FI-90014 University of Oulu, Finland

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Oulu, Finland

***Abstract***

The aim of this study was to explore the prognosis and predictors of outcomes in DSM-III-R schizophrenic psychoses within the Northern Finland 1966 Birth Cohort (NFBC 1966, N = 12 017). Firstly, clinical and social outcomes were explored by using different definitions of good and poor outcomes, and early developmental, socio-demographic, illness-related and school-related predictors of outcome in schizophrenia (N = 59) were studied. Secondly, associations between early motor development and the course of illness in schizophrenia (N = 109) were explored. Thirdly, patterns of psychiatric hospitalisations in schizophrenic psychoses (N = 115) were studied. Fourthly, recovery in schizophrenia (N = 59) and other schizophrenia spectrum psychoses (N = 12) was assessed.

As a result, good clinical outcome varied from 10% to 59%, and good social outcome 15–46%, depending on definition. Poor clinical outcome varied 41–77% and poor social outcome 37–54%. Lack of friends in childhood, father's high social class, lower school performance and earlier age of illness onset predicted poor outcomes. There were some associations between development and learning of basic skills at about age 1 and subsequent illness course. Those who learnt later (within normal limits) had mostly better outcomes, compared to early learners. A total of 81% of patients with schizophrenic psychoses were re-hospitalised during the follow-up and short first hospitalisation and family history of psychosis were linked to increased risk of re-hospitalisations. One (1.7%) schizophrenia subject and three (25%) subjects with other schizophrenia spectrum disorder recovered fully; one (1.7%) schizophrenia subject and two (16.7%) spectrum subjects experienced partial recovery after several years of follow-up.

In this dissertation study outcomes and some predictors were analysed in a population-based sample of individuals with relatively young age and short duration of illness. In general, both clinical and social outcomes were heterogeneous and relatively poor, and the results were influenced by the definitions of outcomes. Persons having a sub-optimal developmental trajectory with family history of psychosis, poor social contacts, poor school performance, and early age of illness onset and those with short first hospitalisation seem to have the worst outcome. In addition, the neuromotor development of these individuals is complex and late development does not associate clearly with poor outcome of illness.

The results of this study indicate that the outcome of schizophrenic psychoses is not good enough and that more effective treatments and rehabilitation for schizophrenia patients are needed. Also, there is a need for structured criteria for good and poor outcome and recovery in schizophrenia.

*Keywords:* course of illness, outcome, predictor, schizophrenia



# **Lauronen, Erika, Skitsofrenian taudinkulku ja ennuste ja niihin liittyvät tekijät. Pohjois-Suomen vuoden 1966 syntymäkohorttitutkimus**

Lääketieteellinen tiedekunta, Psykiatrian klinikka, Kansanterveystieteen ja yleislääketieteen laitos, Oulun yliopisto, PL 5000, 90014 Oulun yliopisto

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## ***Tiivistelmä***

Tämän tutkimuksen tavoitteena oli tutkia DSM-III-R skitsofrenian ja muiden skitsofrenian kaltaisten psykoosien taudinkulkua ja ennustetta sekä niihin liittyviä tekijöitä Pohjois-Suomen vuoden 1966 syntymäkohortissa. Ensimmäiseksi tutkimuksessa selvitettiin skitsofrenian (N = 59) taudinkulkua ja sitä ennustavia sosio-demografisia ja kehitykseen, sairauteen ja koulumenestykseen liittyviä tekijöitä. Toiseksi, tutkittiin varhaislapsuuden kehityksen ja skitsofreenisten psykoosien (N = 109) taudinkulun välistä yhteyttä. Kolmanneksi, skitsofreenista psykoosia sairastavien henkilöiden (N = 115) psykiatrisia sairaalahoitoja ja niihin liittyviä tekijöitä tutkittiin. Neljänneksi tutkimuksessa selvitettiin skitsofreniasta (N = 59) ja muista skitsofreniaspektrin psykooseista (N = 12) toipumista.

Tässä tutkimuksessa 10–59 % potilaista voi kliinisesti hyvin ja 15–46 % sosiaalisesti hyvin kun taas 41–77 % voi kliinisesti ja 37–54 % sosiaalisesti huonosti. Tulokset riippuivat paljolti siitä, mitä hyvän ja huonon taudinkulun kriteereitä käytettiin. Lapsuudessa ystävien puute, isän korkea sosiaaliluokka, huono koulumenestys ja taudin varhainen alkamisikä liittyivät huonoon taudinkulkuun. Aineistosta löydettiin yhteys (normaalirajoissa olevan) myöhäisemmän kehityksen ja hyvän taudinkulun välillä. Seurannassa 81 % potilaista joutui ensimmäisen sairaalahoidon jälkeen uudelleen sairaalaan. Lyhyt ensimmäinen sairaalahoido ja suvussa esiintyvä psykoosi liittyivät kohonneeseen riskiin joutua uudelleen sairaalaan. Skitsofreniapotilaista yksi (1.7 %) oli täysin ja yksi (1.7 %) osittain toipunut. Muista skitsofreniaspektrin potilaista kolme (25 %) oli täysin ja kaksi (16.7 %) osittain toipuneita usean vuoden seurannan jälkeen.

Tässä tutkimuksessa selvitettiin skitsofrenian taudinkulkua ja analysoitiin taudinkulkuun vaikuttavia tekijöitä yleisväestöön pohjautuvassa aineistossa. Tulosten mukaan skitsofreniaa sairastavien henkilöiden sosiaalinen ja kliininen taudinkulku oli vaihteleva ja enimmäkseen suhteellisen huono. Tulokset riippuivat paljon siitä, millaisia hyvän ja huonon taudinkulun kriteereitä käytettiin. Henkilöillä, joilla on suvussa psykooseja, varhainen sairastumisikä, joilla on ollut huono koulumenestys ja vähäisiä sosiaalisia kontakteja lapsuudessa, ja joilla on ollut lyhyt ensimmäinen sairaalahoido, sairauden kulku on usein huono. Skitsofreniaa sairastavien henkilöiden viivästynyt varhainen motorinen kehitys ei ole yksiselitteisesti yhteydessä huonoon taudinkulkuun.

Tämän tutkimuksen tulosten perusteella skitsofrenian ennuste ei ole yleensä hyvä. Yhteiskunnan tulisi entistä enemmän panostaa skitsofreniapotilaiden kokonaisvaltaiseen hoitoon ja kuntouttamiseen. Aiemman kirjallisuuden ja tämän tutkimuksen tulosten perusteella on myös selkeä tarve yhdenmukaisille ja strukturoiduille hyvän ja huonon ennusteen ja toipumisen kriteereille skitsofreniassa.

*Asiasanat:* ennuste, ennustetekijä, skitsofrenia, taudinkulku



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Oulu, December 2006

Erika Lauronen

## Abbreviations

15-D	Fifteen Dimensions (Quality of Life Scale)
95% CI	95% Confidence Interval
APA	American Psychiatric Association
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impression
DAS	Disability Assessment Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders. 3rd ed., revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. 4rd ed.
DUP	Duration of Untreated Psychosis
FHDR	Finnish Hospital Discharge Register
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
ICD	International Classification of Diseases and Causes of Death
ICD-10	International Classification of Diseases and Causes of Death, 10th ed.
IQR	Inter Quartile Range
LCS	Life Chart Schedule
NFBC 1966	Northern Finland 1966 Birth Cohort
OCCPI	Operational Criteria Checklist for Psychotic Illness
OR	Odds Ratio
PANSS	Positive and Negative Symptoms Scale
PAS	Premorbid Adjustment Scale
PIRS	Psychological Impairment Rating Scale
PSE	Present State Examination
R <sup>2</sup>	Nagelgerke's R Square
RDC	Research Diagnostic Criteria
SADS	Schedule for Affective Disorders and Schizophrenia
SANS	Schedule for the Assessment of Negative Symptoms
SAPS	Schedule for the Assessment of Positive Symptoms
SAS	Social Adjustment Scale
SCID	The Structured Clinical Interview for DSM-III-R

SCL	Syndrome Checklist
SD	Standard Deviation
SMR	Standardised Mortality Ratio
SOFAS	Social and Occupational Functioning Assessment Scale
WHO	World Health Organisation

## **List of original publications**

This dissertation is based on the following four original publications, which are referred to in the text by the Roman numerals I–IV.

- I Lauronen E, Miettunen J, Veijola J, Karhu M, Jones PB & Isohanni M (2006) Outcome and its predictors in schizophrenia within the Northern Finland 1966 Birth Cohort. *Eur Psychiatry* (in press).
- II Lauronen E, Miettunen J, Veijola J, McGrath JJ, Murray G, Jones PB & Isohanni M. Associations between early development and outcome schizophrenia – A 35-year follow-up of the Northern Finland 1966 Birth Cohort. (manuscript).
- III Miettunen J, Lauronen E, Veijola J, Koponen H, Saarento O, Isohanni M (2006) Patterns of psychiatric hospitalizations in schizophrenic psychoses within the Northern Finland 1966 Birth Cohort. *Nord J Psychiatry* 60: 286-293.
- IV Lauronen E, Koskinen J, Veijola J, Miettunen J, Jones PB, Fenton WS & Isohanni M (2005) Recovery from schizophrenic psychoses within the Northern Finland 1966 Birth Cohort. *J Clin Psychiatry* 66: 375-383.

In addition, some unpublished data have been added to this dissertation.



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# 1 Introduction

Schizophrenia is a severe mental illness; it may even be one of the most important unsolved disorders afflicting humans. In addition to clinical symptoms, it often causes marked impairments in social, occupational, cognitive and global functioning. The heaviest burden of illness is experienced by patients, but also by their relatives (Magliano *et al.* 2005).

The prognosis of schizophrenia is one of the unanswered questions in psychiatry. Outcome, course of illness and prognosis of schizophrenia are heterogeneous definitions. They can include for example global psychiatric or somatic health, clinical psychiatric symptoms, functioning (such as social abilities, working ability), quality of life, service utilisation, somatic or psychiatric (co)morbidity and death as an extreme of outcome. A wide range and variations of outcomes are possible (Ram *et al.* 1992, Ruggeri *et al.* 2004, Jobe & Harrow 2005). However, some generalisations can be concluded: according to systematic reviews including several different definitions of good and poor outcomes approximately 40% of patients are considered as having a good (Hegarty *et al.* 1994) and 20-40% as having poor outcome (Ram *et al.* 1992, Menezes *et al.* 2006).

Several predictors of outcome in schizophrenia have been presented, such as the age of illness onset (Suvisaari *et al.* 1998, Harrison *et al.* 2001), gender (Angermeyer *et al.* 1990), genetic loading (Verdoux *et al.* 1996, Suvisaari *et al.* 1998), premorbid functioning (Hofer *et al.* 2006), duration of untreated psychosis (DUP) (Marshall *et al.* 2005), and early illness course (Harrison *et al.* 2001). Environmental factors, such as high expressed emotion (i.e. poor emotional environment in the family) (Butzlaff & Hooley 1998, Bebbington & Kuipers 2003) and stress (Bebbington & Kuipers 2003) are suggested to have an effect on the course of illness. The predictive power of most indicators of outcome, however, has been poor (Häfner & an der Heiden 2003).

Though schizophrenia patients often have abnormalities or developmental delays in neuromotor, cognitive, emotional or social functioning (Isohanni *et al.* 2001b, Cannon *et al.* 2003, Niemi *et al.* 2003), the association between early neurodevelopment and subsequent illness course is not well known. According to some studies, a suggestion exists of an association between later childhood development and poor course of illness (Rossi *et al.* 2000).

Schizophrenia is often characterised by a deteriorating course during the first few years of illness, followed by either complete remission or more often a fluctuating course with remissions and relapses. Even though as many as 88% of patients achieve remission after one year, most individuals relapse (82%, Robinson *et al.* 1999) or have re-hospitalisation within 5 years (90%, Eaton *et al.* 1992). Indeed, up until recent years hospitalisation has been an important part of treatment of schizophrenia patients, although extensive reduction of hospital beds in Western countries, also in Finland, has reduced the role of inpatient care.

When someone becomes ill for the first time it is a clinical challenge to estimate their prognosis and chances for a recovery, and to say how likely it is that they will return to their pre-illness level of functioning. Follow-up studies have shown that even over half of patients with schizophrenia may recover (McGlashan 1984, Ram *et al.* 1992), but with more strict criteria, the probability of recovery is 8-27% (Huber *et al.* 1980, Harrison *et al.* 2001, Auslander & Jeste 2004).

The absence of a general definition of good and poor outcome and recovery, variable diagnostics and outcome criteria, as well as cases lost to follow-up cause challenges when studying the course and outcome in schizophrenia and related psychoses. In addition, as indicated by McGlashan *et al.* (1988), unique clinical characteristics of samples from particular clinics or hospitals, particularly the degree of established chronicity, may account for wide differences in the observed outcome rates. The true rate of recovery and other outcomes in schizophrenia can best be established by follow-up of an epidemiologically defined cohort.

The topic of this doctoral thesis is the course of illness and outcome and their determinants in schizophrenic psychoses, mostly schizophrenia. The aim was to analyse four aspects of the topic by utilising the Northern Finland 1966 Birth Cohort. First, the amount of good and poor outcomes as well as early developmental, socio-demographic, and illness-related predictors of outcome in schizophrenia were explored. Second, the association between early motor development and outcome in schizophrenia was analysed. Third, patterns and determinants of hospitalisations in schizophrenic psychoses were analysed. And fourth, recovery in schizophrenic psychoses was studied.

## **2 Literature review**

### **2.1 Schizophrenia**

Schizophrenia is a psychotic disorder, one of the most severe mental illnesses. In addition to clinical symptoms, it often causes marked impairments in social, occupational, cognitive and global functioning, increased mortality and comorbidity (Murray & Lopez 1997), as well as stigma. At the global level, schizophrenia accounts for 1.1% of the global burden of disease, which is similar to the contributions from diseases such as diabetes mellitus (1.0%), osteoarthritis (1.1%) and asthma (0.9%). It is listed as the 8th leading cause of disability-adjusted life years worldwide in the age group 15–44 (WHO 2001).

#### ***2.1.1 Definition, symptoms and diagnosis***

The history of definition of schizophrenia begins from Emil Kraepelin (1909), who classified mental disorders into two groups: manic-depressive psychoses and dementia praecox (i.e. schizophrenia). Kraepelin considered dementia praecox a disorder beginning early in life, leading to chronicity and characterised by hallucinations, delusions, stereotypes, thought disorder, negativism and blunted affect.

Eugen Bleuler (1911) first introduced the term “schizophrenia”. He retained the distinction between manic-depressive illness and schizophrenia, but also thought that affective symptoms could coexist. In addition, instead of hallucinations, delusions and catatonia, Bleuler thought that the primary symptom of schizophrenia was cognitive impairment (such as thought disorder, loosening of associations, attention, autism).

The current idea is that schizophrenia occurs with a wide range of symptoms. One way to classify these symptoms is to divide them into positive symptoms (including hallucinations, delusions, bizarre behaviour, derailment, flight of ideas, and illogicality) and negative symptoms (flattened affect, impaired attention, poverty of speech, apathy, and asociality).

There are currently two main diagnostic systems for diagnosing schizophrenia. These are the American Psychiatric Association's (APA) Diagnostic and Statistical Manual for Mental Disorders (DSM) and the World Health Organisation's (WHO) International Classification of Diseases and Causes of Death (ICD). Whether a person is considered to have schizophrenia depends on the diagnostic system used. For example, the DSM system, which is in addition to clinical use is used for research purposes, requires the duration of symptoms for at least six months (APA 1994), whereas one-month duration of symptoms is sufficient for ICD diagnosis of schizophrenia (WHO 1993). Due to this difference, it may be assumed that the DSM diagnosis of schizophrenia includes more severely ill individuals. The currently used DSM-IV (APA 1994) and ICD-10 (WHO 1993) criteria for schizophrenia are presented in Figures 1 and 2.

**Characteristic symptoms***At least one of the following:*

- Bizarre delusions
- Third-person auditory hallucinations
- Running commentary

*OR two or more of the following:*

- Delusions
- Hallucinations
- Disorganised speech
- Grossly disorganised behaviour
- Negative symptoms

**Duration**

- 1 month of characteristic symptoms
- With 6 months of social or occupational dysfunctioning

**Exclusion criteria**

- Schizoaffective or mood disorders
- Direct consequence of substance use or general medical condition
- Pervasive developmental disorders

**Fig. 1. DSM-IV diagnostic criteria for schizophrenia (APA 1994).****Characteristic symptoms***At least one of the following:*

- Thought echo, thought insertion/withdrawal/broadcast
- Passivity, delusional perception
- Persistent bizarre delusions
- Third-person auditory hallucinations, running commentary

*OR two or more of the following:*

- Persistent hallucinations
- Thought disorder
- Catatonic behaviour
- Negative symptoms

**Duration**

- More than 1 month

**Exclusion criteria**

- Schizoaffective or mood disorders
- Drug intoxication or withdrawal
- Overt brain disease

**Fig. 2. ICD-10 diagnostic criteria for schizophrenia (WHO 1993).**

## 2.1.2 Epidemiology

### 2.1.2.1 Frequency

Schizophrenia exists all over the world, with varying prevalence in the range of 1.4-4.6 per 1,000 population in risk and incidence of 0.17-0.54 per 1,000 population per year, depending for example of the diagnostic system used, and the age, gender and ethnicity of the sample (Jablensky 2003). In a large systematic review of 188 studies published in 1965-2002 across the world the point prevalence of schizophrenia was estimated to be 4.6/1,000 persons (10%-90% quantile 1.9-10.0), and life-time prevalence 4.0/1,000 persons (1.6-12.1) (Saha *et al.* 2005), both of these numbers basing on different studies. The average prevalence of schizophrenia in Finland was 1.3% in the Mini-Finland Health Survey conducted in 1978-1980 (Lehtinen *et al.* 1990). In a register-based study of cohorts of all births between 1940-1969 in an isolate in north-eastern Finland the prevalence was 1.5% by registers and the estimated prevalence by diagnostic interviews in the same sample was 0.7–1.2% (Arajärvi *et al.* 2005).

The results regarding the incidence of schizophrenia are inconsistent. In a large meta-analysis of 161 studies across the world published in 1965-2001 the median incidence rate of all studies was 15.2/100,000 person-years (the 10% and 90% quantiles 7.7-43.0/100,000 person-years (McGrath *et al.* 2004). Thus there was an over 5-fold difference in incidence across the studies. A Finnish study of cohorts born in 1954–1965 shows a declining rate (Suvisaari *et al.* 1999). A care-based cohort study conducted in Canada, however, showed increasing incidence of schizophrenia from 1989 to 1998 in cohorts born in 1975-1985 (Bray *et al.* 2006). In this sample 1.3% of the individuals were born outside Canada and the authors conclude that migration does not explain the findings. There is also a suggestion of unchanged rates of incidence of schizophrenia during a period of 114 years in a sample from the UK (Nixon & Doody 2005).

### 2.1.2.2 Risk factors and aetiology

There are several plausible genetic and environmental risk factors and markers of increased risk for schizophrenia (see reviews of Suvisaari 2004, Isohanni *et al.* 2005, Mäki *et al.* 2005, Isohanni *et al.* 2006). The risk of schizophrenia is found to be higher in males compared to females, the median male/female rate ratio being 1.40 (Kirkbride *et al.* 2006). The highest risk to develop schizophrenia is in early adulthood. For males the illness usually begins at 15-25 years and for females at age 15-29. Females also have another peak in incidence at the time of menopause (Häfner 2003).

According to meta-analyses the incidence of schizophrenia is lower in developing countries (Saha *et al.* 2006). Migrants have shown increased rates of schizophrenia. In the large, representative study of Kirkbride *et al.* (2006) the migrant/native-born rate ratio was 4.6. Urban birth (Haukka *et al.* 2001) may also increase the risk.

There are some genetic, biological and developmental factors that increase the risk of schizophrenia, may be markers of increased risk, or may even have a causal role in the aetiology of the disorder. An adverse event during pregnancy and delivery, central

nervous system infections in childhood and predisposition to infections prenatally, early neuromotor abnormalities and developmental delays, premorbid cannabis use, and poor premorbid cognitive and scholastic performance have been associated with increased risk of schizophrenia. (Isohanni *et al.* 2005, Mäki *et al.* 2005)

Much of the aetiology of schizophrenia is explained by a genetic component. It is suggested that even 80% of heritability is explained by genes, which means that genes account for 80% of the variation between individuals in certain environment. Although various candidate genes for developing schizophrenia have been identified, the genes underlying the disorder still have not been found, and no linkage appears to be consistently replicable across large studies. It may be that the susceptibility for schizophrenia may be caused by several genes and their interaction together and also with the environment. (Riley *et al.* 2003)

There is support for the influence of environmental factors (e.g., communication deviance in the family) and the gene-environment interplay in the development of schizophrenia (Tienari *et al.* 2004, Wahlberg *et al.* 2004). For example schizophrenia in offspring has been linked with problems in mothers' general understanding and management of their children (Jones *et al.* 1994). On the other hand, having a positive relationship with both the mother and the father might be protective against schizophrenia among high-risk children (Schiffman *et al.* 2002). There is also suggestion that unwantedness of pregnancy (Myhrman *et al.* 1994) and early parental loss (Agid *et al.* 1999) increase the risk of schizophrenia.

The aetiology of schizophrenic psychoses remains poorly understood even though one hundred years ago Kraepelin and Bleuler reported that children destined to suffer from schizophrenia developed differently from their peers. Nowadays schizophrenia is considered to be based on neurodevelopmental deficits, beginning as early as in utero and early childhood, and becoming manifest in adolescence and early adulthood (Weinberger 1987, Lieberman 1999, Ashe *et al.* 2001). This hypothesis is supported by observations of increased rates of obstetric complications, intrauterine infections, minor physical anomalies and premorbid neurological and behavioral abnormalities (Weinberger & Marenco 2003), brain structural and functional abnormalities (Wright *et al.* 2000, Liddle & Pantelis 2003) as well as changes in neurotransmitters (Moghaddam & Krystal 2003) among the individuals with the disorder.

It is hypothesised that schizophrenia is a primary brain disease caused by a structural defect in early life, interacting with maturational events, such as neuronal precursor and glial proliferation and migration, dendritic and axonal proliferation, myelination of axons, programmed cell death and synaptic pruning (Lieberman 1999). A neurodevelopmental insult is considered to cause altered morphology and cytoarchitecture and thereby a deficiency in the modulatory capacity of neurons (Duncan *et al.* 1999). To be more specific, it is suggested that subtle abnormalities of cortical development (especially limbic and prefrontal cortices and their connections) increase the risk of developing schizophrenia in adolescence or early adulthood. Deviant dopamine function of prefrontal cortex is proposed to cause both the emergence of negative and positive symptoms and cognitive impairments in schizophrenia. The emergence of schizophrenic symptoms is thus considered to be a result of an interaction of the early developmental deviations with normal maturation events of early adult age. In addition, abnormalities of the circuitry

between cortical regions and cerebellum leading to misconnection is suggested to be one cause. (Weinberger & Marenco 2003)

In spite of evidence supporting neurodevelopmental dysfunctions as a cause for schizophrenia, the entirety of the aetiology of schizophrenia is more than vague. If the illness is caused by neurodevelopmental insult, with interaction during the maturation process of brain, it should end when the maturation of the brain ends in early adulthood. How then to explain features such as the often deteriorating course of illness, recovery of some individuals, and the effects of medication on illness course? Recent research (eg. Cahn *et al.* 2002) gives support also to neurodegenerative processes and demonstrate progress in brain morphology during the illness course. However, many individuals with schizophrenia do not have any evident biological indicators, and it is suggested that for some patients the etiology of the illness is psychological (Bebbington & Kuipers 2003).

## 2.2 Other schizophrenia spectrum disorders

Schizophrenia, and schizophreniform, delusional, and schizoaffective disorder form the schizophrenia spectrum (Wing & Agrawal 2003). Sometimes schizotypal and paranoid personality disorders as well are included in this class (O'Flynn *et al.* 2003). In schizophreniform disorder there are similar symptoms as in schizophrenia, but their duration is, however, too short to fulfil the criteria for schizophrenia. In the follow-up many cases fulfil the diagnostic criteria of schizophrenia (Moilanen *et al.* 2003). In delusional disorder persistent, non-bizarre delusion exists, but the behaviour is not otherwise obviously bizarre. If there are hallucinations, they are not prominent. Schizoaffective disorder was first introduced as a subtype of schizophrenia, but nowadays it forms its own entity in ICD and DSM classifications. Schizophrenic and mood-related symptoms are prominent in this disorder, and a period of psychotic symptoms without affective ones must exist. Schizotypal and paranoid personality disorders have transient psychotic symptoms, but with quick return to previous level of functioning between illness periods. An organic brain disorder should be excluded for to set diagnosis of all the illnesses mentioned above.

The other schizophrenia spectrum disorders are not as widely studied as schizophrenia, perhaps partly due to the low incidence and divergent definitions of these disorders. In addition, studies often combine schizophrenia and other schizophrenia spectrum disorders and do not show the results for these disorders separately. However, as an epidemiological perspective, the lifetime prevalence of schizoaffective and schizophreniform disorder in a Finnish genetic isolate in 1998 was 0.4% (Arajärvi *et al.* 2006). The risk factors for all schizophrenic psychoses are often considered to be the same, and have been described earlier in this thesis. In general, the course of illness of schizoaffective, delusional and schizophreniform disorders is considered less severe when compared to schizophrenia (Achte 1967, Kuusi 1986).

The association of schizophrenia with other schizophrenia spectrum disorders varies. Whereas schizophreniform disorder and schizotypal and paranoid personality disorders are supposed to relate genetically to schizophrenia, most delusional disorders and schizoaffective disorder are considered less related to schizophrenia. (APA 1987)

### 2.3 Treatment of schizophrenia

The treatment of schizophrenia usually includes drug treatment (antipsychotics and, depending on the symptoms, antidepressants and/or anxiolytics as well), psychotherapy (often supportive psychotherapy), social skills training and work rehabilitation and education of patients and their significant others. In addition, monitoring of treatment effectiveness and somatic health (e.g. blood glucose, lipids, BMI) is part of adequate treatment of schizophrenia patients. (Lehman *et al.* 2004, Finnish Psychiatric Association 2001). Nowadays the focus of treatment is on out-patient services. However, since schizophrenia is a severe and often disabling disease, many of the patients need hospital treatment, at least at the beginning of full-blown psychosis.

The treatment of other schizophrenia spectrum psychoses (schizophreniform, delusional and schizoaffective disorder) is very similar to schizophrenia, but may vary depending on symptoms and the length of the illness period.

### 2.4 Outcome and its predictors in schizophrenia

Outcome, course of illness and prognosis of schizophrenia have heterogeneous definitions. They can include for example psychiatric or somatic health and outcome. They can be seen from different viewpoints, such as clinical psychiatric symptoms, functioning (such as social abilities, working ability), quality of life, service utilisation, somatic or psychiatric (co)morbidity and death as an extreme of outcome. The focus of this thesis is on outcomes related to psychopathology, service utilisation and social and occupational functioning, and their predictors. Thus, quality of life, mortality and psychiatric and somatic comorbidity will be only briefly described in the following paragraphs.

In a sample of 404 schizophrenia patients from five different European countries the illness had a huge impact on patients' ordinary life (Thorncroft *et al.* 2004). Patients had decreased quality of life compared to general population, 65% of the patients were single and they had unmet needs regarding daytime activities, company and intimate relationships, psychotic symptoms, psychological distress, and information about the illness. The authors concluded that psychiatric services were ineffective in managing the personal impact of schizophrenia, especially upon work, home and family life.

Persons with schizophrenia have excess mortality with standardised mortality ratio (SMR) of 151, and suicides and accidents play a major role as causes of death (Brown 1997, Harris & Barraclough 1998, Palmer *et al.* 2005). Schizophrenia patients had 2.25 times the risk of death (adjusted with age, sex, education, lifestyle factors and somatic health) compared to other subjects in the Mini Finland Health Study (Joukamaa *et al.* 2006). In addition, the amount of neuroleptic treatment used was positively related to increased risk of death. On the other hand, Tiihonen *et al.* (2006) studied a more recent large register-based sample of schizophrenia and schizoaffective patients and found that patients not taking any antipsychotics had 12 times the risk of dying compared to those who used antipsychotics. In the Northern Finland 1966 Birth Cohort the risk of death in

schizophrenia was 7 times higher than in healthy population, and the leading cause of death among the patients was suicide (Alaraisänen *et al.* manuscript)

Schizophrenia subjects also have high comorbidity of other mental illnesses, especially substance abuse (Negrete 2003), but physical illnesses as well (Goff *et al.* 2004). In the NFBC 1966 schizophrenia patients showed increased blood lipid levels even by the age of 32 years, especially among those using antipsychotic medication, as well as increased risk of metabolic syndrome (Saari 2005).

### ***2.4.1 Definitions of good and poor outcome and recovery***

Outcomes are described as all results that may occur from exposure to causal factor, or from therapeutic or preventive interventions. In general, outcome includes all changes in a person's health that are consequences of dealing with the health problem. (Last 2001) It can be described as a state of syndrome at study end, but also as a state assessed at the last stage of illness or longitudinally over specific intervals (e.g. 5 to 10 years) (Bleuler 1978). Thus, it can be measured both cross-sectionally and longitudinally. Several descriptions for good and poor outcome are presented. For example, good outcome can be seen as improvement of functioning and lack of symptoms, but also, more broadly, as a stable, non-deteriorating course of illness (Ruggeri *et al.* 2004).

Until recent decades, the outcome studies of schizophrenia focused mainly on two dimensions: service utilisation (e.g. the number of hospital episodes) and psychopathology, although during the 1980s a few large outcome studies with multiple outcome measures were presented (McGlashan 1984, Harding *et al.* 1987, Leff *et al.* 1992). Nowadays the multidimensional viewpoint in measuring outcome in schizophrenia is getting stronger. In addition to psychopathology and social and occupational functioning, met and unmet needs for treatment, quality of life and satisfaction with services are considered important. In addition, the importance of the distinction between staff-rated (symptoms and functioning) and patient-rated (needs and quality of life) outcomes is presented. (Ruggeri *et al.* 2004) The trend of multidimensional measuring is, however, still developing.

The course of illness is studied either cross-sectionally, focusing on current status (around the time of examining) or longitudinally prospectively following up or retrospectively following back the sample. Usually course of illness indicates more longitudinal measure compared to definition outcome. Varying types of illness course in schizophrenia have been presented, ranging from four to as many as 79, without any standardised definition. According to a review by Marengo (1994), several patterns of the course of illness exist, first presented by Kraepelin (1909) and Bleuler (1911) and after that by several researchers. Course descriptions are included in diagnostic systems as well. For example, the DSM system include schemes for course classification. The course of illness may be divided into short-, medium-, and long-term course. (Häfner & an der Heiden 2003)

In addition to being an individual healing process towards meaningful life, recovery may be seen as an outcome, a type of end point of the course of illness when the patient's health is totally regained (Resnick *et al.* 2005). Individuals with schizophrenia have

different experiences and perspectives of recovery (Chadwick *et al.* 2003). According to the Substance Abuse and Mental Health Services Administration of the US Department of Health and Human Services the ten fundamental components of mental health recovery are self-direction, individuality, empowerment, holisticity, non-linearity, strength, peer support, respect, responsibility, and hope (www.samhsa.gov). This viewpoint addresses the importance of the individual. It is difficult to separate recovery from remission. Recently, the Remission in Schizophrenia Working Group has proposed consensus-defined criteria for symptomatic remission in schizophrenia (Andreasen *et al.* 2005). These criteria consider symptoms with diagnostic and outcome significance from major symptom domains in schizophrenia and they require at least 6 months' duration for remission. Thus, remission is more a lack of symptoms, for a certain period, rather than gaining improved functioning, for example. Recovery is suggested to occur when remission has lasted for a certain period of time (although no time limit is presented). Recently, when considering patient-rated recovery or "user-perspective" (Ruggeri *et al.* 2004), recovery can be seen as a return to a meaningful and fulfilling life. Unfortunately there is no approved operationalised concepts for good and poor outcome or recovery in schizophrenia.

### ***2.4.2 Good and poor outcomes in schizophrenia***

The amount of good and poor outcome in schizophrenia is not unambiguous, but some generalisations can be made: According to meta-analysis of 320 studies published in 1895-1992, approximately 40% of patients are considered as having a good outcome (Hegarty *et al.* 1994) by using several definitions of good outcome. In addition, a recent systematic review about outcome studies of first-episode psychosis summarises that 42% of patients have good outcome, 35% have moderate and 27% have poor outcome (Menezes *et al.* 2006). Also in this study several definitions of good and poor outcomes were accepted. There is also a suggestion that the prognosis of schizophrenia became worse after the 1970s (Hegarty *et al.* 1994). Schizophrenia has negative effects on work ability. According to the review, only 10-20% of patients are employed in European countries (Marwaha & Jonsson 2004).

There are several classic and important outcome studies that have been reviewed by McGlashan (1988), Angst (1988), and Jobe & Harrow (2005). Bleuler (1978) studied 208 schizophrenia patients (diagnosed by Bleuler's diagnosis that is more broad than e.g. DSM-IV diagnosis) admitted to a psychiatric hospital in Switzerland in 1942-1943 and found that after 5-20 years of follow-up, 20-30% had "recovered" (i.e., were not hospitalised) and approximately 20% had poor outcome. Similarly, Ciompi (1980) followed 289 schizophrenia patients (Bleuler's diagnosis) admitted from the beginning of the 20th century to 1962 in Switzerland and found after 37 years that 27% had remission (in terms of global functioning) and 18% had a deteriorating course. McGlashan (1984) followed 163 chronically ill, medication-resistant DSM-III schizophrenia patients discharged from Chestnut Lodge private hospital in the US between 1950 and 1975. After 15 years of follow-up (global outcome scale) 6% of the patients had recovered, 8% had good outcome, 22% moderate, and 23% had marginal outcome, while 41% were continuously incapacitated. In the Vermont State Hospital study in the US Harding *et al.*

(1987) studied 168 DSM-I schizophrenia patients who participated in a rehabilitation programme between 1955 and 1960. After 20 years of follow-up (when the mean age of the subjects was 61 years) the outcomes were surprisingly good: 61% were employed and 68% showed minimal or no symptoms. One reason for good outcomes in this sample may be the use of rehabilitation and community placement program. Huber *et al.* (1980) followed 502 schizophrenic patients (diagnosed by Schneider's and Bleuler's criteria which are broader than e.g. DSM-IV criteria) admitted to a psychiatric hospital in Germany in 1945-1959. After on average 22 years of follow-up, 22% of patients showed complete remission of symptoms and 35% showed poor outcome. Leff *et al.* (1992) studied altogether 531 schizophrenia patients from eight centres in different countries in an International Pilot Study of Schizophrenia. After 5 years of follow-up the probability of remission varied from 6 to 42%, and good social outcome from 50 to 87%. The problem with these studies is that most were based on patients of selected hospital, and thus the results cannot be generalised to general population. In addition, the studies were often retrospective and had high attrition rate.

Unselected, population-based samples are important if we want to obtain valid results regarding outcomes in schizophrenic psychoses. Studies of this kind are presented in Table 1. According to the studies in Table 1, the outcome and course of illness is heterogeneous. After at least two years of follow-up 10-16% were clinically recovered or in remission, 30-43% had good clinical outcome, 20-74% were employed and 26% had good global outcome, and an additional 39% were globally in moderate condition. 21-72% of patients had poor clinical outcome (e.g. were symptomatic), 56-73% were pensioned or on sick leave, and 35% had poor global outcome. It should be noted that the follow-ups, study areas as well as measures and criteria for outcome and diagnoses vary between the studies.

*Table 1. Studies and results concerning outcomes in schizophrenic psychoses. Only follow-up studies with structured diagnostics, population based sample and presenting numbers of good and poor outcome cases are included.*

Authors (year)	Study design and sample	Diagnostic system	Length of follow-up	Measures of outcomes and analysed predictors	Results	Comments
Biehl <i>et al.</i> (1986)	Germany All first episode in- and outpatients in defined area during one year Ages 15-44 years	ICD	5 years	Outcomes: Symptoms (by PSE), impairment, social disability	26% good, 39% intermediate, and 35% poor outcome 22% psychotic 49% no diagnosable psychiatric condition	Strengths: First-episode patients (i.e. more homogeneous group) 89% of patients successfully followed-up Multidimensional outcome
Helgason (1990)	Iceland Prospective cohort study 107 first-episode schizophrenia in- or outpatients 82 cases at the end of follow-up	ICD 8/9	6-21 years	Outcomes: Mental state, ability to work, social relationships	4% had committed suicide 30% good outcome (no or minor symptoms, no treatment) 33% employed 21% poor outcome (severe symptoms, inpatient treatment) 67% not employed	Strengths: Multidimensional outcome First-episode patients Limitations: Outcome could not be assessed for 23% of patients
Eaton <i>et al.</i> (1992)	Australia, UK, US, Denmark Altogether 25 913 (46-62% males) first-episode schizophrenia patients detected in 1961-1988	ICD-8 DSM-I	Over 5 years	Outcomes: Readmissions	50-90% were re-hospitalised at some point, most of the re-admissions occurring during the first 5 years of illness At 2-year follow-up 35-65% re-hospitalised	Strengths: Very large sample First episode patients Limitations: Register based diagnoses (validity may not be as good as in interview based studies with operationalised, researchers' made diagnosis) The sample may partly overlap with Sytema <i>et al.</i> (2002)
Suvisaari <i>et al.</i> (1998)	Finland All patients with schizophrenia or schizoaffective disorder born in 1950-1969 16 687 cases and 15 733 relatives	ICD-8 DSM-III-R	Several years, not described	Outcomes: Annual duration of hospitalisations, disability pensions, mortality Predictors: Familial loading, age of illness onset	High familial loading was associated with early age of illness onset, long hospitalisation, increased risk of disability pension.	Strengths: Very large sample Limitations: Register based diagnoses

Table 1. (Continued)

Authors (year)	Study design and sample	Diagnostic system	Length of follow-up	Measures of outcomes and analysed predictors	Results	Comments
Goater <i>et al.</i> (1999)	UK Cases making first contact to psychiatric services between 1991 and 1992 in defined area of London 79 cases with psychosis, most having schizophrenia Aged 16-54 years	ICD-9 DSM-III-R	5 years	Outcomes: Symptoms (by PSE, SCL, SANS) Predictors: Ethnicity of the patient	10% of all cases completely recovered in terms of symptoms Black patients had more symptoms than other groups	Strengths: First-episode cases Limitations: Schizophrenia cases of analysed separately from other disorders
Häfner & an der Heiden (1999)	ABC-study in Germany 115 first-episode schizophrenia cases Age range 12-59 years	ICD	5 years	Outcomes: Amount of symptoms (PSE, PIRS, SANS), disability (DAS) Predictors: Social development and illness behaviour at the end of prodromal phase, sex, age of illness onset, depressive and negative symptoms, type of onset	58% of women and 35% of men were able to earn their living Social development around the illness onset predicted functioning (earning living)	Strengths: Thorough assessment of outcomes and predictors Limitations: Analysed cases were only a subsample of the whole sample

Table 1. (Continued)

Authors (year)	Study design and sample	Diagnostic system	Length of follow-up	Measures of outcomes and analysed predictors	Results	Comments
Harrison <i>et al.</i> (2001)	Combination of 18 incidence and prevalence cohorts from several different countries 644 schizophrenia patients Mean age at follow-up 41-51 years	ICD-10	15-25 years	<p>Outcomes: Symptoms (PSE, SANS, PIRS-2), functioning (DAS, GAF), course of illness (LCS)</p> <p>Predictors: Age at first contact, gender, marital status, social contacts, history of substance use, amount of symptoms</p>	<p>16.3% recovered 41-43% not psychotic during last 2 years 57-74% working during last 2 years 11.6% had spent majority of the last 2 years in institutional setting 33.6% continuously ill during the last 2 years SMR 0-8.9</p> <p>Short time spent in psychosis during the first 2 years of illness was best predictor of good outcome (less symptoms and disability, best overall course of illness). Young age at study entry predicted more symptoms. Cases without national health insurance had less disabilities. Family involvement in treatment, blunted affect and drug use were associated to more severe disability.</p>	<p>Strengths: Sample rather large Combination of several cohorts around the world. Also reports of individual cohorts are published, but not described in this table. Multidimensional outcome measures.</p> <p>Limitations: Loss to follow-up 10-30% Data quality control problematic, as usually in multicenter studies The original diagnoses were not operationalised.</p>
Ran <i>et al.</i> (2001)	China Data collected in 1994 Randomly selected individuals in the community screened (123 572 individuals) 510 cases with schizophrenia found, of whom 156 without treatment and followed up Mean age for 156 non-treated cases 48 years	Chinese Classification and Diagnostic Criteria of Mental Disorders ICD-10	2 years	<p>Outcome: Symptoms</p>	<p>13% recovered (criteria not defined) 11% complete remission 12% partial remission 2% relapsed 72% marked symptoms 6% deteriorating illness</p>	<p>Strengths: Truly population based (screening of community) Analysed natural course of schizophrenia</p> <p>Limitations: Outcome measures and criteria not fully described Only 61% of original untreated group analysed</p>

Table 1. (Continued)

Authors (year)	Study design and sample	Diagnostic system	Length of follow-up	Measures of outcomes and analysed predictors	Results	Comments
Svedberg <i>et al.</i> (2001)	Sweden Data collected in 1991-1992 First-episode schizophrenia cases (N=43) treated as inpatients and outpatients in defined geographical area	DSM-IV	5 years	Outcomes: Clinical recovery (patient had regained working ability and was not in need of psychiatric care), sick leave	9% recovered 73% on sick leave	Strengths: First-episode patients Reliable, consensus diagnoses
Systema <i>et al.</i> (2002)	Netherlands, Australia, Italy 11 233 cases (49-57% males) with schizophrenia and related disorders (including also psychosis not otherwise specified) Detected from registers in 1981-1996 Mean ages 36-39 years	ICD-10	0-15 years	Outcomes: Readmissions to hospital Predictors: Length of first hospitalisation, age at first contact to services, the use of day patient services	0.9%-3.3% of patients became revolving door patients (i.e. at least 4 admissions during follow-up and mean no. of admissions per year at least two) Older age, longer first hospitalisation, and no day-patient care decreased the risk of readmissions.	Strengths: Very large sample First-episode patients Limitations: Only patients with at least one hospitalisation were included Heterogeneous group of psychoses Register diagnoses The sample may partly overlap with Eaton <i>et al.</i> (1992)
Rosen & Garety (2005)	UK Sample collected by utilising the Oxford Record Linkage System covering whole defined geographical area Patients with a first contact due to psychotic disorder in 1980-1991 with a primary diagnosis of non-affective psychosis 436 patients	ICD-9	6 years	Outcome: Hospitalisations	15.6% had only single episode of illness 31.2% had multiple episodes with persistent symptoms and no return to normality 6.9% single continuing episode 5.3% had died	Strengths: Valid, consensus diagnostics Outcome could be assessed for 90% of the sample

Table 1. (Continued)

Authors (year)	Study design and sample	Diagnostic system	Length of follow-up	Measures of outcomes and analysed predictors	Results	Comments
Miettinen <i>et al.</i> in press	The Northern Finland 1966 Birth Cohort 113 (59% males) cases with schizophrenic psychoses	DSM-III-R	Mean 11 years	Outcomes: Occupational status Predictors: Gender, premorbid factors, familial risk for psychosis, length of first psychiatric hospitalisation, time spent in psychiatric hospital, educational level	56% on disability pension 44% not on pension 20% worked at least 50% of the time Being married or cohabiting, later age of illness onset and being male predicted good outcome (not being pensioned).	Strengths: Valid diagnostics Large amount of and prospectively collected predictor data Limitations: Outcome assessed by rough register information

DAS = Disability Assessment Scale, GAF = Global Assessment of Functioning, LCS = Life Chart Schedule, PIRS = Psychological Impairment Rating Scale, PSE = Present State Examination, SANS = Schedule for Assessment of Negative Symptoms, SCL = Syndrome Checklist

### 2.4.2.1 Finnish outcome studies

Prognostic studies have a strong tradition in Finland (Achte 1967, Niskanen & Achte 1972, Salokangas 1978, Achte *et al.* 1980, Kuusi 1986, Pakaslahti 1992). Achte *et al.* (1986) presented the results of a series of first admission cohorts in Helsinki in 1950 and 1960 (Achte *et al.* 1967), 1965 (Niskanen & Achte 1972), and 1970 (Achte *et al.* 1980). Each of these samples included 100 schizophrenic psychosis subjects (diagnosed with Scandinavian concept of schizophrenia that is more broad than DSM-IV criteria) who were followed up for 5 years. As a result, the proportion of persons on disability pension varied from 13% to 35%, with a higher frequency in the later cohorts. At the end of the follow-up, 6-22% of the cases were in need of hospital treatment, the amount decreasing in later cohorts. The authors concluded that the different results between the cohorts may be due to changes in treatment and the health care system and development of the social security system. (Achte *et al.* 1986) Concerning the rate of recovery, complete recovery occurred in 2%, and after a five-year follow-up, in 8% of schizophrenia cases. In schizophreniform psychoses, corresponding recovery rates were 62% and 83%. Recovery was defined as the absence of psychotic symptoms, ability to work at the same level as before getting ill and being employed. (Achte 1967)

In the latest cohort (DSM-III diagnosis) of the same series in Helsinki, Kuusi (1986) found that 27.7% of schizophrenia cases recovered (without any symptoms), whereas 52.5% of individuals with schizophreniform disorder had the same outcome. 8.5% of schizophrenia and 12.5% of schizophreniform cases had the worst outcome (severe psychotic symptoms).

Salokangas (1978) studied 50 patients with nuclear schizophrenia and 31 with schizophreniform psychosis, first admitted to hospital in 1965-1967. After a 7.5-year follow-up 48% of these subjects were without psychotic symptoms and 33% were not able to work. Pakaslahti (1992) followed up 133 schizophrenia or schizophreniform disorder cases for 5.5 years. At the end of the study he found 45% of them to be on disability pension.

As a result of the Finnish National Schizophrenia Project in 1981-1987, that aimed to reduce the number long stay patients in hospitals and to develop and increase community-services, the number of hospital beds decreased from 4.1 to 1.9 per 1,000 inhabitants during the period of 1982-1992 (Tuori *et al.* 1998). A national project on Discharged Schizophrenic Patients was launched in Finland in 1987 to evaluate the effects of this deinstitutionalisation process. This study analysed the outcome of thousands of discharged DSM-III-R schizophrenia patients in several hospital districts in Finland in 1982-1994 (Salokangas *et al.* 2002, Honkonen *et al.* 2003). According to this study, deinstitutionalisation did not have an effect on mortality (Salokangas *et al.* 2002), but discharged patients seemed to be in worse condition in later cohorts (after the number of hospital beds was decreased) (Honkonen *et al.* 2003). After three years of follow-up 7% of patients were without symptoms, had no disabilities and were not in treatment (Honkonen *et al.* 2003).

### **2.4.3 Patterns of hospitalisations**

Psychiatric hospitalisation is still an important treatment method and a powerful tool in first aid, protection, careful evaluation and intensive care of some acutely ill, difficult psychosis patients. Hospitalisation may not always correlate with the severity of illness. It may be a result of complex interaction between several variables, such as patient-related variables, the structure of organizations, and the availability, number and functioning of services (Oiesvold *et al.* 2000). Although modern hospital treatment tends to avoid the negative effects of traditional custodial hospital care, it may still cause disengagement from the “normal” social environment, stigmatisation and decrease the quality of life – and give rise to costs. The prevention of re-hospitalisations in particular is therefore an important goal in the treatment of schizophrenia.

Eaton *et al.* (1992, Table 1) studied patients initially hospitalised for schizophrenia. They found that the rate of re-hospitalisation varied from 50% to 90% in different countries, most of the re-admissions occurring during the first 5 years of illness. At 2-year follow-up 35-65% of patients were re-hospitalised. The proportion of schizophrenia patients with frequent psychiatric hospitalisations (also called “revolving door” patients) varies greatly depending on the criteria, from 0.9% (Sytema *et al.* 2002) to 52% (Gastal *et al.* 2000). According to Rosen & Garety (2005) only 16% of patients have single episode of illness (Table 1).

One major goal in treatment of schizophrenia is to prevent relapses, or to postpone or make them milder. Re-hospitalisation is a marker of problems, usually a relapse. Almost 90% of individuals with schizophrenia suffer a relapse (Robinson *et al.* 1999). In principle, the ability to predict re-hospitalisation could give possibilities to influence or even prevent some of them. Hospitalisations in psychiatric disorders have been studied quite extensively; however, this topic is not so well known with regard to schizophrenia patients and general population sample. In order to develop better treatment systems and to ensure adequate hospital treatment of the patients, for example, it is important to know the patterns of and factors related to hospitalisation in schizophrenic psychoses as well.

### **2.4.4 Recovery in schizophrenia**

When someone becomes ill for the first time it is a clinical challenge to estimate chances for recovery, and to say how likely it is that patients will return to pre-illness levels of functioning.

It was Emil Kraepelin who first noted the poor prognosis of schizophrenia in 1898. According to Kraepelin (1909), only 2.6% of patients had a full and permanent recovery, while 13% recovered for a limited period. Eugen Bleuler (1911) broadened the diagnostic definition of schizophrenia, including less severe clinical conditions in it. Although he thought that schizophrenia did not necessarily have a deteriorating course, he wrote that few patients ever recovered fully, and that he had actually not seen one himself.

During the decades after Kraepelin and Bleuler, reports describing prognosis of schizophrenia became more favourable. Studies showed variable recovery or remission rates as high as almost 60% (McGlashan 1988, Ram *et al.* 1992), but the problem was

inconsistent and unclear definition of recovery. As described earlier in this thesis, the definition of recovery should include multiple outcome dimensions and the length of follow-up should be long enough. Outcome studies with proper definition of recovery (assessing both clinical and social dimensions, and both or either of these dimensions assessed for a period of at least two years) are presented in Table 2. According to these studies the probability of recovery varies from 8 to 27%. As can be seen from Table 2, recovery in the only population-based sample was 16.7%.

Some of the studies in Table 2 included also other schizophrenia spectrum psychoses, but unfortunately all of those did not analyse recovery for this group separately. In one study (Angst & Preisig 1995) the amount of recovered individuals with schizoaffective disorder was 16-24%.

*Table 2. Studies and results concerning recovery from schizophrenic psychoses. Only observational studies with sample of at least 15 cases; definition of recovery including both clinical and social dimensions, of which either or both have been followed up for at least two years were included. Trials or intervention studies were excluded.*

Authors (Year)	Study design and sample	Used diagnostic system	Follow-up	Criteria for recovery (all the mentioned criteria must have been fulfilled)	Results	Comments
Stenberg (1948)	Sweden Data collected in 1915-1929 583 (53% males) first-episode and 599 (49% males) patients with other than first-episode of schizophrenia	Not described	10 years	Recovered and able to work Recovered during more than 2 years	17.1% (200/1168) recovered	Strengths: Low rate of loss to follow-up (only 1.2% of the sample) Large sample Limitations: Part of the sample not first-episode patients. Hospital based sample, not generalisable to general population. The used diagnostic system not described.
Hemisiz (1966)	Poland Data collected in 1956 At baseline 249 (43% males) patients Mean age at base line 32 years, range 24-39 years	Not described	7 years	Making good social adjustment, spent short time in hospital, but soon discharged and never returned	24.7% (44/178) recovered	Strengths: First-episode patients Limitations: The used diagnostic system not described. Hospital based sample, not generalisable to all schizophrenia patients.
Huber <i>et al.</i> (1980)	Germany Data collected in 1945-1959 At base line 758 schizophrenia patients	Schneider's and Bleuler's criteria	Mean 6 years	Complete remission for 10 years or more Social recovery	27% (135/500) recovered	Strengths: Large sample Limitations: Hospital based, selected sample. Not generalisable to all schizophrenia patients Not first-episode sample. Outcome could not be assessed for 34% of the original sample (though 19% of the original sample were dead).

Table 2. (Continued)

Authors (Year)	Study design and sample	Used diagnostic system	Follow-up	Criteria for recovery (all the mentioned criteria must have been fulfilled)	Results	Comments
Angst & Preisig (1995)	Switzerland Hospital admissions in 1959-1963 and 114 bipolar schizoaffective patients (12-31% males) Ages at follow-up 66-69 years	DSM-III-R and ICD-9	Median 27 years after illness onset	GAS $\geq 61$ Without relapse within last 5 years	Unipolar schizoaffective patients: 24% (12/49) recovered Bipolar schizoaffective patients: 16% (18/114) recovered	Strengths: Long follow-up Limitations: Not first-episode sample Hospital based sample Over half of the patients had died by the time of follow-up assessment.
Obembe <i>et al.</i> (1995)	Nigeria Range of ages at base line 15-74 years At follow-up 22 schizophrenia patients	ICD	2 years	No social impairments Maintaining occupation No symptoms No readmissions during 2 years	9% (2/22) of patients recovered	Limitations: Hospital based selected sample of relatively chronic patients. Not generalisable to general population. Small sample size. Number of schizophrenia patients at base line not described. Short follow-up
Vazquez-Barquero <i>et al.</i> (1999)	Spain At base line 86 (50% males) patients with schizophrenia with first contact to mental health services at defined geographic area	PSE-GATEGO	3 years	Good social adjustment (DAS) No clinical symptoms during follow-up (SANS/SAPS)	22.4-23.7% (17-18/76) recovered	Strengths: All first-episode patients Limitations: Relatively short follow-up
Harrison <i>et al.</i> (2001)	Combination of 14 incidence cohorts from several different countries Study began in 1970's At base line 502 (51% males) schizophrenia patients Mean age at follow-up 41 years	ICD-10	15 years	4 points (=recovered) on Bleuler rating of recovery and GAF-D points >60 and No treatment episodes during last two years	16.3% of schizophrenia patients recovered	Strengths: Sample rather large Not selected sample. Generalisable to all schizophrenia patients. Combination of different cohorts around the world. Also reports of individual cohorts are published, but not described in this table. Limitations: Loss to follow-up 10-30%

Table 2. (Continued)

Authors (Year)	Study design and sample	Used diagnostic system	Follow-up	Criteria for recovery (all the mentioned criteria must have been fulfilled)	Results	Comments
Modestin <i>et al.</i> (2003)	Switzerland Analysed the original sample of Manfred Bleuler by utilising clinical charts and Bleuler's notes Age of patients at the study base line: mean 40 years, range 16-67 years 140-208 (48% of original sample were males) cases with Bleuler's or re-diagnosed schizophrenia, with hospitalisation between 1942 and 1943	DSM-IV DSM-III-R ICD-10 RDC Eugen Bleuler's criteria Schneider's criteria	Cross-sectional	Full employment Reassumed social roles No psychotic symptoms on examination (except some eccentricity or residues) All above constant conditions maintained for over 5 years	Rates of recovery by diagnostic system: DSM-IV: 12% DSM-III-R: 12% ICD-10: 15% RDC: 15% Eugen Bleuler's criteria: 22% (this sample includes also schizoaffective patients) Schneider's criteria: 24%	Strengths: The outcome could be assessed for 98.5% of original sample. Valid and reliable re-diagnostics Limitations: Hospital based sample, not generalisable to all schizophrenia patients. Retrospective analysis of Bleuler's original sample Recovery assessed only from clinical charts and notes.
Auslander <i>et al.</i> (2004)	Independently living patients from Outpatient Center in San Diego, US 155 schizophrenia patients enrolling the clinic at 1990's Age range 45-70 years	DSM-III-R DSM-IV	Cross-sectional	Clinically in full remission Have been living independently for the past 2 years No psychiatric hospitalisation for the last 5 years Psychosocial functioning within the "normal range" At most one half of the highest daily dose (since enrollment to the study) of antipsychotic medication	8% of patients recovered (12/155, 10 males)	Strengths: Diagnoses based on structured criteria, valid (consensus) diagnoses Limitations: The sample not clearly described Results generalisable to older individuals with schizophrenia. Patients with dementia were excluded. Selected sample. The initial sample included also cases not living independently, and thus most probably having poorer outcome.
DeLisi <i>et al.</i> (1998)	US 50 (64% males) patients hospitalised for first-episode schizophrenia, schizoaffective or schizophreniform disorder Mean age at first hospitalisation 27 years, range 16-47 years	DSM-III-R	5 years	By GAS and BPRS: Normal functioning No evidence of any psychopathology in 3-5 years of illness	10% (5/50) recovered	Strengths: First episode patients Limits: Recruitment of patients not clearly described. May be selected sample. Definition of recovery not clearly described No analyses for schizophrenia separately

Table 2. (Continued)

Authors (Year)	Study design and sample	Used diagnostic system	Follow-up	Criteria for recovery (all the mentioned criteria must have been fulfilled)	Results	Comments
Robinson <i>et al.</i> (2004)	US Study began at 1986 Mean age at study entry 25 years At base line 118 patients (52% males) with first episode schizophrenia (70% of the sample) or schizoaffective disorder	RDC	5 years	No worse than "mild" (score 3) for certain SADS-C psychosis items (delusions, hallucinations, understandability, derailment, illogical thinking, bizarre behavior) No worse than "moderate" (score 3) for certain SANS global ratings (affective flattening, alogia, avolition- apathy, anhedonia-asociality) Appropriate role functioning (e.g. ability to work), ability to perform day-to-day living tasks without supervision, proper social contacts (these all assessed by SAS)	16.4% had full recovery	Strengths: Both in- and outpatients. First-episode patients, all in the same phase of illness Clear definition of recovery Limitations: 38% of cases lost to follow-up and not analysed Schizophrenia and schizoaffective patients not analysed separately Treated sample. All patients followed a treatment algorithm with several possibilities for drug treatment and psychotherapies.

BPRS = Brief Psychiatric Rating Scale, DAS = Disability Assessment Scale, GAF-D = Global Assessment of Functioning - Disability, GAS = Global Assessment Scale, RDC = Research Diagnostic Criteria, SADS = Schedule for Affective Disorders and Schizophrenia, SANS = Schedule for Assessment of Negative Symptoms, SAPS = Schedule for Assessment of Positive Symptoms, SAS = Social Adjustment Scale

### 2.4.5 Predictors of outcome

Different dimensions of outcomes may have specific predictors (Ruggeri *et al.* 2004, Hofer *et al.* 2006), but in general, good outcome has been predicted by later age at illness onset (Suvisaari *et al.* 1998) and being female (Salokangas 1983, Harding *et al.* 1987, Angermeyer *et al.* 1990, Harrison *et al.* 1996, Suvisaari *et al.* 1998), although one recent study showed better outcome in men (Kua *et al.* 2003). Low genetic loading has been a good sign in most (McGlashan 1986, Verdoux *et al.* 1996, Suvisaari *et al.* 1998) but not all (Johnstone *et al.* 1995) studies. Being married (Harding *et al.* 1987), well educated (Jonsson & Nyman 1991, Johnstone *et al.* 1995) and belonging to higher social class at inception (Jonsson & Nyman 1991) are also related to good prognosis. Compared to developed countries, the outcome of schizophrenia is suggested to be better in some developing countries, and this has been explained by factors such as better acceptance of individuals with schizophrenia by family members and low expressed emotions (Leff *et al.* 1992). However, the idea of better outcome in developing countries and the favourable effect of socio-cultural factors on outcome in these countries has been questioned (Patel *et al.* 2006). Even though some patients seem to do well without drug treatment (Fenton & McGlashan 1987), antipsychotics, early intervention (Miyamoto *et al.* 2003) and psychosocial treatments (Craig *et al.* 2003) have a significant and favourable effect on the course of illness. Surprisingly, birth trauma has also been suggested to predict a favourable course of illness (Johnstone *et al.* 1995).

Conversely, male sex (Suvisaari *et al.* 1998) early age at illness onset (Jonsson & Nyman 1991, Suvisaari *et al.* 1998, Harrison *et al.* 2001), poor premorbid functioning (Jonsson & Nyman 1991, Hofer *et al.* 2006), premorbid alcohol use (Häfner & an der Heiden 2003) and being unmarried (Harrison *et al.* 1996, Salokangas *et al.* 2001), long duration of untreated psychosis (Marshall *et al.* 2005) and cannabis use (Linszen *et al.* 1994) are supposed to predict poor outcome. Environmental factors also seem to have an effect: high expressed emotion (i.e. poor emotional environment in the family) (Butzlaff & Hooley 1998, Bebbington & Kuipers 2003) and stress (Bebbington & Kuipers 2003) have been associated with increased risk of relapse in schizophrenia. Unfavourable course of illness has also been associated with brain structural (Staal *et al.* 1999) and functional (Wood *et al.* 2006) changes.

There have been a few studies about the predictors of re-hospitalisation in schizophrenia. An early onset age has predicted re-admission in schizophrenia in several studies (Eaton *et al.* 1992, Mortensen *et al.* 1994, Appleby *et al.* 1996, Sytema *et al.* 2002). Familial loading for mental illness has also been associated with a higher re-hospitalisation rate (Feldmann *et al.* 2001). Appleby *et al.* (1996, 1993) found in two studies that in addition to male gender, short hospitalisation (less than 31 days) predicts shorter time to re-admission. The association between short first hospitalisation and increased risk of re-hospitalisation was also presented by Sytema *et al.* (2002). Appleby *et al.* (1996) also characterised those patients who would benefit from longer first hospital treatment (e.g. male gender and young age). Some of the schizophrenia studies mentioned above present results on re-hospitalisation after first admission (Eaton *et al.* 1992, Mortensen *et al.* 1994, Sytema *et al.* 2002), but some results are based on patients having previous hospitalisations as well (Appleby *et al.* 1993, Appleby *et al.* 1996, Feldmann *et al.* 2001).

Compared to non-recovered cases, patients with both symptomatic and social recovery are suggested to have shorter duration of untreated psychosis, better cognitive performance and more cerebral asymmetry (Robinson *et al.* 2004).

The predictors of outcomes in epidemiological studies are presented in Table 1.

### ***2.4.6 Early development and outcome in schizophrenia***

Although there is convincing evidence that children who have delays in neurocognitive and motor development have a small but significantly increased risk of developing schizophrenia (Jones *et al.* 1994, Cannon *et al.* 2000, Isohanni *et al.* 2001b, 2004, Cannon *et al.* 2002, Niemi *et al.* 2003), once illness develops, the association between these markers and the subsequent course of the illness remains poorly understood.

Jonsson and Nyman (1984, 1991) found that schizophrenia cases with poor outcome had significantly more neurological symptoms (e.g. bad coordination of muscles or speech, difficulties in reading and writing) during childhood and adolescence when compared to good outcome cases. Rossi *et al.* (2000) found that schizophrenia cases with early origin (pre- or perinatal) and constant behavioural abnormalities had more severe negative symptoms when compared to cases having slight but increasing behavioural abnormalities. In the Northern Finland 1966 Birth Cohort within the whole cohort late learners had slightly poorer educational outcome (Taanila *et al.* 2005). To my knowledge, the association between early neuromotor developmental milestones and later course of illness in schizophrenia has not been studied so far.

## **2.5 Methodological difficulties in outcome studies of schizophrenia**

The absence of a general definition of recovery and good and poor outcome, variable diagnostics and outcome criteria, and cases lost to follow-up cause challenges when studying the course and outcome in schizophrenic psychoses. As indicated by McGlashan *et al.* (1988), unique clinical characteristics of samples from particular clinics or hospitals, particularly the degree of established chronicity, may account for wide differences in observed recovery rates.

Six methodological elements that are important when studying the outcome in schizophrenia and when comparing the results from different studies have been presented. These factors include diagnosis with operational criteria, adequate demographic characterisation of the sample, multidimensional outcome measures, independence of data collection, reliable ratings, and analysing the non-participating subjects. (McGlashan 1984) Harding *et al.* (1987) added the importance of length of follow-up, various sources of data, the use of structured interviews, and multiple cross-sectional assessments.

Different study designs have different methodological strengths and problems (Gilbody *et al.* 2002). Studies based on interviews may suffer from high attrition, but they have often relatively valid information regarding diagnosis and different markers of outcomes. If the study is based on information gained from hospital notes, there may be a

lack of adequate information due to incomplete recording in the notes. Some outcome studies are solely or partially based on register information, which has its disadvantages (rough data, no information about subjective factors such as quality of life, no information on the observed status of individual, poor validity of diagnosis due to false diagnostics), but important advantages as well (high-quality information, large samples, no recall bias).

In addition to factors mentioned above, a common difficulty in studies of predictors of outcomes is the quality of predictor variables. They may have been collected retrospectively by asking the patient or relatives and there may be difficulties in remembering the past and reporting things truthfully.

## **2.6 Earlier related studies in the Northern Finland 1966 Birth Cohort (NFBC 1966)**

In the NFBC 1966 several studies concerning the life-course developmental trajectory to psychoses or other severe mental illnesses and a few studies about the outcome of schizophrenia have been presented. Later achievement of developmental milestones around age one have been linked with mental retardation (von Wendt *et al.* 1984), poor educational capacity at age 14 (Rantakallio *et al.* 1985), and the risk of schizophrenia and other psychoses (Isohanni *et al.* 2001b). In addition, those psychosis subjects who learned to stand later also had lower achievement at school, especially in the motor domain, at the age of 16 years. The schizophrenia group achieved developmental milestones later and showed a strong correlation in developmental gradient when compared with non-psychotic controls. Thus, the developmental trajectories in schizophrenia seem to be different from controls. (Isohanni *et al.* 2001b, 2004).

According to Murray *et al.* (2006), schizophrenia cases with slower motor development had poorer executive functioning, verbal learning and visuospatial immediate memory at the age of 33 years. In addition, subtle brain abnormality mainly not mediated by genetic or obstetric risk (Tanskanen *et al.* 2005) and (on a trend level) reduced total, grey and white matter volumes in the brains of schizophrenia subjects (Tanskanen *et al.* manuscript) have been found. Ridler *et al.* (2006) demonstrated that the normal relationship between infant development at age 1 and adult brain structure and executive functions 34 years later is disturbed in schizophrenia (“developmental dysmetria”).

According to Alaräisänen *et al.* (manuscript), 7% of NFBC 1966 schizophrenia cases had committed suicide by the year 2001. Surprisingly, good school performance was associated with higher risk of suicide among psychotic patients and to a lesser extent among patients with schizophrenia. Among non-psychotic population of the NFBC 1966 good school marks were associated to decreased risk of suicide (Alaräisänen *et al.* 2006). Somatic comorbidities were also common among schizophrenia patients (Saari 2005).

Miettunen *et al.* (in press) studied occupational status in schizophrenic psychoses. (see Table 1). They found that 56% of patients were on disability pension after a mean of 10.6 years follow-up. In comparison, 2.3% of all cohort members were on disability pension at the time of study. The average time from first psychiatric hospital admission to pension

among individuals with schizophrenic psychosis was 3.3 years. After adjusting for gender, being unemployed at onset, educational level and proportion of time spent in psychiatric hospitals, those who were married or cohabiting at the time of onset of illness were less often on pension than those who were single.

## 2.7 Summary of the literature

In spite of wide scientific interest and the clinical relevance of outcomes, prognosis and its predictors in schizophrenia, much is still unresolved. Many studies have yielded divergent results concerning proportions of good and poor outcome and the significance of certain predictors. The number of unselected, population-based studies is low (Table 1) and, to my knowledge, there are no related birth cohort studies.

The outcome of schizophrenia and related psychoses is very heterogeneous and individual (Tables 1 and 2). According to meta-analyses or reviews, approximately 40% of patients have good outcome (Hegarty *et al.* 1994), 35% have moderate and 27% have poor outcome (Menezes *et al.* 2006).

Several predictors of outcome have been presented, such as age of illness onset (Jonsson & Nyman 1991, Harrison *et al.* 1996, Suvisaari *et al.* 1998, Harrison *et al.* 2001), gender (Salokangas 1983, Angermeyer *et al.* 1990, Harding *et al.* 1987, McGlashan 1986, Kua *et al.* 2003, Ruggeri *et al.* 2004), genetic loading (McGlashan 1986, Jonsson & Nyman 1991, Verdoux *et al.* 1996, Suvisaari *et al.* 1998), birth trauma (Johnstone *et al.* 1995) and neurodevelopmental abnormalities in childhood (Jonsson & Nyman 1991). Long duration of untreated psychosis, use of cannabis, as well as illness and life-style related factors around illness onset have also been associated with different outcomes (Häfner & an der Heiden 2003). Environment related factors, such as high expressed emotion (i.e. poor emotional environment in the family) (Butzlaff & Hooley 1998, Bebbington & Kuipers 2003) and stress (Bebbington & Kuipers 2003) are suggested to have an effect on the course of illness. Developmental delays in early neuromotor functioning among schizophrenia patients have been found, and these markers of adulthood schizophrenic psychoses appear to have some stability in their developmental trajectory (Cannon *et al.* 2002, Isohanni *et al.* 2004). In spite of interest in the neurodevelopmental model of schizophrenia, no earlier studies have examined the association between early neuromotor development and the course of illness in schizophrenia.

50-90% of individuals with schizophrenia have rehospitalisation during their lifetime, and many rehospitalisations happen during first years of illness (Eaton *et al.* 1992). Suggested predictors of rehospitalisation are early onset age (Eaton *et al.* 1992, Mortensen *et al.* 1994, Appleby *et al.* 1996, Sytema *et al.* 2002), familial loading for mental illness (Feldmann *et al.* 2001), gender, short first hospitalisation (less than 31 days) (Appleby *et al.* 1996, 1993).

True recovery in schizophrenia is less studied topic, when compared to other outcomes. The results concerning complete recovery in schizophrenia vary from 8% to 25% (Table 2).

Methodological flaws and difficulties have a major role when estimating the probabilities of good and poor outcome and recovery and when comparing the results of different studies. The absence of a general definition of good and poor outcome and recovery, variable diagnostics and outcome criteria, variations in the length of follow-up and cases lost to follow-up pose a challenge when studying prognosis in schizophrenic psychoses. McGlashan (1988) indicated that unique clinical characteristics of samples from particular clinics or hospitals, particularly the degree of established chronicity, may account for wide differences in observed outcome rates. The true rate of good and poor outcome and recovery in schizophrenia, however, can only be established by follow-up of an epidemiologically defined cohort.

### **3 Aims of the study**

The studies of this dissertation that utilised the Northern Finland 1966 Birth Cohort data of subjects with schizophrenia and other schizophrenia spectrum psychoses aimed to:

1. find out the distribution and predictors of good and poor clinical and social outcome of the subjects until the age 35 years (original article I).
2. find out whether the same children who achieved developmental milestones (i.e., learning to stand, walk, and speak) later also show poorer course of schizophrenia, compared with early learners (original article II).
3. study the patterns and predictors of psychiatric hospitalisations in schizophrenic psychoses (original article III).
4. discover if any of the subjects with schizophrenic psychoses had recovered fully or partially by age 35 (original article IV).

## **4 Material and methods**

### **4.1 Study design**

This is epidemiological, prospective, longitudinal and geographically defined birth cohort study. The whole sample has been followed-up until recent years and the data includes information from several study points during 35 years (Figure 3).

### **4.2 Data collection**

#### ***4.2.1 The Northern Finland 1966 Birth Cohort***

In the middle the 1960s Professor Paula Rantakallio started a remarkable task when she founded the Northern Finland 1966 Birth Cohort. The cohort is an unselected, general population birth cohort ascertained during mid-pregnancy. It is based upon 12,058 live-born children in the provinces of Lapland and Oulu (Rantakallio 1969). The data include all subjects alive and living in Finland at age 16 years (N=11,017). During the years, information concerning pregnancy and delivery, early development, socio-demographic factors, education as well as illness- and health-related factors have been collected by questionnaires, special examinations and field studies (Figure 3). Subjects have the opportunity to retire from the study at any moment, and altogether 83 subjects have forbidden the use of their data and have been excluded to date.

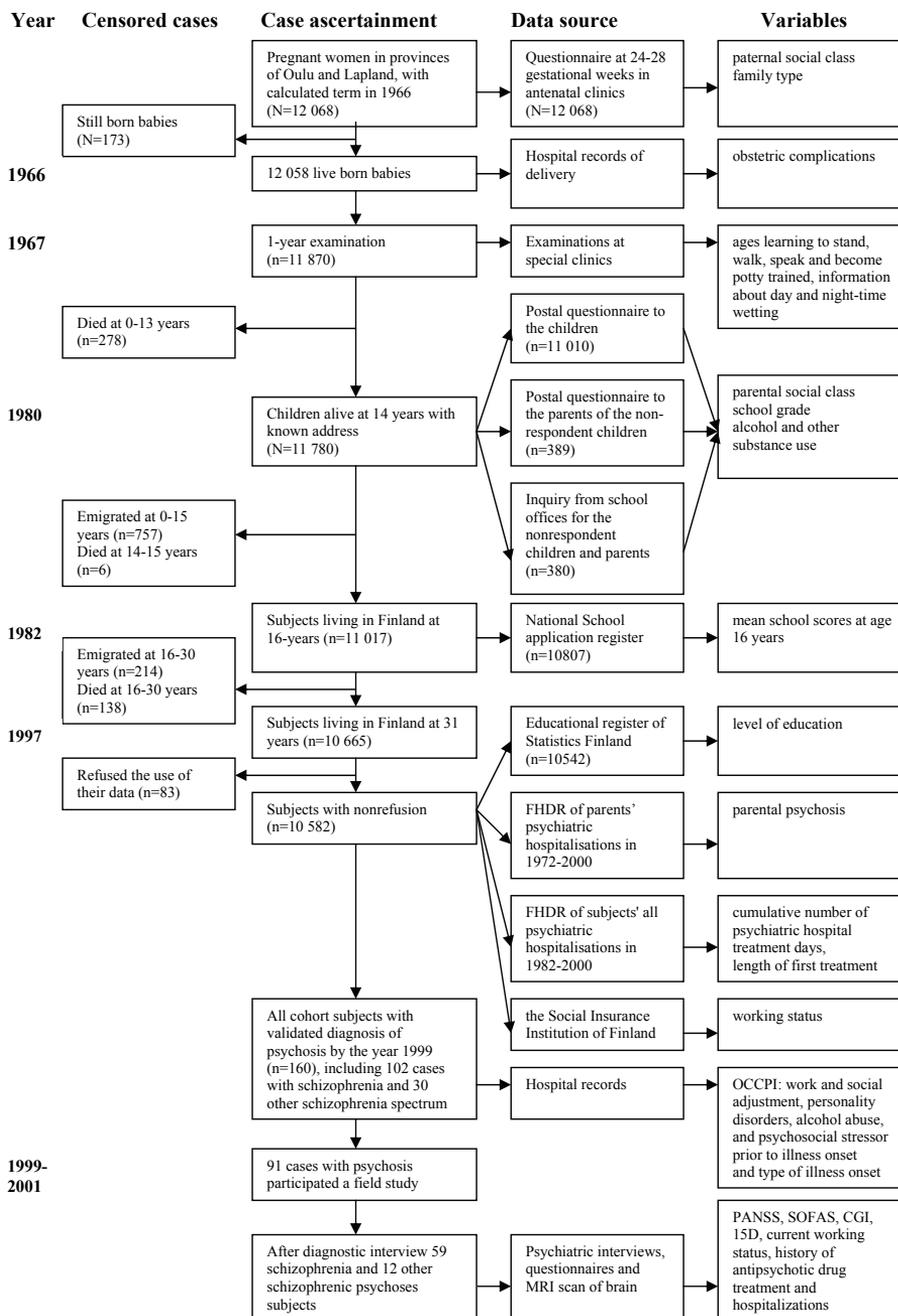


Fig. 3. Data collection of the NFBC 1966.

### 4.2.1.1 Diagnostics

The nationwide Finnish Hospital Discharge Register (FHDR) covers all mental and general hospitals, as well as beds in local health centres and private hospitals nationwide. In Finland, until recent years, most patients experiencing an episode of schizophrenic psychosis were hospitalised (Isohanni *et al.* 1997) and will appear in the FHDR. The proportion of schizophrenia patients who do not receive hospital treatment is still quite low (Arajärvi *et al.* 2005).

For the psychiatric subprojects of the NFBC 1966 all cohort members over 16 years appearing on the FHDR until the end of 1997 for any mental disorder (i.e., ICD-8 290-309, DSM-III-R diagnoses 290-316, and ICD-10 F00-F69, F99) were identified. All case records were scrutinised and diagnoses were assessed for DSM-III-R criteria, after which the diagnoses were re-reviewed by a professional panel. The reliability for schizophrenia diagnoses of this procedure was calculated ( $\kappa=0.85$ ). A more detailed description of the validation processes of the cohort have been published earlier (Isohanni *et al.* 1997, Moilanen *et al.* 2003). Information about deaths and the causes of death before the year 2001 was ascertained from the death certificates from Statistics Finland.

## 4.3 Study samples and assessment of adult psychiatric morbidity

Altogether 160 subjects with known psychotic episodes until the year 1999 were detected, 102 of them having schizophrenia. The detection of subjects and validation of diagnoses are described in Isohanni *et al.* (1997) and Moilanen *et al.* (2003). The number 160 includes three schizophrenia cases treated solely as outpatients (two of them detected by the year 1993 and one in 1998), and information about them was received from the Oulu outpatient record or by asking all the 20 Finnish psychiatrists with district management responsibilities (Isohanni *et al.* 1997). One schizophrenia patient was detected from the psychiatric ward of Oulu University Hospital in 1999. Fourteen (8.8%) persons had died by the year 2001; 10 of them had schizophrenia and one had other schizophrenia psychosis. In this study, only subjects with schizophrenic psychosis were included; subjects with non-schizophrenic psychoses were excluded.

The development of number of subjects in each original article is presented in Table 3 and in following chapters.

*Table 3. The development of number of subjects in each original article.*

Original article	Number of subjects at baseline	Number of excluded subjects	Number of subjects in the analyses
I	<p>According to validation until the end of year 1994: 142 subjects with psychosis, including 88 subjects with schizophrenia and 20 subjects with other schizophrenia spectrum psychosis</p> <p>142 subjects includes two outpatients with schizophrenia.</p> <p>According to validation in 1997: 155 subjects with psychosis, including 102 subjects with schizophrenia and 30 subjects with other schizophrenia spectrum psychosis</p> <p>155 subjects includes two outpatients with schizophrenia (detected in validation until the end of 1994).</p> <p>Invitations to the field study in 1999-2001: All subjects with psychosis, mostly according to validation in 1997, were invited to the field study in 1999-2001. At the beginning of the invitation process, the invitations were based solely on the validation in 1994.</p> <p>Of the subjects with psychosis who were invited based on validation until the end of 1994, one was not validated in 1997 and two were diagnosed as non-psychotic.</p> <p>In addition to two outpatients detected earlier, one outpatient detected in 1998 and one subject from the ward in 1999 were invited to the study.</p> <p>See above how 59 schizophrenia subjects were found.</p> <p>In addition, non-participating (to the field study in 1999-2001) 40 and 10 deceased subjects with schizophrenia were included.</p>	<p>91 patients participated and after diagnostic interviews there were 61 subjects with schizophrenia.</p> <p>Two of these (one detected in 1998 and one in 1999) were excluded because their follow-up was too short.</p>	<p>59 subjects with schizophrenia</p>
II	<p>91 patients participated the field study in 1999-2001 and after diagnostic interviews there were 61 subjects with schizophrenia.</p> <p>Two of these (one detected in 1998 and one in 1999) were excluded because their follow-up was too short.</p> <p>All schizophrenia subjects in the NEBC by the year 1999, excluding two subjects with too short follow-up (N=109).</p> <p>A sub-sample of 59 schizophrenia subjects detected in the field study 1999-2001.</p>	<p>All schizophrenia subjects in the NEBC by the year 1999, excluding two subjects with too short follow-up (N=109).</p> <p>A sub-sample of 59 schizophrenia subjects detected in the field study 1999-2001.</p>	<p>All schizophrenia subjects in the NEBC by the year 1999, excluding two subjects with too short follow-up (N=109).</p> <p>A sub-sample of 59 schizophrenia subjects detected in the field study 1999-2001.</p>

Table 3. (Continued)

Original article	Number of subjects at baseline	Number of excluded subjects	Number of subjects in the analyses
III	<p>Subjects for this part of the study were detected according to validation in 1997; i.e., two patients considered as psychotic in the 1994 validation, but re-considered as non-psychotic in the 1997 validation, as well as one subject not validated in 1997 were not included in this sample.</p> <p>Only subjects treated in psychiatric hospitals or wards offering specialised psychiatric care were included. Two subjects treated solely as outpatients were excluded.</p> <p>153 subjects with diagnosis of psychosis, including 127 subjects with schizophrenia psychosis.</p>	<p>Eleven deceased subjects</p> <p>One subject treated in military hospital</p>	115 subjects with schizophrenic psychosis
IV	<p>According to validation until the end of year 1994:</p> <p>142 subjects with psychosis, including 88 subjects with schizophrenia and 20 subjects with other schizophrenia spectrum psychosis</p> <p>142 subjects includes two outpatients with schizophrenia.</p> <p>According to validation in 1997:</p> <p>155 subjects with psychosis, including 102 subjects with schizophrenia and 30 subjects with other schizophrenia spectrum psychosis</p> <p>155 subjects includes two outpatients with schizophrenia (detected in validation until the end of 1994).</p> <p>Invitations to the field study in 1999-2001:</p> <p>All subjects with psychosis, mostly according to validation in 1997, were invited to the field study in 1999-2001. At the beginning of the invitation process, the invitations were based solely on the validation in 1994.</p> <p>Of the subjects with psychosis who were invited based on validation until the end of 1994, one was not validated in 1997 and two were diagnosed as non-psychotic.</p> <p>In addition to two outpatients detected earlier, one outpatient detected in 1998 and one subject from the ward in 1999 were invited to the study.</p>	<p>91 patients participated and after diagnostic interviews there were 61 subjects with schizophrenia and 12 subjects with other schizophrenia spectrum psychosis.</p> <p>Two of these (one detected in 1998 and one in 1999) were excluded because their follow-up was too short.</p>	<p>59 subjects with schizophrenia</p> <p>12 subjects with other schizophrenia spectrum psychosis</p> <p>40 subjects with schizophrenia and 8 with other schizophrenia spectrum psychosis, who did not participate the field study in 1999-2001.</p> <p>Ten deceased schizophrenia and one subject with other schizophrenia spectrum psychosis.</p>

### ***4.3.1 Outcome and its predictors in schizophrenia (original article I)***

During follow-up in 1999-2001, all 146 living subjects (83 males, 57%) with a known psychotic episode were recruited. Ninety-one (62%) subjects agreed to participate in the field study and gave written informed consent. The diagnoses for all participating subjects were re-checked. For assessing diagnoses, Structured Clinical Interview for DSM-III-R, the SCID (Spitzer *et al.* 1989), was the main diagnostic instrument together with all anamnestic information available, including hospital case notes. In the field study in 1999-2001, altogether 61 schizophrenia patients were detected (Tanskanen *et al.* 2005). Two of these had received the diagnosis of psychosis the first time in 1998-1999 and due to too short follow-up, these cases were excluded from the analyses. Thus, in the field study 59 subjects with schizophrenia (DSM-III-R diagnoses: 295, except 295.4 and 295.7) and 12 subjects with other schizophrenia spectrum disorders (including schizophreniform psychosis, 295.4; schizoaffective disorder, 295.7; and delusional disorder, 297.1) were detected. The sample of original study I was restricted to these 59 schizophrenia cases and due to small number of other schizophrenia spectrum cases and thus lack of statistical power they were excluded.

### ***4.3.2 Early development and outcome in schizophrenia (original article II)***

The analyses for early development and outcome were made in two categories:

- 1) Register-based information about outcome was used for the individuals receiving a diagnosis of DSM-III-R schizophrenia by the year 1999. Also deceased subjects were included. Two subjects that received the diagnosis of psychosis the first time in 1998-1999 and thus had too short follow-up were excluded from the analyses (N=109).
- 2) In addition, data from assessments based on personal interviews were used for a subset of schizophrenia subjects diagnosed and interviewed in the field study in 1999-2001 (N=59).

### ***4.3.3 Patterns of hospitalisations in schizophrenic psychoses (original article III)***

After the re-validation in 1997 (Moilanen *et al.* 2003) and by the end of 1997 there were 153 subjects (90 men, 59%) occurring in the FHDR with a known psychotic episode in their life. This number excludes one subject detected from psychiatric ward in 1999 and three subjects who were treated solely as an outpatients. This number is also different of the original articles I, II and IV, since in this study the diagnoses were based solely on the validation in 1997 where three patients who had a diagnosis of psychosis in the validation 1994 were re-considered as non-psychotic.

Of the 153 cases, 127 (75 men, 59%) were given the diagnosis of schizophrenic psychosis in the validation process. Eleven (9 men, 82%) of these were deceased by the end of the year 2000 and one male subject had only been treated in a military hospital. These subjects were excluded from this study.

This study includes all living subjects with schizophrenic psychoses treated in psychiatric hospitals or wards providing specialised psychiatric care (N=115). This is also one reason why the number of subjects is different compared to other studies of this dissertation. This study sample included 88 schizophrenia cases (DSM-III-R diagnoses: disorganised schizophrenia, 295.1, n=9; catatonic schizophrenia, 295.2, n=2; paranoid schizophrenia, 295.3, n=24; undifferentiated schizophrenia, 295.9, n=53) and 27 other schizophrenia spectrum cases (schizophreniform psychosis, 295.4, n=14; schizoaffective disorder, 295.7, n=4; delusional disorder, 297.1, n=9).

#### ***4.3.4 Recovery in schizophrenic psychoses (original article IV)***

The sample consisted 59 individuals with schizophrenia and 12 with schizophrenia spectrum psychosis detected from the field study in 1999-2001 and described earlier (see 4.3.1), fifty-five subjects with any psychosis (38% of all 146 living cases) who could not be reached or refused to participate in the field study, and the 14 subjects with any psychosis (8.8%) who had died by the year 2001 (Figure 4; Updated from article I, Figure 1).

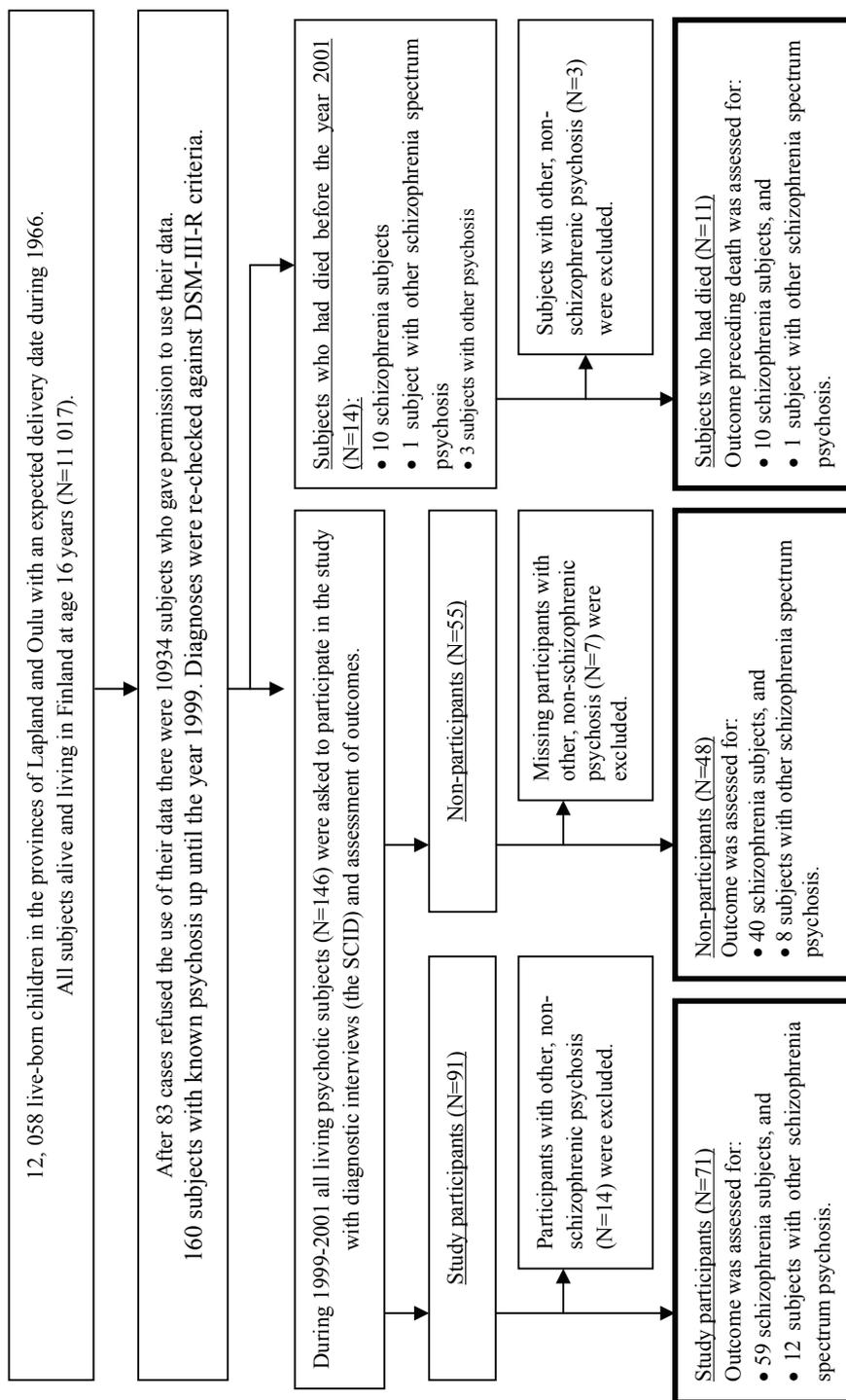


Fig. 4. Recovery from schizophrenic psychoses in the Northern Finland 1966 Birth Cohort: data collection until the end of 2003.

#### *4.3.4.1 Non participants of the field study in 1999-2001*

Fifty-five subjects (38% of all 146 living cases; 31 males, 56%) with earlier known psychosis could not be reached or refused to participate in the field study in 1999-2001 (Figure 4). Given that the extent of non-participation was fairly high in this study, it was considered important to track the maximum number of non-interviewed cases and assess outcomes for them. During 2002-2003, information for these persons was gathered from FHDR and medical records from health centers and hospitals. If there was not enough information in FHDR or medical records, a personal questionnaire was sent or the subject was contacted by telephone. Of the non-participants, 40 had a diagnosis of schizophrenia (27 men, 66%) and eight cases (3 men, 38%), other schizophrenia spectrum psychosis.

Of the 160 cases, 14 (8.8%) had died by the year 2001. Until 2001, ten subjects (9 men) with schizophrenia and one female subject with schizophreniform psychosis had died. Causes of death for schizophrenia cases were suicide (7 subjects), accident or trauma (2 subjects) and unknown (1 case). The cause of death for the subject with schizophreniform psychosis was suicide.

When participating cases with any schizophrenic psychosis (N=71) and non-participants with any schizophrenic psychoses (N=48) were compared there were no significant differences in distribution of sex, parental social class in 1966 or in 1980, educational level or age at the onset of illness. However, non-participants had spent longer episodes in psychiatric hospitals (non-participants median 245 treatment days vs. participants median 112 treatment days). Thus, it may be that the non-participants had a somewhat more severe illness.

### **4.4 Assessment of outcomes and course of illness**

Several clinical, social and global indicators of outcome and course of illness were used. The variables are described in Table 4.

Table 4. *Used measures of outcomes and course of illness.*

Outcome variable	Description of variable	Source of variable	The use of variable (number of original article)
Age of illness onset	Age when the subject experienced first psychotic symptoms.	Hospital records (Räsänen <i>et al.</i> 1999)	II
Age at first hospital admission	Age of the subject at the first hospitalisation due to psychosis.	Hospital records	III
Clinical Global Impressions (CGI)	The Severity of Illness subscale of the CGI was used when rating the severity of illness. It has seven different rating groups with scores ranging from 1 (not ill at all) and 2 (no disturbances or minor symptoms) to 7 (among the most extremely ill). (Guy 2000).	Field study in 1999-2001	IV
Positive and Negative Symptoms Scale (PANSS)	Was used to measure the amount of psychopathological symptoms during the previous week (Kay <i>et al.</i> 2000). Higher scores reflect greater levels of psychopathology.	Field study in 1999-2001	I, II, IV
Social and Occupational Functioning Assessment Scale (SOFAS)	The SOFAS is derived from the Global Assessment Scale (GAS) and was used to rate social and occupational functioning of the patients during the previous week (Spitzer <i>et al.</i> 2000). Higher scores reflect better functioning.	Field study in 1999-2001	I, II, IV
Self reported psychiatric hospitalisations	Subjects were asked about psychiatric hospitalisations during the previous two years.	Field study in 1999-2001	I, II, IV
Antipsychotic medication	Medication usage at the time of interview. Antipsychotic medications were converted to chlorpromazine equivalents, and the cases were divided into those on low dose (300mg or under as chlorpromazine equivalents) versus high dose (over 300mg as chlorpromazine equivalents) (Lehman <i>et al.</i> 1998, 2004).	Field study in 1999-2001	II, IV
Occupational status	Subjects were asked about working status: full-time employee, part-time employee, unemployed, pensioned, on sick leave, student.	Field study in 1999-2001	I, II, IV
Marital status	Subjects were asked about their marital status: married, cohabiting, divorced, widowed, single.	Field study in 1999-2001	II, IV
15D	A generic, standardised, self-administered measure of health-related quality of life. It has 15 separated dimensions, assessing physical, mental and social well-being (Sintonen 2001). A single index number is generated from the scores and this number range from 0 to 1, high scores meaning good quality of life.	Field study in 1999-2001	II
Psychiatric hospitalisations	Median number of episodes, median days in hospital, median proportion of time spent in hospital after diagnosis (%).	Data until the year 2000 from the Finnish Hospital Discharge Register.	I-III
Educational level	The educational level that the subject had attained by the year 1997.	The Statistics Finland	II
Occupational status	Information about disability pensions.	The Social Insurance Institution of Finland	I-III
Early death	Death by the year 2001.	Death certificates from the National Population Register of Statistics Finland.	II
Suicide	Suicide as cause of death.	Death certificates from the National Population Register of Statistics Finland.	IV

#### ***4.4.1 Criteria of good and poor clinical and social outcomes (original article I)***

The information of outcomes for original article I was received from the field study in 1999-2001 and from national registers (Table 4).

##### *4.4.1.1 Criteria of good and poor clinical outcomes*

Clinical outcomes were assessed using three different definitions:

- *Hospitalisations*. Information about psychiatric hospitalisations. Good outcome = not hospitalised during the last two years. Poor outcome = hospitalised during the last two years.
- *Remission*. The remission criteria of Andreasen *et al.* (2005) were used with the exception that the duration of remission of six months was not used, because in this dissertation study symptoms were assessed only once (for previous week). This led to two categories of outcome: good outcome = remission, i.e. maximum score of 3 in PANSS items P1, P2, P3, N1, N4, N6, G5, G9; and poor outcome = no remission.
- *Global clinical outcome*. The definition developed by our research group. Good outcome = maximum score of 2 on any positive or negative items of PANSS and no psychiatric hospitalisations during the last two years; moderate outcome = maximum score of 4 on any positive or negative items of PANSS and no psychiatric hospitalisations during the last two years. Poor outcome = the remainder of the cases that did not fulfil the criteria of good or moderate outcome.

##### *4.4.1.2 Criteria of good and poor social outcomes*

Social outcomes were assessed by using two definitions:

- *Occupational status*. Good outcome = not on disability pension and not on sick leave at the study moment. Poor outcome = on disability pension or sick leave.
- *Global social outcome*. The definition developed by our research group. Good outcome = at least 61 points on the SOFAS, meaning not more than minor, temporary problems in social and occupational functioning, and not on a disability pension and not on sick leave. Moderate outcome = score on SOFAS 41-60, meaning at most severe decrease in functioning, but not in many areas of life. Poor outcome = the remainder of the cases who did not fulfil the criteria of good or moderate outcome.

#### 4.4.2 *Criteria of good and poor outcomes (original article II)*

##### 4.4.2.1 *Symptom profile, functioning and quality of life by the age of 35 years*

Of those who agreed to participate to the field study and interviews in 1999-2001 (N=59), we obtained the following measures (Table 4) that were dichotomised:

- *PANSS* (Positive and Negative Syndrome Scale, Kay *et al.* 2000). Good outcome = scores of under median. Poor outcome = scores of median or over.
- *SOFAS* (Social and Occupational Functioning Assessment Scale, Spitzer *et al.* 2000). Good outcome = scores of median or over. Poor outcome = scores of under median.
- *15D* (15 Dimensions, Sintonen 2001). Good outcome = scores of median or over. Poor outcome = scores of under median.

##### 4.4.2.2 *Psychiatric hospitalisations*

Though amount of hospitalisations is an imperfect measure of severity of illness, it is widely used as a proxy measure in several earlier outcome studies (e.g. Suvisaari *et al.* 1998, Harrison *et al.* 2001). The following variables (Table 4) were used as dichotomised for the whole sample (N=109).

- *Cumulative number of psychiatric hospital episodes.*
- *Cumulative number of days in psychiatric hospital.*
- *Proportion of time spent in hospital after first psychiatric diagnosis (%) per patient.*

Regarding all these variables: Good outcome = median or under treatment episodes, days or proportion. Poor outcome = over median treatment episodes, days or proportion.

##### 4.4.2.3 *Other measures of general outcomes*

Also following measures of outcomes were used (Table 4):

- *Age of illness onset* (Räsänen *et al.* 1999). Good outcome = median or over age of illness onset. Poor outcome = under median age of illness onset.
- *Usage of antipsychotic medication at the time of interview in 1999-2001.* The subjects were divided into two groups: Good outcome = no or low dose (300mg or under as chlorpromazine equivalents) and poor outcome = high dose (over 300mg as chlorpromazine equivalents).
- *Occupational status.* Good outcome = not on disability pension. Poor outcome = on disability pension.
- *Marital status.* Good outcome = married or cohabiting. Poor outcome = divorced, not married or not cohabiting.

- *Early death.* Good outcome = alive. Poor outcome = dead.
- *Educational level.* Good outcome = secondary or tertiary level. Poor outcome = basic educational level.

#### 4.4.3 *Patterns of hospitalisations (III)*

Information on psychiatric hospitalisations was collected from FHDR until the end of 2000. All treatment periods with psychiatric diagnoses in psychiatric hospitals and other wards offering specialised psychiatric care after onset of psychotic symptoms were included. A large majority (80%) had their first hospitalisation in a psychiatric hospital (29% had first hospitalisation in psychiatric ward of Oulu University Hospital and 51% in other psychiatric hospital in Finland). Twenty percent had their first hospitalisation in other University hospital or general hospital or health centre ward providing psychiatric specialised care.

The following patterns of hospitalisation were used:

- *Time to re-hospitalisation.* Time to first re-hospitalisation was studied as a continuous variable. It was also studied whether the subject was re-hospitalised within two years after discharge from the first psychiatric hospitalisation or within the follow-up time. Time to re-hospitalisation was measured from day of discharge to day of re-hospitalisation.
- *First 3 admissions in 3 years.* Frequently admitted patients who had their first 3 admissions in 3 years were studied. The reason for the cut-off of three years was that the subjects were followed-up for at least for that length of time. This definition is also in line with some earlier studies focusing on frequently admitted or so-called “revolving door” patients (Lewis & Joyce 1990, Saarento *et al.* 1997).
- *Number of days in psychiatric hospitalisation.* The number of days in psychiatric hospitalisation was used as a confounder, as this variable is a proxy of the severity of illness. As the variable was extremely skewed it was transformed by taking a natural logarithm. This is a common approach when studying hospital days (Haywood *et al.* 1995, Daniels *et al.* 1998). Because of differences in the length of follow-up times, we also used the proportion of time in hospital after the age of illness onset as a variable describing the severity of the illness.
- *Age at first admission.* As this sample is a birth cohort with all subjects born in 1966 this variable adjusts both for onset age and period effect. Taking the period effect into account is important, as there has been a notable decrease from 1982 to 1992 in the number of hospital beds in Finland during the study period (Tuori *et al.* 1998).

#### 4.4.4 *Assessment and criteria of recovery (IV)*

Information to assess the outcome and possible recovery of subjects with schizophrenic psychosis was collected in three groups (Figure 4): 1. For subjects agreeing to be interviewed (participants) in the 1999-2001 study, personal interviews, hospital discharge registers, hospital records, and other anamnestic information were used. 2. For non-

participants of the field study, hospital discharge registers, hospital and health center records, personal questionnaires, and telephone interviews were used during 2002-2003. 3. For deceased subjects, information about the causes of death and medical records from latest treating psychiatric hospitals and health centers were used.

The information about indicators of outcomes (hospitalisations, occupational ability, symptoms, medication) was based on interviews in 1999-2001, on hospital notes in some cases, and on a questionnaire or telephone interview for a minority of the cases.

#### *4.4.4.1 Criteria for full and partial recovery*

For full recovery case should have 1) one or two points in CGI (1=not ill at all, 2=no disturbances or minor symptoms); 2) at least 71 points in SOFAS (not more than minor, temporary problems in social and occupational functioning); 3) at most 36 points total score on PANSS and in addition at most 2 points (minor symptoms) in each items of positive or negative scale of PANSS; 4) no psychiatric hospitalisations during the last two years; 5) no or low dose (300 mg or under as chlorpromazine equivalents, Lehman *et al.* 1998) antipsychotic medication; and 6) ability to work (not on disability pension and not on sick leave).

For partial recovery, subjects had to meet the criteria for CGI, have at most 36 total score on PANSS, have no hospitalisations during last two years, and score at least 61 in SOFAS (not more than some problems in social and occupational functioning).

#### *4.4.4.2 Assessment and criteria of recovery for non-participating cases*

Ascertaining the outcome for the non-participants was based on information about psychiatric hospital treatment during the last two years, current medication, and occupational status. It was not possible to get information about CGI, SOFAS and PANSS, and thus the full or partial recovery for the non-participants could not be evaluated. In summary, the purpose was to identify subjects having poor outcome and non-recovery and to cut down the amount of lost cases and missing information.

#### *4.4.4.3 Assessment and criteria of recovery for dead cases*

Suicide as a cause of death was seen as a sign of poor outcome. However, the outcome preceding death was analysed for those subjects, who had died by accident or trauma or who had an unknown cause of death (Figure 4). The outcome was analysed by utilising information about psychiatric hospitalisations during the last two years when living, antipsychotic medication, and occupational status derived from FHDR and medical records from the latest treating hospital or health center.

## 4.5 Predictors of outcomes

### 4.5.1 Predictor variables of good and poor clinical and social outcome (I)

Several developmental, family, environment and illness-related predictors of clinical and social outcome in schizophrenia were analysed.

#### 4.5.1.1 Development-related factors

- *Gender*. Men vs. Women.
- *Perinatal risk*. Preterm birth (< 37 weeks) or low birth weight (<2500 g) or perinatal brain damage. Ascertained from the questionnaires collected by the antenatal clinics (Jones *et al.* 1998).
- *Social relationships during childhood*. None vs. at least one close friend. Information from the PAS (Premorbid Adjustment Scale (Cannon-Spoor *et al.* 1982)) asked from subject's mothers in the field study at 1999-2001.
- *School grade at the age 14 years*. Not at school, under normal grade or in special school vs. normal grade or above in standard school. Information from the questionnaire for child, parents or school nurses at the child's age of 14 years (Isohanni *et al.* 1998).
- *School marks at the age of 16 years*. Mean school marks for all school subjects. School marks range from 4 to 10. Each set of marks is defined in the following way: 4 is rejected, 5-6 poor, 7-8 satisfactory and 9-10 are excellent. Information ascertained from the school administration of Finland (Isohanni *et al.* 1998).
- *Alcohol drinking by the age 14 years*. Drinking or tried vs. never tried. Information from the questionnaire for the child at the age of 14 years (Isohanni *et al.* 1993).

#### 4.5.1.2 Family- and environment-related factors

- *Family history of psychosis*. First degree relative having vs. not having non-organic psychosis. In the case of the cohort members with schizophrenia, all hospital notes and available outpatient notes (information about sisters', brothers' and parents' psychosis) and parents' hospitalisations during 1972-2000 from the FHDR were checked to find out whether or not a first-degree relative had experienced a psychotic episode. Additionally in a field survey during 1999-2001, all of the participating patients underwent Family Interview for Genetic Studies (FIGS; Maxwell 1992). In the FIGS procedure the patient and the mother, or if the mother was not willing or able to participate, the father or one of the siblings, were asked whether any first-degree relatives had experienced psychotic symptoms.

- *Alcoholism in the family*. First-degree relative suffering vs. not suffering from alcoholism. Information from the interview at the field study at 1999-2001 and information about mothers' and fathers' hospitalisations (the FHDR) due to alcoholism between 1972-2001.
- *Father's social class in 1980*. Paternal social classes I-II (high) vs. III-V (low). Information was collected from the questionnaire for child, parents or school nurses at the child's age of 14 years. Classes I-II included those with the highest professions, III-IV included skilled and unskilled workers, respectively, and V included farmers.
- *Family structure at the child's age of 14 years*. Single-parent family vs. two-parent family. Information from the questionnaire for child, parents or school nurses at the child's age of 14 years (Moilanen *et al.* 1988).

#### 4.5.1.3 *Illness related factors*

- *Age of illness onset*. Mean age of illness onset was ascertained from medical records and defined as the age when having the first evident psychotic symptoms (Räsänen *et al.* 1999).

#### 4.5.2 *Early development as a predictor of illness outcome (II)*

Developmental data obtained during children's visits to child health clinics were obtained during a special examination performed at age one year. In 96% of the cases the information was collected at the age of 11.5 months or later (Rantakallio *et al.* 1985). The following developmental milestones were examined at this 1-year examination and have been presented in earlier reports from NFBC 1966 (Isohanni *et al.* 2001b, 2004):

- *Age of standing without support and walking with and without support*. Parents were asked the age (in months) when the child learnt these skills. We used the following categories for analyses: *standing without support* (at 10 months or before vs. at 11 months or after) and *walking without support* (at 11 months or before vs. not learned by 12 months).
- *Age of learning to talk*. Parents were asked when and how many words the child spoke. For analyses following categories were used: at least one word vs. no words by age one year.

In addition to these the *Infant Motor Development* summary score (*IMD*) (Murray *et al.* 2006) was used. This is a summary score of three measures of motor development for each study subjects: age of learning to stand without support (months), learning to walk with support and learning to walk without support. *IMD* was done by principal components analysis. Positive *IMD* scores denote relatively delayed development, while negative scores denote early development. To illustrate how the *IMD* corresponds to the traditional developmental milestones, the score 0.6 corresponds to a hypothetical infant

who can walk without support at 10.2 months, stand without support at 11.8 months, and walk without support at 12.5 months. (Murray *et al.* 2006)

Some individuals were unable to perform standing and/or walking at the time of the developmental assessment so we imputed their scores using an a priori conservative method: we attributed a value equal to the age at the time of the developmental assessment plus one month (Murray *et al.* 2006).

### 4.5.3 Predictors of rehospitalisations (III)

Information on predictors of patterns of hospitalisation was collected from registers and hospital notes. Various socio-demographic factors as well as illness-related variables were analysed:

- *Gender*. Male vs. female. Gender was also used as a confounding variable.
- *Pre-morbid factors*. Information on pre-morbid factors was collected with a retrospective review of hospital notes using the Operational Criteria Checklist for Psychotic Illness (OCCPI) (McGuffin *et al.* 1991). The ratings of OCCPI in the NFBC 1966 has been described earlier (Isohanni *et al.* 1997, Moilanen *et al.* 2003). The variables referred to the time before or around the onset of illness. The following variables were used: *Mode of onset* (acute or gradual/insidious), where insidious onset refers to onset over a period longer than 6 months. *Poor work adjustment* (no/yes) was scored e.g. if the patient was unable to keep any job for more than 6 months, had a history of frequent changes of job or was only able to sustain a job well below that expected by his/her educational level. *Poor pre-morbid social adjustment* (no/yes) refers e.g. to difficulties in maintaining normal social relationships or to persistent social isolation. *Pre-morbid personality disorder* (no/yes) refers to any evidence of personality disorder present prior to the onset of psychosis. *Alcohol abuse within one year of onset of psychotic symptoms* (no/yes) was rated if the quantity was excessive (rater judgment) and alcohol-related complications had occurred. *Definite psychosocial stressor* (no/yes) was scored if a severely threatening event had occurred prior to onset of disorder that was unlikely to have resulted from the subject's own behaviour. Information on *marital status* (married/single) and *unemployment at onset* (no/yes) were also used. OCCPI data were available in some form for 112 (97.4 %) subjects of the sample, although some more data were missing on individual OCCPI items. The reasons for missing data were lack of hospital notes or insufficient information given in the notes.
- *Family history of psychosis*. First-degree relative having vs. not having non-organic psychosis. Assessed by hospital notes and by using data on mothers' and fathers' hospitalisations due to psychosis (FHDR) between 1972-2000. (see 4.5.1.2)
- *Length of first psychiatric hospitalisation*. The length of first hospitalisation was used as a categorised variable (1-7 days, 8-14 days, 15-30 days and 31 days or more). This categorisation is comparable with some earlier studies on the topic (Appleby *et al.* 1993, Saarento *et al.* 1998, Oiesvold *et al.* 2000). Due to the limited sample size, the first two categories were pooled in the multivariate analyses.

## 4.6 Confounding and mediating factors

The following variables were used as confounding and mediating factors (the number of original article where the confounder has been used):

- *Gender*. Men vs. women. Gender has been found to associate with educational outcome in an earlier report from NFBC 1966 (Isohanni *et al.* 1998) but not with the educational level of schizophrenia cases (Isohanni *et al.* 2001a). (I-III)
- *Family history of psychoses*. First-degree relative having vs. not having non-organic psychosis. Assessed by hospital notes and by using data on mothers' and fathers' hospitalisations due to psychosis (FHDR) between 1972-2000. (see 4.5.1.2) (I-III)
- *Age of illness onset for psychosis*. Ascertained from medical records and defined as the age when having the first evident psychotic symptoms (Räsänen *et al.* 1999). This variable was analysed as continuous when used as confounder. (I-III)
- *Perinatal risk*. Yes vs. no. This variable included some of the following: low birth weight (<2500g) or short gestation (<37 weeks) or perinatal brain damage). Earlier in NFBC 1966 low birth weight (<2500g) and a combination of low birth weight and short gestation (<37 weeks) and severe perinatal brain damage were associated with increased risk for developing schizophrenia by the age 28 years (Jones *et al.* 1998). This variable did not have influence on the associations between developmental milestones and risk of schizophrenia, or on persistent developmental deviance (Isohanni *et al.* 2001b, 2004) in schizophrenia. (II)
- *Father's social class in 1980*. Paternal social classes I-II vs. III-V. Information from the questionnaire for child, parents or school nurses at the child's age of 14 years. (see 4.5.1.2) (II)

## 4.7 Statistical methods

Cross-tabulations, non-parametric tests and regression models adjusted for confoundings were used for analysing associations between exposure and outcome variables. For analysing the statistical significance within the frequency tables chi-square test or, when appropriate, Fisher's exact test was used. All the analyses were done with different versions of SPSS, the new analyses for summary part of the thesis were done with SPSS 14.0 (SPSS Inc. 2005).

*Original article I.* The frequency and percentage distributions of the socio-demographic and clinical factors are reported, together with mean and median values with dispersion statistics. Predictor variables were analysed against all five definitions of outcomes. Differences between outcome groups were analysed with chi-square test (categorical variables) and independent samples t-test (continuous variables with normal distribution).

Logistic regression analysis was used to account for the effect of possible confounding variables on the association between predictors and outcome definitions. Possible confounders were selected according to the standard and commonly accepted use of gender and family history of psychosis suggested by previous literature (Kua *et al.* 2003).

For analysing the proportion of the variability in outcomes explained by the predictors we used Nagelgerke's R Square (R<sup>2</sup>) of the logistic regression model. Because of the relatively large number of predictor variables and multiple testing, Bonferroni's correction was used. Since the same predictor variables were used for predicting different outcomes, the significance level for P-value was corrected by the number of predictor variables (corrected P-value 0.0045).

*Original article II.* Statistical analyses were made with SPSS 11.5 for Windows. Outcome variables were dichotomised. Using the median as a cut-off point was employed for continuous outcome variables. Differences in outcomes between ages learning to stand (divided in two strata: 'early' = 10 months or less, 'late' = at 11 months or later), walk (divided in two strata: 'early' = 11 months or less vs. 'late' = 12 months or later), and talk (divided in two strata: 'early' = at least some words by 12 months, 'late' = no words by the age 12 months) were analysed with cross-tabulations. The relationships between the variables of interest were assessed with and without adjustment for potential confounding by sex, obstetric complications, family history of psychosis, father's social class, and the age of illness onset by logistic regression model.

*Original article III.* Differences between outcome groups were analysed with chi-square-test and odds ratios (dichotomised variables), trend test (linear-by-linear association statistic, ordinal variables), or Mann-Whitney U -test (continuous variables). Survival analysis with Log Rank test statistics was used to study the time to first relapse when comparing patients with short and long first hospitalisation. Survival curves are presented for males and females separately. Logistic and Cox regression analyses were used to adjust for confounding. In these multivariate analyses gender, age at first admission and the number of psychiatric treatment days (natural logarithm) were used as confounders.

*Original article IV.* The number of recovered cases and characteristics of the sample was analysed.

## 4.8 Ethical considerations

The Faculty of Medicine Ethics Committee of the University of Oulu keeps the study design of the NFBC 1966 under review, and data protection has been scrutinised by the Privacy Protection Agency. The plan for this doctoral thesis was officially approved by the Postgraduate Research Committee of the Faculty of Medicine, University of Oulu on 7 October 2003.

Permission for gathering register data for the entire NFBC 1966 was obtained from the Ministry of Social Welfare and Health Affairs in 1993. The 31-year follow-up survey of NFBC 1966 was approved by the Ethical Committee of Faculty of Medicine, Oulu University on 17 June 1996. The research plan for Cohort 1966 psychiatric follow-up in 1999-2001 was approved on 30 March 1998.

In the field surveys conducted in 1997 and in 1999-2001, subjects were given a complete description of the study, its aims and requirements: all subjects had the opportunity to refuse to participate and gave written informed consent.

## **4.9 Personal involvement**

I have participated in the Northern Finland 1966 Birth Cohort study as a researcher since 2000. During the field study in 1999-2001, I worked as a research assistant assisting in data collecting and saving the data.

All the original articles were designed in collaboration with the research group, and I have been accorded permission to use the data. For original article I, I made the study design and statistical analyses in collaboration with the research team. I analysed the sample for original article II. The study design for original article III was done together with the first author who did the statistical analysis for the article. I was responsible for the “Introduction” and “Discussion” parts of original article III. For original article IV I designed the methods, analysed the data and collected the information for non-participants in collaboration with other co-authors. I have done all the literature searches and reviews, writing of original articles (with the exception of article III, where I was responsible for parts of the manuscript) and this summary part of dissertation.

## 5 Results

### 5.1 Characteristics of the sample

Since the number of subjects in this study and in original articles varies, sample characteristic will be presented separately for each original paper.

#### *5.1.1 Outcome and its predictors in schizophrenia (I)*

Fifty-eight percent (n=34) of the subjects with schizophrenia who participated the field study in 1999-2001 were men. The mean age of illness onset was 23 years ( $\pm$  SD 4.1). Individuals had been ill for a median of 11 years (IQR 7, 15) and had spent a median of 134 days (IQR 38, 496) in psychiatric inpatient care. Five percent of the sample were in hospital, 72% were outpatients and 71% were using antipsychotic medication at the time of the study. Thus, almost one third of the schizophrenia group was not on current antipsychotic medication.

Participating schizophrenia subjects had a relatively good educational level, albeit they were often unable to work. Nineteen percent of the cases had a basic level of education (9 years or less), 75% secondary (10-12 years), and 7% tertiary level (13 years or more). In comparison, of the general population without psychiatric hospitalisations 12% had attained basic, 62% upper secondary and 26% tertiary level education or vocational training in the Northern Finland 1966 Birth Cohort (Isohanni *et al.* 2001). The social and occupational functioning among schizophrenia subjects was relatively poor; 54% of subjects were on disability pension or on sick leave. The median SOFAS score was 50 (IQR 36, 55). The median score for PANSS was 53 (IQR 41, 67), the median on positive dimension being 12 (IQR 9, 17) and on negative dimension 13 (IQR 7, 26).

### ***5.1.2 Early development and outcome in schizophrenia (II)***

This part of the study included 59 schizophrenia subjects whose characteristics have been presented earlier in paragraph 5.1.1.

In addition to 59 patients detected in the interview in 1999-2001 the analysis in this part of the study was also done for those who did not participate to the field study (N=40) and deceased subjects (N=10). Within this part of the sample there were 109 schizophrenia patients of whom 70 (64%) were males. The mean ( $\pm$  SD) age of illness onset for these cases was 22.3 years  $\pm$  4.1 years (range 14-31). The median age of illness onset was 22 years (IQR 19, 26). The subjects had median of 269 (IQR 85, 618) days spent in inpatient psychiatric care and had spent median of 8.2% (2.4, 18.8) of time in inpatient care. Sixty percent of the subjects were on disability pension. Thirty percent of the subjects had basic education, 63% had secondary and 6% had tertiary level of education.

There was information about developmental milestones for 95 individuals with schizophrenia. Of these, 24 (25%) learned to stand unsupported by the age 10 months, 27 (28%) learned to walk by the age 11 months and 71 (72%) spoke at least some words by the age 12 months. The mean IMD score was 0.00 (SD 1.00) and median 0.217 (IQR -0.602, 0.695).

### ***5.1.3 Patterns of hospitalisations in schizophrenic psychoses (III)***

There were 115 patients with schizophrenic psychoses in this sample. The mean ( $\pm$ SD) age at first hospitalisation due to psychosis (not the same as age of illness onset) was 23.8  $\pm$  4.2 years (range 15.2-31.6). The first hospitalisations due to psychosis took place during 1981-1997; except for one case where the first treatment in psychiatric ward, after onset of psychosis, took place in February 1998. The mean follow-up time of the sample was 10.5 $\pm$ 4.1 years. The median length of the first treatment was exactly one month (31 days).

### ***5.1.4 Recovery in schizophrenic psychoses (IV)***

This part of the study included 59 schizophrenia patients whose characteristics have been presented earlier in paragraph 5.1.1.

In addition, 12 subjects with other schizophrenia spectrum psychosis were studied. There were 4 (33%) males and the mean age of illness onset was 25.5 years (SD 3.5). Cases had been ill for approximately 7 years (median 6.9; IQR 6, 10) and they had spent median of 78 days (IQR 25, 121) in inpatient care. One-fourth (25%) of spectrum cases had been hospitalised during last two years and one-third (33%) used neuroleptic medication at the study moment. The median SOFAS score was 65 (IQR 56, 81). The median score for PANSS was 34 (IQR 30, 39). Among cases with schizophrenia spectrum

disorder 8% had basic educational level, 83% had secondary and 8% had tertiary level education. None was pensioned.

## **5.2 Outcome and its predictors in schizophrenia (I)**

### ***5.2.1 Good and poor clinical and social outcomes***

There was one subject who could not be interviewed because of very severe and chronic illness. Living in supported housing, he required help in all daily activities, had psychotic symptoms and was on disability pension. He was considered as having a poor outcome in both clinical and social domains. There was also one subject with intellectual disability who was mute. She received a disability pension and scored 35 on SOFAS. There was no information for her PANSS and thus her clinical outcome could not be assessed.

The distribution of subjects into different outcomes by gender is presented in Table 5. The amount of good and poor outcomes depended on the outcome definition used. Concerning clinical outcome, 59% had not been hospitalised during the last two years, 23% had remission, and 10% had good global clinical outcome. The prevalence of poor clinical outcome ranged between 41% and 77% depending on the criteria used. In terms of social outcome, 46% were not on disability pension, and 15% had a good global social outcome. The prevalence of poor social outcome ranged from 37% to 54%. Males and females had very similar outcomes.

Table 5. Outcomes in schizophrenia within the Northern Finland 1966 Birth Cohort by using different outcome criteria. (From original article I, Table 1.)

Criteria for outcome	Males (N=34) n (%)	Females (N=25) n (%)	Total (N=59) n (%)
Clinical outcome			
Hospitalisation <sup>1</sup>			
Good	20 (59)	15 (60)	35 (59)
Poor	14 (41)	10 (40)	24 (41)
Remission <sup>2</sup>			
Good	7 (21)	6 (25)	13 (23)
Poor	27 (79)	18 (75)	45 (77)
Global clinical outcome <sup>3</sup>			
Good	4 (12)	2 (8)	6 (10)
Moderate	5 (15)	4 (17)	9 (16)
Poor	25 (74)	18 (75)	43 (74)
Social outcome			
Working ability <sup>4</sup>			
Good	14 (41)	13 (52)	27 (46)
Poor	20 (59)	12 (48)	32 (54)
Global social outcome <sup>5</sup>			
Good	6 (18)	3 (12)	9 (15)
Moderate	16 (47)	12 (48)	28 (48)
Poor	12 (35)	10 (40)	22 (37)

Due to lack of information Remission and Global clinical outcome could not be assessed for one female.

<sup>1</sup> Good outcome = Not hospitalised during the last 2 years; Poor outcome = Hospitalised during the last 2 years

<sup>2</sup> Modified remission criteria of Andreasen *et al.* (2005). Good outcome = Remission, i.e. maximum score of 3 in PANSS items P1, P2, P3, N1, N4, N6, G5, G9; Poor outcome = No remission

<sup>3</sup> Good outcome = Maximum score of 2 on any positive or negative items of PANSS and no psychiatric hospitalisations during the last two years; Moderate outcome = Maximum score of 4 on any positive or negative items of PANSS and no psychiatric hospitalisations during the last two years; Poor outcome = The remainder of the cases that did not fulfil the criteria of good or moderate outcome

<sup>4</sup> Good outcome = Not on disability pension and not on sick leave; Poor outcome = On disability pension or sick leave

<sup>5</sup> Good outcome = At least 61 points on the SOFAS, not on disability pension and not on sick leave; Moderate outcome = At least score 41 on SOFAS; Poor outcome = The remainder of the cases who did not fulfil the criteria of good or moderate outcome

### 5.2.2 Predictors of outcomes

For statistical analyses, outcome groups were collapsed into poor vs. good/moderate outcome groups if necessary. This was done because of the small amount cases in some of the good or moderate groups and because of the clinical importance of the poor outcome group. The prediction of outcomes concentrated on predicting the definitions of outcomes done by our research group (global clinical and global social outcomes), but statistically significant predictors will be briefly reported for other outcome measures as well.

### 5.2.2.1 Predictors of clinical outcome

There were no statistically significant predictors of global clinical outcome (Table 6).

School marks and age of illness onset predicted remission. Individuals without remission had significantly lower school marks compared to those with remission (7.4 vs. 8.4). and this difference remained statistically significant after adjusting for family history of psychosis and gender (Wald chi-square test 8.11, P-value 0.004, odds ratio (OR) 4.7, 95% confidence interval (CI) 1.6-13.8). Those without remission also had earlier age of illness onset compared to those remitted (22.4 vs. 25.2 years), the difference remaining statistically significant after adjusting for family history of psychosis and gender (Wald chi-square test 4.26, P-value 0.039, OR 1.2, 95% CI 1.0-1.4). After adjustment, father's low social class protected from having poor outcome in terms of hospitalisations during the last two years: 77% of good outcome cases and 54% of poor outcome cases had low social class (III-V) in adolescence (Wald chi-square test 5.89, P-value 0.015, OR 0.19, 95% CI 0.05-0.7). This difference was not statistically significant in crude analysis.

When using Bonferroni correction the only significant predictors were school marks and social class. There were no other predictors of clinical outcome definitions.

Regarding the predictive power of putative prognostic variables, school marks explained 27% ( $R_2 = 0.268$ ) of the variance between remission groups, while onset age explained 11% ( $R_2 = 0.114$ ). Combined, these variables explained 35% ( $R_2 = 0.346$ ) of the variance. Social class in adolescence, family history of psychosis and gender, taken together, explained 21% ( $R_2 = 0.212$ ) of the variance of outcome groups of hospitalisation.

### 5.2.2.2 Predictors of social outcome

Having close friends in childhood, school performance and age at illness onset predicted some dimensions of social outcome. Individuals who had no close friends in childhood ( $n = 5$ ) had more often poor global social outcome compared to those who had close friends (100% vs. 29%, Fisher's Exact Test P-value 0.005) (Table 6). Since the number of cases with no close friends in childhood was small, no adjustment for confounders could be made. Individuals with poor global social outcome also had earlier age of illness onset compared with good outcome cases (20.6 vs. 24.5 years); this difference remained after controlling for family history of psychosis and gender (Wald chi-square 11.0, P-value 0.001, OR 0.8, 95% CI 0.6-0.9). Those under normal grade at high school ( $n = 12$ ) were more often on disability pension compared to those in normal grade (92% vs. 45%). This association remained statistically significant after adjusting for family history of psychosis and gender (Wald chi-square 5.81, P-value 0.016, OR 14.1, 95% CI 1.6-121.9). There were no other significant predictors of outcomes.

Age at illness onset explained 28% ( $R_2 = 0.275$ ) of the variance between different outcome groups (of social outcome), while school grade explained 21% ( $R_2 = 0.206$ ) of the variance in working ability.

After Bonferroni correction, age of illness onset was the only statistically significant predictor of social outcome.

Table 6. Predictors of clinical and social outcome in schizophrenia (n=59) in the Northern Finland 1966 Birth Cohort. (From original article I, Table 2)

Predicting variable	Global clinical outcome				Global social outcome				
	Good/moderate outcome (n=15)		Poor outcome (n=43)		Good/moderate outcome (n=37)		Poor outcome (n=22)		P-value
	n	%	n	%	n	%	n	%	
Male gender	9/15	60	25/43	58	22/37	60	12/22	55	0.71
Perinatal complications	3/15	20	4/43	9	5/37	14	3/22	14	>0.99
1 <sup>st</sup> degree relative having psychosis	6/15	40	12/43	28	13/37	35	5/22	23	0.32
Alcoholism in the family	3/15	20	12/43	28	11/37	30	4/22	18	0.33
Father's social class III-V at age 14 years	11/15	73	28/43	65	25/37	68	15/22	68	0.96
Single-parent family at age 14 years	5/15	33	13/43	30	11/37	30	7/22	32	0.87
No close friends during childhood	0/10	0	5/26	19	0/22	0	5/14	36	0.005 <sup>1</sup>
Tried drinking by the age 14 years	9/12	75	22/33	67	23/30	77	8/16	50	0.066
Not in normal grade at the age 14 years	3/15	20	9/43	21	5/37	14	7/22	32	0.11
School marks at the age 16 years (mean)	7.8		7.5		7.7		7.4		0.20
Age of illness onset (years, median)	24.0		23.0		25.0		19.0		<0.001 <sup>2</sup>

\* One of the 59 participating subjects had limited intelligence, and could not answer the interview adequately. There is not information concerning the clinical outcome for this person. Because of missing data, there was not information concerning all variables for all the cases.

<sup>1</sup> Since the number of cases with no close friends in childhood was very small, adjusting for confounders could not be made.

<sup>2</sup> Tests statistics when adjusted with familiarity and gender: Wald chi-square 11.0, p-value 0.001, OR 0.8, 95% CI 0.6, 0.9

### 5.3 Early development and outcome in schizophrenia (II)

Analyses were first made in the 109 cases detected by the year 2001 (Table 7), and additional variables were examined within the subgroup of 59 subjects who participated in the field study in 1999-2001.

Compared to those who achieved motor milestones early, individuals with schizophrenia who learnt to *stand without support* later had statistically significantly later age of illness onset (Odds Ratio 0.19, 95% Confidence Interval 0.07-0.55), fewer treatment days in the hospital (OR 0.20, 95% CI 0.07-0.57), and had spent smaller proportion of time in the hospital after getting ill (OR 0.28, 95% CI 0.10-0.77). And those who learnt to *walk without support* later had similarly less treatment days (OR 0.33, 95% CI 0.13-0.83), and had spent smaller proportion of time in the hospital (OR 0.27, 95% CI 0.11-0.72), compared to those learning earlier. When gender, obstetric complications, family history of psychosis, father's social class and age of illness onset were included as confounding most of the association between age of learning developmental milestones and outcome in schizophrenia mostly remained. The crude and adjusted results concerning these associations are presented in Table 7.

Some statistically significant associations occurred after adjusting for confounders. Compared to early learners, when age of illness onset was taken into account, those who learnt to *speak* later had spent statistically significantly smaller amount of time in hospital (OR 0.35, 95% CI 0.13-0.91). When gender, obstetric complications, family history of psychosis, and father's social class were included into the analyses those who learnt to *stand without support* later were statistically significantly better educated (OR 0.31, 95% CI 0.11-0.94) compared to early learners. Contrary, after adjusting for these same confounders those who learnt to *walk without support* later had statistically significantly higher total score on PANSS (OR 5.13, 95% CI 1.13-23.38). There were no statistically significant associations in crude analyses regarding age of learning developmental milestones and outcome variables assessed in the field study in 1999-2001 (N=59).

Regarding IMD, each increase in IMD (meaning later development) decreased the risk of having a poor outcome (over median days in hospital) (OR 0.61, 95% CI 0.39-0.94), but this was no longer statistically significant when adjusting with confounders. Each increase in IMD also decreased the risk of having spent over median proportion of life in hospital (0.63, 0.41-0.97), but the statistically significant association did not remain after adjusting. Some statistically significant associations occurred after adjusting with confounders. Each increase in IMD decreased the risk of having early age of illness onset (under median) (0.60, 0.38-0.95) and decreased the risk of having basic education (0.55, 0.33-0.92).

Table 7. The age of achieving developmental milestones and the course of illness in schizophrenia. Outcome information ascertained from national registers by the year 2001. (Table 1 from original article II)

Outcome variables*	Schizophrenia patients (n/N, %)		Reference	Odds Ratios (95% CI) for outcome variables**
	Early learners	Late learners		
Learnt to stand without support	-10 months N=24	11+ months N=71	-10 months	11+ months
Under median age of illness onset***	18/24, 75%	26/71, 37%	Reference	0.19 (0.07-0.55) <sup>1</sup>
Over median psychiatric treatment days***	18/24, 75%	26/69, 38%	[Ref.]	0.20 (0.07-0.57) <sup>2,3</sup>
Over median time spent (%) in hospital***	17/24, 71%	28/69, 41%	[Ref.]	0.28 (0.10-0.77) <sup>4,5</sup>
Basic educational level	11/24, 46%	21/71, 30%	[Ref.]	0.50 (0.19-1.29)
Pensioned	17/21, 81%	37/64, 58%	[Ref.]	0.32 (0.10-1.07)
Deceased	3/24, 13%	7/71, 10%	[Ref.]	0.77 (0.18-3.23)
Learnt to walk without support	-11 months N=27	12+ months N=68	-11 months	12+ months
Under median age of illness onset	15/27, 56%	29/68, 43%	[Ref.]	0.60 (0.24-1.46)
Over median psychiatric treatment days***	18/27, 67%	26/66, 39%	[Ref.]	0.33 (0.13-0.83) <sup>6,7</sup>
Over median time spent (%) in hospital***	19/27, 70%	26/66, 39%	[Ref.]	0.27 (0.11-0.72) <sup>8,9</sup>
Basic educational level	11/27, 41%	21/68, 31%	[Ref.]	0.65 (0.26-1.64)
Pensioned	17/23, 74%	37/62, 60%	[Ref.]	0.52 (0.18-1.51)
Deceased	4/27, 15%	6/68, 19%	[Ref.]	0.56 (0.14-2.15)
Learnt to talk by age 12 months	At least some words N=71	No words N=27	At least some words	No words
Under median age of illness onset	32/71, 45%	14/27, 52%	[Ref.]	1.31 (0.54-3.19)
Over median psychiatric treatment days	35/69, 51%	11/27, 41%	[Ref.]	0.67 (0.27-1.65)
Over median time spent (%) in hospital	38/69, 55%	9/27, 33%	[Ref.]	0.41 (0.16-1.03)
Basic educational level	24/71, 34%	8/27, 30%	[Ref.]	0.83 (0.32-2.16)
Pensioned	42/62, 68%	14/26, 54%	[Ref.]	0.56 (0.22-1.42)
Deceased	9/71, 13%	1/27, 4%	[Ref.]	0.27 (0.03-2.20)

\* Medians for outcome variables: age of illness onset, 22 years; psychiatric treatment days, 269; time spent in hospital (%), 8.22; \*\* Non adjusted Odds Ratios, \*\*\*p-value < 0.05  
 Adjusted Odds Ratios (95% CI) (adjusted for gender, obstetric complications, family history of psychosis, father's social class): <sup>1</sup>Standing at 11 months and risk of having under median age of illness onset OR=0.15 (0.05-0.46)\*\*\*, <sup>2</sup>Standing at 11 months and risk of having over median days spent in hospital OR=0.20 (0.07-0.61)\*\*\*, <sup>3</sup>Standing at 11 months and risk of having over median proportion of time spent in hospital OR=0.31 (0.11-0.89)\*\*\*, <sup>4</sup>Walking at 12 months or later and risk of having over median days spent in hospital OR=0.36 (0.14-0.95)\*\*\*, <sup>5</sup>Walking at 12 months or later and risk of having over median proportion of time spent in hospital OR=0.33 (0.12-0.89)\*\*\*  
 Adjusted Odds Ratios (95% CI) (adjusted for onset age): <sup>6</sup>Standing at 11 months and risk of having over median days spent in hospital OR=0.34 (0.11-1.05), <sup>7</sup>Standing at 11 months and risk of having over median proportion of time spent in hospital OR=0.34 (0.12-0.96)\*\*\*, <sup>8</sup>Walking at 12 months or later and risk of having over median days spent in hospital OR=0.35 (0.12-0.99)\*\*\*, <sup>9</sup>Walking at 12 months or later and risk of having over median proportion of time spent in hospital OR=0.29 (0.11-0.78)\*\*\*

Due to the surprising findings about association between late learning and better outcome, some additional, developmental factors in the sample were analysed, by using the age of learning to stand as an example (Table 8). There were statistically significant differences in obstetric complications, school marks and age of illness onset between the groups classified according to the age of learning how to stand. Those who learned to stand later had more often obstetric complications, and worse school marks but later age of illness onset. Compared to early learners, those who learned to stand later had more often a family history of psychosis, although this result was statistically inconclusive.

*Table 8. Some factors related to development in different groups of ages learning to stand.*

Learnt to stand without support (months)	-10 N=26	11 N=25	12+ N=47	p-value
Male gender, N (%)	15 (58%)	17 (68%)	31 (66%)	0.71
Family history of psychosis, N (%)	4 (15%)	7 (28%)	17 (36%)	0.17
Obstetric complications, N (%)	0 (0%)	2 (8%)	10 (21%)	0.013
Traumatic brain injury, N (%)	4 (15%)	1 (4%)	4 (9%)	0.39
Age of illness onset (median, years)	20	23	23	0.005
School marks for all subjects (mean)	7.8	7.5	7.2	0.013

#### 5.4 Patterns of hospitalisations in schizophrenic psychoses (III)

In this part of the study, the first psychotic hospitalisations of the sample took place during 1981-1997; except for one case where the first treatment in psychiatric ward, after onset of psychosis, took place in February 1998. The mean follow-up time of the sample was  $10.5 \pm 4.1$  years. The mean length of the first hospitalisation due to psychosis was about 2 months ( $63.0 \pm 95.3$  days). The median length of the first treatment was exactly one month (31 days).

The re-hospitalisation rate within two years was 60.0% (69/115 subjects). Almost all subjects were followed for 5 years (107/115, 93%). In this sub-sample the re-hospitalisation rate was 73.8% (79/107 cases) within 5 years. In total 80.9% (93/115) cases were re-hospitalised during the follow-up; mean time to re-hospitalisation was  $17.8 \pm 24.4$  months. Correspondingly, one fifth (22/115, 19%) of the subjects had no re-hospitalisations during the follow-up. Almost half of the subjects had their first 3 admissions within 3 years (53/115, 46%).

Among subjects with schizophrenia 67.0% (59/88) were re-hospitalised during first two years and 86.4% (76/88) during the whole follow-up time. In other schizophrenia spectrum psychoses the numbers were 37% (10/27) and 63.0% (17/27), respectively.

The socio-demographic and clinical characteristics of the subjects are presented in Table 9 by different hospitalisation variables. Marital status, definite psychosocial stressor prior to onset and length of the first treatment were associated with one or more of the hospitalisation variables.

*Table 9. Socio-demographic and symptom variables of living subjects with schizophrenia psychoses by different hospitalisation variables within the Northern Finland 1966 Birth Cohort. (Table 1 from original article III)*

Pre-morbid factors	Re-hospitalised within 2 years *		Re-hospitalised during follow-up time †		First 3 admissions within 3 years	
	n	%	n	%	n	%
Gender (n=115)						
Male (n=65)	39	60.0	55	84.6	32	49.2
Female (n=50)	30	60.0	38	76.0	21	42.0
Mode of onset (n=103)						
Insidious (n=49)	31	63.3	42	85.7	24	49.0
Gradual (n=34)	18	52.9	28	82.4	12	35.3
Acute (n=20)	10	50.0	13	65.0	9	45.0
Marital status (n=95)						
Single (n=60)	39	65.0	55	91.7	33	55.0
Other (n=35)	19	54.3	23	65.7	13	37.1
Unemployed at onset (n=106)						
Yes (n=38)	25	65.8	33	86.8	18	47.4
No (n=68)	37	54.4	52	76.5	29	42.6
Poor work adjustment (n=100)						
Yes (n=30)	21	70.0	26	86.7	14	46.7
No (n=70)	39	55.7	53	75.7	28	40.0
Poor pre-morbid social adjustment (n=70)						
Yes (n=34)	23	67.6	29	85.3	16	47.1
No (n=36)	22	61.1	24	66.7	15	41.7
Pre-morbid personality disorder (n=62)						
Yes (n=18)	11	61.1	1	77.8	9	50.0
No (n=44)	26	59.1	3	84.1	17	38.6
Alcohol abuse within 1 year of onset (n=108)						
Yes (n=12)	10	83.3	11	91.7	7	58.3
No (n=96)	53	55.2	76	79.2	40	41.7
Psychosocial stressor prior to onset (n=111)						
Yes (n=10)	3	30.0	5	50.0	2	20.0
No (n=101)	63	62.4	85	74.2	48	47.5
Familial risk for psychosis † (n=115)						
Yes (n=24)	18	75.0	21	87.5	13	54.2
No (n=91)	51	56.0	72	79.1	40	44.0
Length of first treatment						
1 to 7 days (n=20)	17	85.0	18	90.0	13	65.0
8 to 14 days (n=15)	10	66.7	11	73.3	9	60.0
15 to 30 days (n=22)	12	54.5	18	81.8	12	54.5
31 days or over (n=58)	30	51.7	46	79.3	19	32.8

\*,† Time to re-hospitalisation was measured from day of discharge to day of re-hospitalisation, † Mean follow-up time 10.5 years (SD = 4.1 years), ‡ Collected from hospital notes for all 1<sup>st</sup> degree relatives (n=77), and additionally for parents from the Finnish Hospital Discharge Register until the end of the year 2000 (n=115). Statistically significant (p<0.05; chi-square test, except trend test if more than two categories) differences are *in italics*.

The risk for re-hospitalisation within two years increased when the length of first hospitalisation decreased. Eighty-five per cent (17/20) of the subjects who had a very short (1-7 days) first treatment were re-hospitalised within two years; the corresponding percentage was 67% (10/15) for those whose first treatment lasted 8-14 days, 55% (12/22) for those whose first treatment lasted 15-30 days, and 52% (19/58) for those whose first treatment lasted more than 30 days.

Due to the small sample size, the results are presented with the genders pooled, although there were a few statistically significant differences in the variables of Table 9 between genders. Males were more often single at the time of onset (chi-square test,  $\chi^2=10.389$ ,  $df=1$ ,  $p=0.001$ ), they had more often poor pre-morbid social adjustment ( $\chi^2=5.803$ ,  $df=1$ ,  $p=0.016$ ) and they had more often alcohol/drug abuse within one year of onset of psychotic symptoms ( $\chi^2=3.960$ ,  $df=1$ ,  $p=0.047$ ).

Table 10 presents adjusted odds ratios for the predictors of patterns of hospitalisations in this sample of schizophrenic psychoses.

*Table 10. Predicting re-hospitalisation within 2 years and frequent admissions in living subjects with schizophrenia psychoses within the Northern Finland 1966 Birth Cohort. (Table 2 from original article III).*

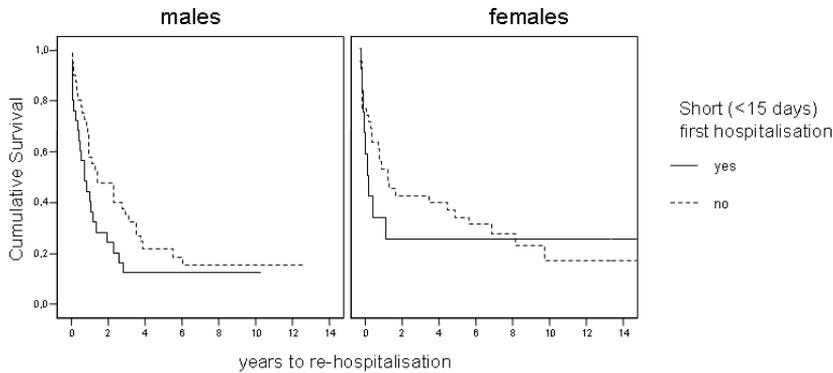
Predictors	Re-hospitalisation within 2 years * OR (95% CI)	First 3 admissions within 3 years OR (95% CI)
Length of first treatment [reference > 30 days]		
1 to 14 days	<i>6.39 (2.00-20.41)</i>	<i>13.77 (3.92-48.36)</i>
15 days to 30 days	1.62 (0.51-5.15)	<i>3.84 (1.04-14.16)</i>
Other predictors		
Male gender	0.85 (0.38-1.94)	1.22 (0.53-2.83)
Insidious onset	1.19 (0.50-2.86)	0.95 (0.38-2.38)
Marital status, single	1.19 (0.38-3.74)	1.09 (0.36-3.31)
Unemployed at onset	1.19 (0.48-2.94)	0.82 (0.32-2.10)
Poor work adjustment	1.55 (0.58-4.15)	1.06 (0.41-2.77)
Poor pre-morbid social adjustment	0.57 (0.16-2.02)	0.45 (0.12-1.72)
Pre-morbid personality disorder	0.89 (0.21-3.85)	4.42 (0.79-24.62)
Alcohol abuse within one year of onset	4.10 (0.74-22.88)	1.92 (0.45-8.12)
Psychosocial stressor prior to onset	0.39 (0.09-1.79)	0.55 (0.09-3.22)
Familial risk for psychosis	<i>3.36 (1.09-10.39)</i>	2.21 (0.78-6.26)

\* Time to re-hospitalisation was measured from day of discharge to day of re-hospitalisation. Odds ratios are adjusted for gender, age at first admission and the number of psychiatric hospital days (transformed using natural logarithm). Statistically significant (chi-square test,  $p<0.05$ ) differences are *in italics*.

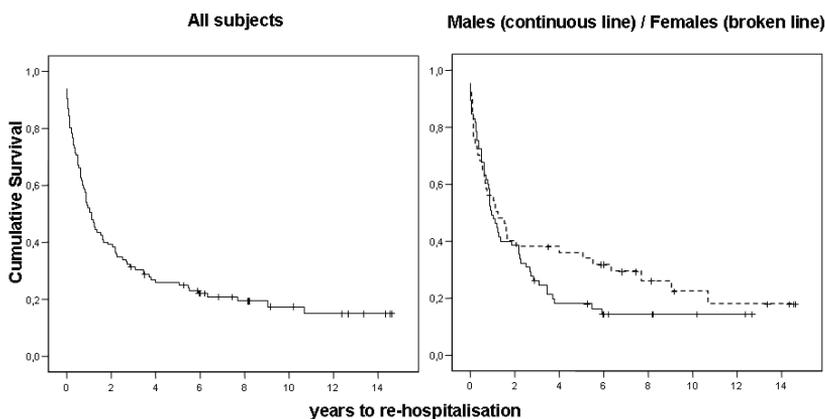
After adjusting for confounders when compared to long first hospitalisation (31 days or more), a short (1-14 days) first hospitalisation predicted re-hospitalisation within two years (adjusted OR 6.39; 95% CI 2.00-20.41). A short first hospitalisation also predicted frequent admissions (first 3 admissions in 3 years) (13.77; 3.92-48.36). Intermediate long (15-30 days) treatment was also a risk for frequent admissions (3.84; 1.04-14.16) when compared to long treatment. The only other statistically significant risk factor was family

history of psychosis, which associated with re-hospitalisation within two years (3.36; 1.09-10.39).

The survival curves for time to re-hospitalisation in this sample for males and females are presented in Figure 5. There are separate curves for subjects by the length of their first hospitalisation (1-14 days vs. 15 days or more). Subjects with short first hospitalisation were re-hospitalised sooner. The survival curves for patients with a short first hospital period flattened after two years, whereas flattening of the curves took place considerably later for those with long first treatment. In crude tests for equality of the curves, the differences were non-significant. When adjusted for age at first admission and the number of psychiatric treatment days in Cox regression analysis, the survival curves were statistically significantly different between those with short and long first hospitalisation (males, Wald chi-square test = 7.704,  $p=0.006$ ; females, 4.370,  $p=0.04$ ). This difference was statistically significant in the total sample as well (Wald chi-square test = 2.231,  $p=0.001$ ). The survival curve for the total sample without stratifying for the length of the first hospitalisation was flattening after approximately five years (Figure 6).



**Fig. 5. Survival curves for re-hospitalisation for males and females by the length of first hospitalisation (1-14 days vs. 15 days or more) in living subjects with schizophrenia psychoses within the Northern Finland 1966 Birth Cohort. (Figure 1 from original article III)**



**Fig. 6. Survival curve for re-hospitalisations for whole sample of schizophrenic psychoses and strata by males and females within the Northern Finland 1966 Birth Cohort.**

## 5.5 Recovery in schizophrenic psychoses (IV)

### 5.5.1 Recovery among participants

One (1.7%) out of a total of 59 cases with schizophrenia whereas three (25%) out of 12 schizophrenia spectrum disorder cases met all the criteria for full recovery. Thus, in total, full recovery occurred in 6% (4/71) of subjects with schizophrenia or schizophrenia spectrum disorder. In addition, one (1.7%) schizophrenia subject and two (16.7%) schizophrenia spectrum subjects had partial recovery, but did not fulfill the criteria for full recovery. Recovered schizophrenia subjects have been described in detail earlier (fully recovered: case 3 and partially recovered: case 5, Isohanni *et al.* 1999). Briefly, the subject with full recovery performed very well at school, studies, and professional life, and was married. His acute psychosis just fulfilled the six-month duration criterion of DSM-III-R schizophrenia. The subject who had partially recovered had bizarre behaviour even before the school age, had difficulties in studies and working, and was living alone. Though his course was predicted to be chronic by the end of 1994, until the end of 2001 he shows only minor signs of illness. Altogether 3.4% (2/59) of schizophrenia and 41.7% (5/12) of schizophrenia spectrum disorder subjects had fully or partially recovered. Results and distribution of subjects within different outcome variables are shown in detail in Table 11.

Characteristics of the whole sample and current outcomes for recovered subjects are presented in Table 12. There are missing data concerning PANSS, SOFAS, occupational status, antipsychotic medication, and familial risk for a few participating subjects, but the rate of missing data in any of the variables did not exceed 7% for all participants.

*Table 11. Criteria and results concerning each recovery dimensions in the Northern Finland 1966 Birth Cohort Study. (From the original article IV, Table 1)*

Assesment of outcome	Schizophrenia (N=59)		Schizophrenia spectrum <sup>6</sup> (N=12)	
	N	(%)	N	(%)
CGI <sup>1</sup>				
1 or 2 points (fully and partially recovered)	2	(3.4)	5	(42)
PANSS <sup>2</sup>				
Total scores $\leq 36$ and $\leq 2$ in all positive and negative items (fully recovered)	7	(12)	5	(42)
Total scores $\leq 36$ (partially recovered) <sup>3</sup>	3	(5.1)	3	(25)
SOFAS <sup>4</sup>				
$\geq 71$ (fully recovered)	2	(3.4)	5	(42)
$\geq 61$ (partially recovered) <sup>3</sup>	8	(14)	3	(25)
Hospitalisation				
No psychiatric hospitalisations during last two years (fully and partially recovered)	42	(71)	9	(75)
Medication <sup>5</sup>				
No or low dose (fully recovered, not a criterion for partial recovery)	38	(64)	11	(92)
Working capacity				
Not on disability pension or sick leave (full recovery, not a criterion for partial recovery)	31	(53)	12	(100)
Recovery rates				
Full recovery	1	(1.7)	3	(25)
Partial recovery	1	(1.7)	2	(16.7)
Total	2	(3.4)	5	(41.7)

<sup>1</sup> CGI: Clinical Global Impressions

<sup>2</sup> PANSS: Positive And Negative Symptoms Scale

<sup>3</sup> Including only cases meeting the criteria for partial recovery, not full recovery.

<sup>4</sup> SOFAS: Social and Occupational Functioning Assessment Scale

<sup>5</sup> Medication: Transformed as chlorpromazin equivalents per day, low dose = 300 mg chlorpromazin equivalents per day or less

<sup>6</sup> Schizophreniform psychosis (n=3), schizoaffective disorder (n=7) and delusional disorder (n=2)

Table 12. Outcomes (by the end of 2001) of fully and partially recovered DSM-III-R schizophrenia and other schizophrenia spectrum psychosis subjects, as well as some characteristics of all participants and non-participants in the Northern Finland 1966 Birth Cohort Study. (From original article IV, Table 2)

Cases	Clinical outcome						Social outcome			
	DSM-III-R diagnosis	Age at illness onset (years)	Sex	Family history of psychosis	CGI	PANSS	Current medication	Hospitalisation during past two years	SOFAS	Ability to work
Full recovery										
Schizophrenia case 1 (case 3 in Isohanni <i>et al.</i> 1999)	295.30	27	Male	No	1	30	No	No	90	Employed
Spectrum case 1	295.40	20	Female	No	1	30	No	No	81	Unemployed
Case 2	295.40	19	Male	No	1	30	No	No	90	Employed
Case 3	295.40	26	Male	No	1	30	No	No	80	Student
Partial recovery										
Schizophrenia case 1 (case 5 in Isohanni <i>et al.</i> 1999)	295.30	25	Male	No	1	30	No	No	61	Employed
Spectrum case 1	297.10	31	Female	No	1	30	Low-dose	No	81	Unemployed
Case 2	297.10	28	Female	No	2	34	No	No	75	Maternity leave
All cases in the study (N=71)	295.1 (N=12) 295.3 (N=16) 295.6 (N=1) 295.9 (N=30) 295.4 (N=3) 295.70 (N=7) 295.71 (N=2)	Mean 23.5	Male (N=38) Female (N=33)	No (N=56) Yes (N=10) (7 missing data)	Mean 4.58	Mean 52.19 (2 missing data)	No (N=25) Low-dose (N=24) High-dose (N=21) (1 missing data)	No (N=52) Yes (N=19)	Mean 50.40 (3 missing data)	Employed (N=14) Unemployed (N=11) Pensioned (N=26) Student (N=6) Other (N=13)
Non-participants (N=48)	295.1 (N=6) 295.3 (N=12) 295.9 (N=22)	Mean 22.4	Male (N=30) Female (N=18)	No (N=8) Low-dose (N=4) High-dose (N=14) (22 missing data)			No (N=8) Low-dose (N=4) High-dose (N=14)	No (N=27) Yes (N=11)		(2 missing data) Employed (N=6) Unemployed (N=5) Pensioned (N=23) Student (N=0) Other (N=1)
	295.4 (N=4) 295.71 (N=4)									(13 missing data)

### ***5.5.2 Recovery among non-participants***

During the second phase of data collection in 2002-2003, information for 39 non-participants with schizophrenic psychosis was received. For these individuals, however, full information of all the indicators of outcome (hospitalisations, antipsychotic medication, occupational status) was not obtained, because at that time our research group did not have register data about pensions and the FHDR data for the previous two years. For 11 (28%) subjects (all having schizophrenia) the information was adequate to exclude both full and partial recovery, and altogether for 29 (74%) at least full recovery could be excluded (26 of these were subjects with schizophrenia). Eleven (29%) had received psychiatric hospital treatment during the last two years, 14 (54%) used high-dose (over 300 mg chlorpromazine equivalent per day) antipsychotic medication and 23 (66%) were pensioned.

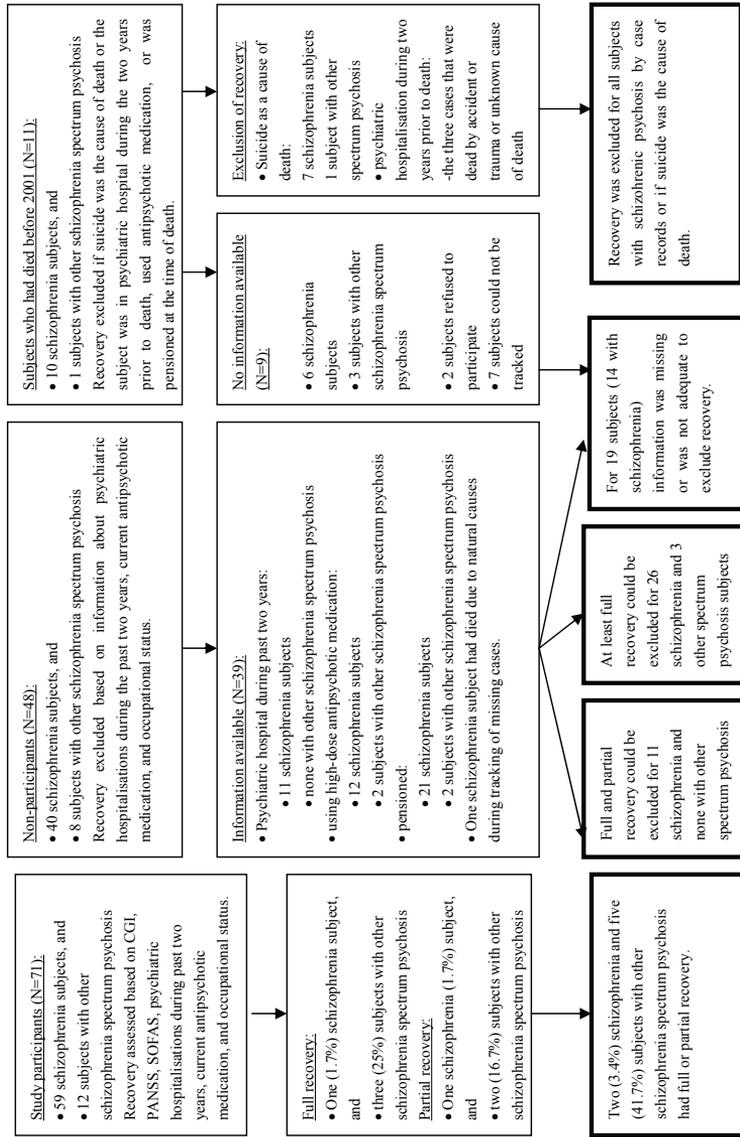
Six (15%) of the non-participants had not been hospitalised during the past two years, used no or low-dose antipsychotic medication, and were not pensioned, and thus could possibly be fully recovered.

One subject with schizophrenia died by natural death during the tracking of non-participants. For this subject, there were no medical records available, and it was impossible to assess his outcome before death.

Among three subjects who had died by accident, trauma, or by unknown cause of death, recovery was excluded. Each of these subjects had been hospitalised during the past two years before death. For subjects who had died by suicide, the cause of death could be considered as a sign of poor outcome and non-recovery.

Finally, it was not possible to obtain any information for 9 subjects with schizophrenic psychosis (6% of all 146 living cases). Seven of these did not reply to the questionnaire and could not be reached by telephone. Two refused to participate. When the treatment and sociodemographic variables across subjects for whom there was not adequate or no information (N=19) and participants and non-participants with adequate information (N=100) were compared there were no statistically significant differences in sex, parental socioeconomic status in 1966 or 1980, educational level, age at the onset of illness, or number of psychiatric inpatient admissions.

Figure 7 shows a summary of results for participants and non-participants and those subjects who had died.



**Fig. 7. Recovery of participating and non-participating subjects with schizophrenia and other schizophrenia spectrum psychosis within the NFBFC 1966. (Modified from Figure 2, original article IV)**

## **6 Discussion**

### **6.1 Main findings**

The main findings of the study corresponding to the presented aims are:

1. The outcome of schizophrenia was relatively poor: good clinical outcome varied from 10% to 59%, and good social outcome from 15% to 46%, depending on the definition of outcomes. Prevalence of poor clinical outcome varied from 41% to 77% and that of poor social outcome from 37% to 54%. Lack of friends in childhood, father's high social class, lower school performance and earlier age of illness onset predicted poor outcomes. (Original article I)
2. While delayed motor milestones are associated with an increased risk of schizophrenia in the general population, within those with schizophrenia delays in these same milestones did not predict adverse outcomes. Unexpectedly, individuals with schizophrenia who learnt to stand, walk and speak later required significantly fewer days in the hospital, and those learning to stand later had also later age of illness onset and were better educated. However, those who learnt to walk later had higher total score on PANSS, compared to early learners. (Original article II)
3. Sixty percent of the subjects with schizophrenic psychoses were re-hospitalised within two years after first hospitalisation due to psychosis and 81% were re-hospitalised during the entire follow-up of approximately 10.5 years. Almost half of the subjects had their first 3 admissions within 3 years. Familial risk for psychosis predicted re-hospitalisation within two years. A short first hospitalisation (1-14 days) also predicted frequent hospitalisations and re-hospitalisation within two years, and the risk for re-hospitalisation increased when the length of the first hospitalisation decreased. (Original article III)
4. Very few subjects with schizophrenia recover from the illness by the age 35 years. Only 3.4% of subjects with schizophrenia were fully or partially recovered. Among the subjects with other schizophrenia spectrum psychosis, recovery seems to be more likely, with 41.7% of the subjects recovered. (Original article IV)

## 6.2 Discussion of results

### 6.2.1 *Good and poor clinical and social outcome (I)*

In this thesis study, the outcome of relatively young people with schizophrenia was quite poor, especially when considering the clinical dimension. The prevalence of good clinical outcome varied from 10% to 59%, and that of good social outcome from 15% to 46%, depending on the definition of outcomes. Poor clinical outcome varied from 41% to 77% and poor social outcome from 37% to 54%.

This sample shows similar, but also poorer outcomes compared with earlier studies (Table 1, Salokangas *et al.* 1983, Hegarty *et al.* 1994), depending on the outcome dimension considered. The results of this thesis study showed a somewhat higher percentage of poor outcome cases compared with the summary of Menezes *et al.* (2006). According to Hegarty *et al.* (1994), after approximately 5-6 years of follow-up good outcome occurs in 40%, decreasing during the end of the century to 36%. Similar results were presented by Menezes *et al.* (2006), who systematically reviewed 37 outcome studies of first episode schizophrenia published in 1966-2003. Their report showed that 42% of the patients had good outcome and 27% had poor outcome. Comparison with the results of Hegarty *et al.* (1994) and Menezes *et al.* (2006) is very complicated, since they combined several different studies with several definitions of good and poor outcomes. For example, in Hegarty *et al.* (1994), improved (i.e. good outcome) was defined as patient either recovered, in remission, well without residual symptoms, minimally or mildly symptomatic, improved without significant deficit, socially recovered, or working or living independently.

In the International Study of Schizophrenia Harrison *et al.* (2001) indicated that 51-60% of schizophrenia cases had good social functioning after 15-years of follow-up, and 79% had not been hospitalised during the last two years. As a comparison, in this thesis study 59% of individuals with schizophrenia were not hospitalised during last two years. The diagnostic system in Harrison *et al.* (2001) was broader (ICD-10) and follow-up longer than in this study, which is probably one reason for the better outcome in that sample, as well as for the differences in outcome definition.

The results of this NFBC 1966 sample are similar (Pakaslahti 1992) or somewhat poorer (Achte *et al.* 1986) compared to earlier Finnish outcome studies. In samples of Achte *et al.* (1986), 13-35% of schizophrenia cases were on disability pension, with higher percentages in later cohorts. According to Pakaslahti (1992), 45% of schizophrenia or schizophrenia spectrum cases were on disability pension. It may be that these divergent results are at least partly due to different diagnostic and outcome criteria, changes in treatment and the health care system, and development within the social security system, as suggested by Achte *et al.* (1986). It also may be, that working environment and requirements have changed and nowadays labour market is increasingly demanding. The Finnish social security system is good, but for example receiving disability pension may also have disadvantages, such as separation from working community and society. Work has played an important part especially for Finnish men, and thus inability to work may have severe negative effects on self-esteem. In addition,

approximately one-third of the subjects did not use any antipsychotic medication at the study moment. Is this a marker of good outcome or a lack of adequate treatment?

### ***6.2.2 Predictors of clinical and social outcome (I)***

In this study, early age of illness onset and lack of close friends in childhood were associated with poor global social outcome. Having no remission was predicted by low school marks and early age of illness onset. In addition, being under normal grade at school predicted being on disability pension. Social class in adolescence predicted outcome in terms of hospitalisations, but this association was significant only in the adjusted model.

Comparing results from predictor studies is not straightforward. Studies have used predictors from different stages of life, often retrospectively collected, and these predictors are analysed against a very heterogeneous group of outcome indicators. Age of illness onset as predictor of outcome in schizophrenia is well known in epidemiologically defined (Suvisaari *et al.* 1998, Harrison *et al.* 2001) and hospital-based samples (Jonsson & Nyman 1991), but in many studies the age of illness onset predicts clinical, rather than social outcome (Suvisaari *et al.* 1998, Harrison *et al.* 2001). According to Jonsson & Nyman (1991), early age of illness onset predicted 14- to 17-year poor global outcome within cases of broadly defined schizophrenia. Contrarily, Wiersma *et al.* (1998) did not find any differences in the age of illness onset between good and poor outcomes within an epidemiological sample of ICD diagnoses and the rate of psychotic symptoms as an outcome measure.

Hofer *et al.* (2006) studied 60 outpatients with ICD-10 schizophrenia or schizoaffective disorder with mean length of illness 10 years. They found that better premorbid school performance (measured by PAS) correlated to patient's better employment status, though not to other outcome measures (quality of life, marital status, living situation). In this current thesis study school performance (either school marks or school grade) were associated with both clinical and social dimensions of outcome. Hofer *et al.* (2006) also found that better social adjustment in childhood and adolescence (measured by PAS) was correlated with better functioning according to the Global Assessment of Functioning-scale. McGlashan (1986) found that being a loner in terms of social relationships in adolescence was associated with poor global outcome in a 9-year follow-up of 57 individuals with DSM-III schizophrenia.

Surprisingly, in this dissertation study it was found that, after considering potential confounding variables, father's low social class (classes III-V, i.e. skilled and unskilled workers, farmers) when the subject was 14 years old protected from poor outcome (no hospitalisation during the last two years). Naturally, this may be a chance finding due to multiple comparisons. There are not many earlier studies focusing on social class in adolescence. McGlashan (1986) studied father's social class as a predictor of outcome, but did not specify what time period the social class concerned; in addition, there was no significant association.

One important finding in this study was that gender and family history of psychosis did not play a significant role as predictors. Lack of gender differences in incidence and

age of illness onset within this NFBC 1966 sample has been presented earlier (Räsänen *et al.* 1999). The lack of association between family history and poor outcome in this NFBC 1966 sample is a surprise. It may also relate to the limited statistical power as well as relatively young age of the study sample.

Clinically practical predictors of outcome in schizophrenia include gender, age at illness onset and premorbid personality (Häfner & an der Heiden 2003). Of these, in this thesis study predictive value was found for the age at illness onset and premorbid personality (lack of friends in childhood). Commonly presented predictors usually explain a minority, 27-30%, of the variance in outcomes (McGlashan 1986), and their predictive power is considered to be very limited (Wiersma *et al.* 1998). In this thesis study, predictor variables explained 11-35% of the variance. Thus, this study partly supports the idea of difficulties in predicting the prognosis of schizophrenia, especially when using very early premorbid predictors.

### ***6.2.3 Early development and outcome in schizophrenia (II)***

While delayed motor milestones are associated with an increased risk of schizophrenia in the general population, within those with schizophrenia delays in these same milestones do not always predict adverse outcomes. While early motor milestones appears to ‘protect’ against the risk of schizophrenia, the pattern of association between these milestones and various measures of outcome reveals a more subtle and nuanced pattern. When adjusted for confounding, most associations between later learning and better outcomes remained. The implication of association between age of learning milestones and age of illness onset especially is interesting. The early learners had a significantly earlier age of illness onset for psychosis, which has already been briefly reported in an earlier report of the cohort (Isohanni *et al.* 2001b).

According to the results of this thesis study (Table 8), it seems that among the early learners there is a group of individuals with schizophrenia who do not have the traditional risk factors for schizophrenia (e.g. obstetric complications, genetic risk, poor school performance). Early learners as a group also have earlier age of illness onset and a somewhat poorer course of illness in terms of some outcome indicators. Whether the individuals with early learning, early age of illness onset and poor outcome are the same, needs further examination of this sample.

Though the results of this dissertation study are inconclusive, some speculations can be made. Perhaps these persons with relatively good premorbid functioning had a rapid illness onset and illness with more pronounced symptoms that acquired more hospital treatment. Or maybe there is some unknown factor or process that occurs near illness onset and affects the postmorbid development. It may also be that the underlying neurobiological correlates associated with delayed motor milestones do not travel across time as a group within those with schizophrenia, i.e. the pattern is not straightforward, as in sick brain – late walking – increased risk of schizophrenia – worse outcomes.

Although developmental abnormalities act as a risk factor for developing schizophrenia, these abnormalities do not seem to relate to or predict poor outcome of the disorder. Even though a patchy association between early development and outcome was

found, the link is difficult to examine due to small sample size and lack of power. There were some associations between late learning and better outcome (later age of illness onset, less service utilisation), but also worse outcome (more symptoms) and thus firm conclusions are difficult to draw.

According to Jonsson & Nyman (1984, 1991) neurological symptoms (e.g. bad coordination of muscles or speech, difficulties in reading and writing) during childhood and adolescence were associated with poor outcome in schizophrenia. The authors do not give any detail about the age when the persons were having these symptoms. Rossi *et al.* (2000) found an association between early present and stable behavioural abnormalities and more severe symptoms in schizophrenia, but they did not assess motor development. Thus, the results of these studies and the current thesis study are difficult to compare.

### 6.2.4 *Patterns of hospitalisations (III)*

In this sample, 60% of individuals with any schizophrenic psychosis were re-hospitalised in two-year follow-up, and most of the cases (81%) were re-hospitalised during the entire follow-up. Among subjects with schizophrenia 67% were re-hospitalised during first two years and 86% during the whole follow-up time. In other schizophrenia spectrum psychoses the numbers were 37% and 63%, respectively.

Previous studies have presented re-hospitalisation rates of up to 50-90% in different samples (Eaton *et al.* 1992) and 35-65% for two years (Eaton *et al.* 1992, Mason *et al.* 1996); the results of this thesis study are in line with these percentages. In this sample the survival curve was flat after 5 years, which has also been found e.g. by Eaton *et al.* (1992), who studied altogether over 24,000 ICD-8 or DSM-I schizophrenia cases with first psychotic hospitalisation in Australia, USA, Denmark and England. In study by Mason *et al.* (1996) the flattening of the curves started 3 years after discharge.

Sytema *et al.* (2002) followed for several years cohorts of first-admitted patients with ICD-10 schizophrenia disorders from three different mental health service systems (Australia, Italy and the Netherlands). They found that 0.9%-3.3% of the sample of 11,233 cases were “revolving door” patients with the strict criterion of at least four psychiatric hospitalisations during the follow-up period, with a mean number of at least two admissions per year. When the criteria of Sytema *et al.* (2002) were applied to the NFBC 1966 sample (N=115), the number of “revolving door” subjects was 4 (3.5%), which as a percentage is quite similar to that of Sytema *et al.* (2002). It should be noted that Sytema *et al.* (2002) had somewhat shorter follow-up and they used broader definition for schizophrenia disorders; for example, they also included psychosis NOS in their study. In a large Brazilian study, over half (52%) of the schizophrenia subjects were recidivists (at least 4 admissions during the follow-up of 5 to 24 years) in a study by Gastal *et al.* (2000).

Re-admission is a result of complex interaction between several variables, such as patient-related variables, the structure of organisations and the availability, number and functioning of services (Oiesvold *et al.* 2000). Re-admission is multifactorially determined and these interactions must be considered. In general, the relations between service use, the psychiatric services and the whole health care system are complex.

Furthermore, re-admission is not always a bad thing; it may be an adequate reaction on the part of the health care system to the patient's changed need for care (Saarento *et al.* 1998), but it may also reflect the insufficiencies of outpatient care (Oiesvold *et al.* 2000). When considering the group of psychotic patients, the receipt of aftercare seems to decrease the risk for re-admission (Oiesvold *et al.* 2000).

In the current thesis study, there were only two significant predictors (familiality and length of first hospitalisation) of hospitalisation patterns. Previous studies have presented very divergent findings of the topic as well. There are probably several factors related to patients (e.g. denial of illness, non-compliance or lack of motivation), treating persons, ways of treatment, organisation and family that affect the length of hospitalisation. Unfortunately we do not have information on all of these variables, which may confound the associations found in this study.

The finding that familial risk for psychoses predicts re-hospitalisation within two years is new. In an intervention study Feldmann *et al.* (2001) found that family history of mental illness predicted increased risk for re-hospitalisation within a five-year follow-up. Familial loading of psychosis has also been associated with increased annual duration of hospitalisations in schizophrenia (Suvisaari *et al.* 1998). The author of this thesis is not aware of other studies related to familiality and the risk of re-hospitalisations.

There are studies with results similar to the current thesis study concerning the length of first hospitalisation and the risk of re-hospitalisation. Appleby *et al.* (1993, 1996) found that short hospitalisation (less than 31 days) predicted shorter time to first re-admission in schizophrenia. In their study males with young age at illness onset had a statistically significantly higher risk of sooner re-admission. However, the sample of Appleby *et al.* (1996) did not include first admission patients only. Interestingly, regarding the categorisation of the length of the first treatment, in this thesis sample of patients with schizophrenic psychoses, the patients treated for 1-14 days were at a much higher risk for re-hospitalisation than patients who were treated for 15-30 days.

In this study, a short first hospitalisation also predicted frequent hospitalisations. As far as the author of this thesis knows, there have not been studies on this topic solely in schizophrenic psychoses. In samples with multiple diagnoses, the risk for frequent admissions has been found to be higher for patients with long first or previous treatment (Korkeila *et al.* 1998, Gastal *et al.* 2000, Oiesvold *et al.* 2000). These results may be caused by the fact that the studies mostly included other than psychotic patients. These studies are not comparable to this thesis study, as they do not report specific results for schizophrenic psychoses.

The categorisation for length of the first hospitalisation was based on earlier studies (Appleby *et al.* 1993, Saarento *et al.* 1998, Oiesvold *et al.* 2000). The definition of short first hospitalisation is one of the methodological problems related to studies of this kind. The definitions of "short" admission vary between studies, from at most 14 days (Appleby *et al.* 1993) to at most 40 days (Gastal *et al.* 2000), for example. Appleby *et al.* (1996) noted that when studying the length of first treatment, it is important to take into account possible differences in treatment places and their policies regarding the length of treatment. In this current sample a large majority of the subjects (80%) had their first treatment in a psychiatric hospital and the differences in length of the first treatment did not differ between psychiatric hospitals and other treatment places. The length of stay is a manipulable administrative variable influenced by admission rates, treatment philosophy

and number of beds (Appleby *et al.* 1996). The length of stay also depends on the possibility to refer the patients discharged from the hospital to community services for further care (Sytema *et al.* 2002).

It may be that a short first hospitalisation is a marker of the patient's unwillingness to undergo treatment (including outpatient treatment). It is strongly suggested that severely mentally ill patients need continuity of care in order to be maintained in the community, and that the duration of hospitalisation seems to be associated with the probability of aftercare (Saarento *et al.* 1998). It seems that longer stay in inpatient care is associated with later outpatient treatment, and this may be also a matter of the patient's motivation to treatment (Nieminen *et al.* 1994).

### 6.2.5 Recovery (IV)

The results of this part of the study are much more pessimistic when compared to other follow-up studies (Table 2), especially concerning schizophrenia patients: only 1.7% of schizophrenia and 16.7% of schizophrenia spectrum cases recovered fully. This difference is probably partly due to the strict definition of recovery, combination of several measures of outcome and sample with DSM-III-R schizophrenia psychoses, but it also may be due to poorer effectiveness or quality of treatment.

When compared to earlier Finnish studies, the results are somewhat similar (Achte 1967), but also different (Salokangas 1978, Kuusi 1986). Achte (1967) reported complete recovery for 2% or 8% of schizophrenia subjects, depending on the length of follow-up. In schizophreniform psychoses, the recovery rates were much higher than in this current thesis study, 62% and 83%. The recovery criteria were quite similar to those in this study (defined as absence of psychotic symptoms, ability to work at the same level as before getting ill and being employed), but structured diagnostics was not used in Achte's examination. To compare, in this study the recovery rate for schizophrenia was similar, but for schizophrenia spectrum disorder the results were more pessimistic.

The results for recovery concerning schizophrenia spectrum disorder were similar to earlier findings (Tsuang & Coryell 1993, Harrison *et al.* 2001). Tsuang & Coryell (1993) found no differences between outcomes for schizophrenia and schizoaffective disorder: in both groups, none of the patient showed recovery. In this thesis study, none of the subjects with schizoaffective disorder were recovered.

According to a recent ongoing meta-analysis of "true" recovery from schizophrenia that considers both very good clinical and social outcome as criteria for recovery, the recovery percentage among the studies is between 2-25% and the mean recovery rate 14.7% (Lauronen *et al.* 2006, Miettunen *et al.* 2006). The meta-analysis includes the original article IV of this thesis and it seems that compared to many other studies, the amount of recovered subjects in the NFBC 1966 is much smaller. The results of the ongoing meta-analysis are more pessimistic than earlier results suggesting that as many as almost 60% of patients recover (McGlashan 1988). It may be that in some older but also recent studies the authors have misleadingly called e.g. asymptomatic state or remission as recovery, and have thus obtained a higher number of "recovered" cases.

## 6.3 Methodological discussion (I-IV)

### 6.3.1 Diagnostics

DSM-III-R criteria for schizophrenia may select schizophrenia patients who are destined to have a poor prognosis. According to the DSM-III-R manual (APA 1987), full remission does occur, but it is not common. Limited diagnostic accuracy and varying diagnostic criteria may be one reason why the proportion of recovery varies from study to study. Hegarty *et al.* (1994) found that the outcome was poorer in studies using Kraepelinian diagnoses (DSM-III-R schizophrenia) compared to non-Kraepelinian systems (schizophrenia spectrum disorders). Modestin *et al.* (2003) rediagnosed the original patient sample of Manfred Bleuler with several diagnostic systems. They found that when using a more narrow diagnosis (e.g. DSM-III-R) of schizophrenia, the recovery rate decreased to 12%, whereas the recovery appeared to be 22% diagnosed by Bleuler's criteria. According to Angst (1988), diagnostic differences are the main methodological issue affecting the divergence of recovery and other outcomes in studies.

In this study, the diagnosis of the participants was based on the SCID interview and extensive anamnestic data, including hospital case notes of all participants. With non-participants, good diagnostic accuracy was obtained (Isohanni *et al.* 1997, Moilanen *et al.* 2003). However, the entry criteria were rather strict, based upon a narrow definition of schizophrenia and, in most cases, hospital admission and discharge at a relatively young age. Thus, on one hand the sample may be biased towards the most severely ill, but on the other hand participants of the field study 1999-2001 may represent those with milder illness as suggested by Tanskanen *et al.* (2005).

### 6.3.2 Definition of good and poor outcome and recovery

Differences in definitions and cut-off for good and poor outcomes have significant importance, and may be one of important factors affecting the heterogeneity and comparing of results of outcome studies. The importance of standardised outcome criteria in schizophrenia has lately received increased interest (Ruggeri *et al.* 2004, Andreasen *et al.* 2005, van Os *et al.* 2006).

Recovery is a multi-dimensional concept, involving different areas of functioning, such as clinical symptoms, social functioning, working ability, and the patient's satisfaction with life. When defining individual recovery, a persons' premorbid level of functioning should be considered. But what is the level of functioning that we require for recovery? Should a patient return to the pre-illness level of functioning? And what is the pre-illness level if, as some studies suggest, the developmental deviance among schizophrenia patients already begins in childhood (Isohanni *et al.* 2001b;2004, Cannon *et al.* 2003) or even in utero (Jones *et al.* 1998). Should the person return to the age-specific level of functioning in terms of education, occupation, and mature adult identity? All of these usually develop rapidly between the ages of 20 and 30. For example, in Finland, nearly all adolescents attend secondary school. Most people - even those with

adult psychosis – complete at least vocational training; 62-70% of schizophrenia cases, compared to 62% of the general population without psychiatric hospitalisations, have attained upper secondary education or vocational training (Isohanni *et al.* 2001a). This is why occupational status was included as a criterion of good outcome and recovery in this thesis study. However, the rate of unemployment is relatively high, and it is not unusual that “healthy” persons are without occupation and receive unemployment benefit from the state. This is why unemployment was not considered a sign of non-recovery. It should be noted that while in this sample 53% of schizophrenia patients were not on disability pension or unemployment at follow-up, this is a crude measure of occupational functioning and the precise proportion of patients working full or part-time is not known.

In this thesis study the clinical and social outcomes were separated, because they are shown to have divergent courses (Salokangas 1997). The definitions of good, moderate and poor outcomes were based on earlier literature (Angst 1988, McGlashan 1988, Ram *et al.* 1992) and clinical and research views about when a person is in good condition or doing poorly. The severity of symptoms (Harrison *et al.* 2001, Robinson *et al.* 2004, Wiersma *et al.* 1998), psychiatric hospitalisations (Suvisaari *et al.* 1998, Kua *et al.* 2003) and working ability (Suvisaari *et al.* 1998, Kua *et al.* 2003, Jäger *et al.* 2004) are common outcome measures. In addition, GAS ratings, from where the SOFAS is derived, have been used (Jäger *et al.* 2004).

The recovery criteria used here assessed both the clinical condition (CGI, PANSS, hospitalisations, antipsychotic medication) and social abilities (SOFAS, working ability) of the study subjects. In addition, healthy external appearance of subjects was required (assessed using CGI, PANSS and moderate drug dose). Because of various criteria and the use of CGI - which were all rated by experienced clinicians - recovery in this study was defined by eliminating the functionally and clinically relevant signs of the illness widely.

In this study both interview- and register-based indicators of outcome were used, which is why this information can be seen as being reliable, and the amount of missing information was low. However, register information may be relatively superficial and coarse and relate only minimally to clinical symptomatology. In addition, factors such as the length of hospitalisations are no more than a proxy measure of outcome. In addition, more detailed information about the outcome exists for those cases who participated in the field study with personal interviews and extensive examination.

### **6.3.3 Predictors of outcomes**

The quality of information regarding predictors of outcome may vary. In many studies the predictor variables have been collected retrospectively by asking the patient or relatives, and this may introduce a reporting bias. Furthermore, when collected from hospital notes, the quality of information may vary. In this thesis study, most of the predictors were collected prospectively from questionnaires or hospital notes or retrospectively from registers.

Another problem in outcome studies is that predictors of outcomes are usually presented for individual outcome measures, and good outcome in one dimension does not

necessarily mean good outcome in another. Until a standard definition of good, moderate and poor outcome is agreed upon, there is no reasonable model to select the limits for each of these outcomes, which is why comparison remains difficult.

In this dissertation study, several predictors were analysed against different outcomes. Some of poor outcome groups were very large, and thus perhaps too heterogeneous, compared with relatively small good outcome groups, and this may partly explain the presence of only few significant predictors. Some of the findings may be due to chance, although an attempt was made to ensure that the comparisons were guided by hypotheses and used a Bonferroni correction.

Regarding the variables of early development (ages of learning to stand, walk, and talk), the assessment at age 1 year was too early for assessing e.g. age of walking. The selection of cut off for early and late learning was difficult. For example the group of later learning to stand may have been too heterogeneous and large in this study. It includes ages 11 months and 12 months but, it also may include those learning at age 13 months, 14 months etc. This same principle applies to the age of leaning to walk. Since the heterogeneity of the groups of late learning it would be more accurate to interpret from the results of original article II that *earlier* learning was associated to *worse* outcomes.

### 6.3.4 Sample

The population of this study is different than in many earlier follow-up studies. For many subjects the age of the illness onset was still rather low, which is related to difficult clinical symptomatology and poor prognosis (Harrison *et al.* 2001) and may to some extent explain the results. Follow-up has been very short for subjects who became ill recently, and only cases having early onset have had a sufficiently long follow-up to assess full or partial recovery in the long term.

Earlier studies were often based on selected first-admission patient cohorts in hospitals, admitted in certain time periods. These studies may suffer from selection bias, and the patients are not fully representative of those in the general population. There are at present few outcome studies of unselected epidemiological samples (e.g. Leff *et al.* 1992, Suvisaari *et al.* 1998, Goater *et al.* 1999, Harrison *et al.* 2001).

Variations between treatment systems in different countries should be considered. In Finland it has been very common that a patient suffering a first episode of schizophrenic psychosis is hospitalised (Isohanni *et al.* 1997, Arajärvi *et al.* 2005). This study included only three schizophrenia patients who were treated solely as outpatients. Thus, it can be assumed that an outcome study based on the Finnish Hospital Discharge Register includes schizophrenia patients with various prognoses.

In the Northern Finland 1966 Birth Cohort 83 individuals have forbidden the use of their data up until now and there is no information about their health. It may be that among these individuals there are some with psychiatric problems, e.g. paranoid features. Since the number of subjects in the statistical analysis in this study were relatively small, each missing subject with schizophrenic psychosis might have relatively large impact on the results.

### **6.3.5 Length of follow-up**

The age of onset of illness among this sample varies (from 16 to 31 years, mean 23.5 years), and thus the follow-up period differs for each case (from 3 to 18 years, mean 10.2 years). The length of follow-up in different studies may vary from a few years to over three decades, and may also influence recovery and other outcome rates reported. In previous studies the follow-up periods have often been longer, and this sample may also have more favourable outcomes after longer follow-up. Although decreased functioning in certain dimensions of outcome is found to be stable (Fenton & McGlashan 1987), the outcome of patients may change and become more favourable over time (Harrison *et al.* 2001), and recovery or remission is possible even after years of illness (Harding *et al.* 1987). It is also suggested that social improvements appear later, happening slowly after clinical healing (Salokangas 1997). Some of the 1966 NFBC subjects may be in the beginning of their healing process.

Questions have even been raised about whether recovery from schizophrenia is possible. Given that relapses occur, the length of follow-up becomes a key factor. It is difficult to determine whether the illness is in remission or whether the patient has recovered permanently. In a follow-up study of Rund (1990) and Torgalsboen & Rund (1998), half of recovered patients relapsed after ten years. These results suggest that recovery from schizophrenia may take the form of time-limited remission.

### **6.3.6 Non-participants – a potential source of bias**

It is possible that missing cases may contain both of the extreme variations of outcome: recovered cases (e.g. wanting to seal over their psychotic experience) or cases having very poor outcome (e.g. very sick, paranoid persons avoiding all contact). It is often assumed that psychosis patients with poor prognosis are more often lost to follow-up (Wiersma *et al.* 2000, Harrison *et al.* 2001), and this seems to be true also in the NFBC 1966 (Tanskanen *et al.* 2005, Haapea *et al.* manuscript). For example, the median days spent in psychiatric inpatient care was 134 among those schizophrenia subjects who participated the field study in 1999-2001 (N=59), but when all schizophrenia cases, including those not participating the field study, were included (N=109), the median days spent in psychiatric inpatient care increases to 269.

However, there are also studies showing no difference in variables with prognostic significance between examined and lost cases (Leff *et al.* 1992, Mason *et al.* 1995). According to Fenton & McGlashan (1987), there are schizophrenia patients who do very well without any medication. Because these patients do not necessarily need any treatment, they may more often be lost to follow-up.

In the original article I it was not possible to assess recovery and clinical and social outcomes among non-participants. Instead, subjects with indicators of non-recovery were identified. It is also possible that there were subjects who recovered among those about whom no information was received (N=9), or among those about whom the information received was not adequate to exclude recovery (N=10). The missing data were analysed

as extensively as possible. Most of the final missing subjects (N=9) denied the delivery of their addresses or phone numbers, which may have been due to paranoid thoughts.

## 6.4 Theoretical discussion

### 6.4.1 *Early development and outcome in schizophrenia (II)*

Nowadays, schizophrenia is not considered merely a functional disorder. More and more evidence exists for the theory of neurodevelopmental, but also of neurodegenerative aetiology (Weinberger 1987, Lieberman 1999, Ashe *et al.* 2001). The neurodevelopmental model suggests that schizophrenia results from abnormalities in early brain development that are manifest in different ways according to the stage of brain maturation; in this context psychosis is an age-dependent manifestation. Rapid development at about age 1 may be a big challenge, especially for a person with schizophrenic vulnerability. In the light of the neurodevelopmental hypothesis, clinical outcome can be seen as an expression of the pathological process behind the illness (Lieberman 1999, Weinberger & Marenco 2003).

If true, how does the association between late learning and better outcome fit the neurodevelopmental hypothesis? It may be that those persons who are destined to have schizophrenia and who learn early need a stronger stress or trigger to become ill, and because of this hit they continue to have a deteriorating course of illness. Or perhaps there are several types of aetiology behind schizophrenia, maybe neurodevelopment is not the only factor as suggested by MacCabe *et al.* (2002).

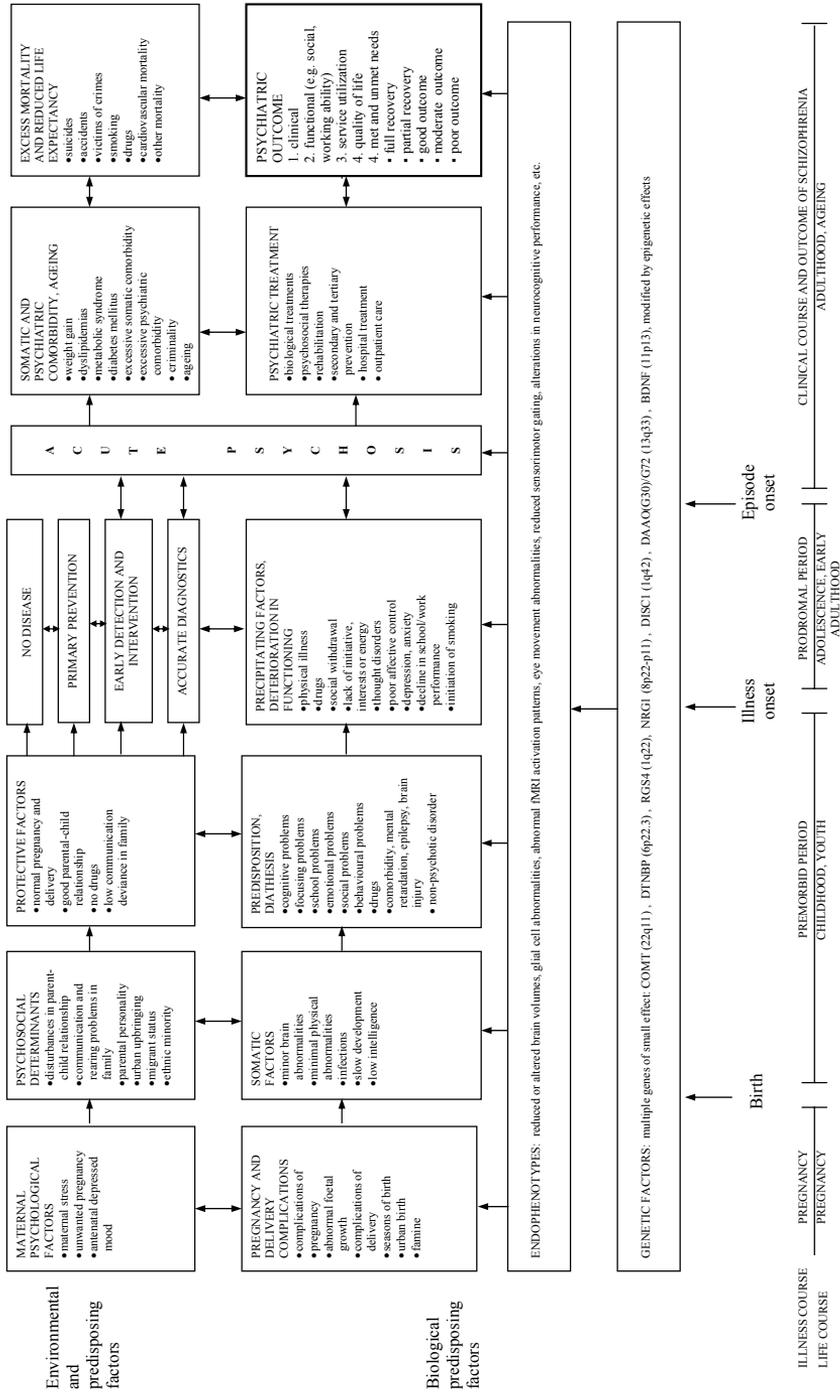
Murray *et al.* (1992) hypothesised two subtypes of schizophrenia: a neurodevelopmental subtype with genetic risk, obstetric complications, male gender, later developmental milestones, poor school performance and poor course of illness, and non-neurodevelopmental type with less genetic risk and obstetric complications, female gender, relatively normal development and good outcome. This thesis data, which show later development associated with better outcomes, argues against this simple classification. Taken together with the previous schizophrenia research in the NFBC 1966, which details associations in the disorder between later infant development and poorer school performance (Isohanni *et al.* 2004) and poorer cognitive function in some domains (Murray *et al.* 2006), but no relationship between infant development and adult brain structure in schizophrenia (Ridler *et al.* 2006), these data suggest that the relationships between neurodevelopmental markers and adult outcomes in schizophrenia is highly complex. This may reflect the complex multifactorial aetiology of the disorder involving interactions between multiple genes of small effect and multiple environmental risk factors of small effect (McGuffin & Southwick 2003). It has been proposed, based on the NFBC 1966 sample and MR brain imaging, that the development of schizophrenia cases is not similar to controls, and they do not seem to have a 'normal' relationship between early development and later brain structures (Ridler *et al.* 2006). This disruption of the anatomical system provides a mechanistic link between the developmental deviances prior to schizophrenia and adult cognitive abnormalities and psychotic

features. It may be that this “developmental dysmetria” relates to the clinical and social outcomes and severity of illness as well, but this hypothesis needs future studies.

#### ***6.4.2 Descriptive life span model of schizophrenia***

In the NFBC 1966, several studies of pre- and post morbid development in schizophrenia have been published (Isohanni *et al.* 2005, Mäki *et al.* 2005, Isohanni *et al.* 2006). These studies suggest several plausible environmental and genetic risk factors for developing schizophrenia (Figure 8). According to these studies, some individuals with schizophrenia show deviances in motor, cognitive and behavioural development even early in the childhood, and these developmental deviances are suggested to continue through adolescence (Isohanni *et al.* 2004) to adulthood (Ridler *et al.* 2006). Compared to normal population, as a group, schizophrenia cases seem to have a developmental pathway that lacks flexibility and responsiveness (Isohanni *et al.* 2006).

How do the results of this thesis study fit into this model and what happens after the onset of psychosis? According to original article II, later development around the age of 1 year was not uniformly associated with poor outcome in schizophrenia. Thus, it may be that the risk factors for schizophrenia are different from the risk factors for poor outcome. It may be that different factors (e.g. treatment, social support) affect the development of illness after the onset of schizophrenia. It has been proposed that the best predictors of outcome in schizophrenia are those occurring near the onset of illness (e.g. premorbid functioning, very early course of illness) (Häfner & an der Heiden 2003).



**Fig. 8. Descriptive life span and multilevel model of schizophrenic psychoses. Known aetiological and disease course components are presented. Hypothetical ideas on protective factors are not necessarily evidence-based. The figure is modified from Figure 1. in Isohanni et al. (in press).**

## 6.5 Strengths and limitations of the study (I-IV)

### 6.5.1 Strengths

The sample of this study is population-based, which is important for estimating the true prognosis and outcome in schizophrenic psychosis. In original article III the sample included all cases with schizophrenic psychoses treated in psychiatric hospitals or in wards offering psychiatric specialised care. Actually the sample included all subjects with schizophrenia psychoses occurring in the FHDR, since none was treated solely in e.g. ward in health center. Thus, drop-outs and non-participants were not a problem in this study.

This study is rare in being both population- and register-based, and the study thereby provides new and more valid information compared to most earlier studies. This study included register data from the whole country, not from a single hospital or from a group of hospitals, as has been the case in some previous studies.

As discussed earlier in this thesis, the diagnostics should be accurate; the diagnoses for the entire sample were re-checked twice by professionals (Isohanni *et al.* 1997, Moilanen *et al.* 2003). The diagnostic system is strict as well as more advanced because the aim was to study narrow schizophrenia and other schizophrenia-like disorders separately.

In this cohort, the data are extensive and collected since pregnancy, giving the possibility to analyse some reliable early predictors (e.g. birth complications) of outcomes in schizophrenia. The data of early development in original article II were standardised childhood data collected prospectively in a special examination near the time point when developmental milestones took place. In original article IV, due to tracking of non-participants, the number of missing subjects with schizophrenic psychosis was finally rather low.

Unlike in the earlier studies, in this study it was possible to study the effect of familial risk on hospitalisation patterns (original article III). In general, most of the predictor variables were collected prospectively and from several registers.

One advantage is the use of several criteria for good and poor outcome and recovery. These criteria were not based on a single measure but considered several dimensions of outcomes (e.g. clinical, social, treatment aspects). Relatively strict definitions of full and partial recovery were used, which is an advantage because the aim was to study explicit, global recovery, or even 'normal health' and 'cure'.

### 6.5.2 Limitations

The subjects in this study were young (35 years), and the length of follow-up differs between subjects, which may affect the comparability of our results to those presented earlier. Some subjects have been ill for a short time (minimum 3 years) and have a potentially better prognosis than cases with an earlier onset. At this point it was not possible to determine if they were recovered. Also, the other illness outcomes may change during the time. According to McGlashan (1988) the course of illness in

schizophrenia often plateaus after 5-10 years of illness. Considering this finding, the length of follow-up in this thesis study was not long enough to assess the long term outcome of schizophrenia.

Population-based samples have an advantage, but compared to clinical cohort studies, sample size tends to be small, as it was in this study. In original article I for example, some of the results that did not reach statistical significance were suggestive and they may have been statistically significant if the sample size would have been larger.

For the non-participants the psychiatric diagnosis was only known by hospital discharge registers, and medical records and all the desired information for all cases was not received. According to Haapea *et al.* (manuscript), compared to participants, those subjects with psychosis who did not participate the field study in 1999-2001 had more severe illness (more inpatient treatment periods and more often disability pension). The outcomes for non-participants and for subjects who had died could not be assessed, although it was possible to exclude recovery for most cases. In addition, there may be some selection bias: the group of 83 subjects who have forbidden the use of their data may include some individuals with psychosis, as discussed earlier.

Regarding the original article II, the assessment of developmental milestones around age 1 may have been too early regarding some of the developmental variables (e.g. age of walking). Some individuals were unable to perform standing and/or walking at the time of the developmental assessment and their standing or walking scores were imputed by using an a priori conservative method: a value equal to the age at the time of the developmental assessment plus one month was attributed (Murray *et al.* 2006). Due to this, the imputed scores for those individuals who learnt at 14 months or later are not accurate.

Because this is a birth cohort sample, it was not possible to study the effect of de-institutionalisation and onset age on the risk of re-hospitalisation (original article III). However, age at first admission was used as a confounder and this adjusts largely also for the effect of the notable decrease in hospital beds in Finland and for other changes in treatment policies during the study period 1981-1998 (Korkeila *et al.* 1998). In addition, there is no outpatient information (about treatment contacts and medications), which would have been an important variable to include in the analyses.

Several predictors of outcomes in schizophrenia were studied; the results may thus be a chance finding and need replication. Though most predictors were assessed prospectively, information about the number of friends in childhood was asked retrospectively and may not be quite as accurate.

The information concerning pre-morbid factors in original article III was collected from hospital notes using the OCCPI procedure. Case notes do not invariably provide the same information entered clearly and unambiguously (McGlashan *et al.* 1988). It is likely that in some hospital notes the information related to the used OCCPI variables was not presented well enough to give the pre-morbid personality disorder diagnosis, for example. However, it is more unlikely that there are wrong positive ratings. The rating procedure of OCCPI in the NFBC 1966 has been described earlier (Isohanni *et al.* 1997). Four researchers did the ratings. Unfortunately the reliability of the used OCCPI variables was not studied. The reliability of outcomes measures (except diagnosis) of the field study 1999-2001 was not formally assessed either.

For original articles I-III several statistical analyses were performed, and thus chance findings are possible.

## **7 Conclusions**

### **7.1 Main conclusions**

In this dissertation study outcomes of schizophrenic psychoses and some predictors of outcomes were analysed in a population-based sample of individuals with relatively young age and short duration of illness. Although good outcome existed in this sample, in general, both clinical and social outcomes were heterogeneous and relatively poor, and compared to earlier Finnish outcome studies the amount of individuals on disability pension was higher. The definition of outcome had strong influence on the results. Persons having a sub-optimal developmental trajectory with poor social contacts, poor school performance, and an early age of illness onset seem to have the worst outcome.

The results regarding association between early development and outcome in schizophrenia were inconclusive and need further studies on the topic. In spite of early motor deviation being a marker of increased risk to schizophrenia, late learning did not uniformly predict poor outcome but instead was mostly associated to more favourable course of illness.

Most of the subjects were re-hospitalised after first hospital treatment due to psychosis. When considering the results of a shorter first hospitalisation and increased risk of re-hospitalisations, the basic question is: is the relation causal? Although this is a methodologically complex and, in an epidemiological design such as this, partly unsolvable question, based on this study this causal explanation cannot be rejected.

When only considering recovery, the results are somewhat closer to those reported by Kraepelin than to results from more recent studies. According to this study, recovery from DSM-III-R schizophrenia in an epidemiological sample is possible but uncommon, at least until early middle age. In milder schizophrenic psychosis, recovery is more likely, as has been presented in earlier studies.

## 7.2 Implications of the study

The results of this study have significance when planning health care systems. If recovery from schizophrenia is unlikely and the outcomes are in general relatively poor, how will this impact health care? Is the treatment for schizophrenia patients optimal and effective? Could we and should we do something differently? Has the prognosis worsened during the last decades? Still we have quite a minimal data on the long-term outcome of schizophrenia and the influence of care on it. Is illness plasticity influenced by care and what is the magnitude of illness changeability? One reason for our limited data are important ethical issues; it is not possible to randomise schizophrenic patients to no treatment arm.

The results of this study also have importance when informing patients and relatives about the prognosis of schizophrenic psychosis. Of course, consideration should be used when reporting results like these. It should be noted that although the criteria in this study were strict, focusing on full and complete recovery, and there were still a few recovered cases. In addition, the results for moderate or good outcome in schizophrenia are more hopeful. Maybe over longer follow-up periods, the chances for recovery and good outcome increase. In addition, these reported results may encourage patients to comply with medication and other treatment, and thus providing tools for good outcomes.

The information on factors associated with poor prognosis in schizophrenia are of importance for clinical work as well. By emphasising the potential risk factors for poor outcome, it may be possible to help the person with schizophrenia better. Based on these results, special effort could be put into the follow-up and treatment of those schizophrenia subjects who have already shown some problems in childhood and in school and who have their illness at a very early age.

In Finland the number of psychiatric hospital beds has decreased greatly during the last decades, and the treatment we are offering may not be as good as expected. According to the Finnish Current Care guideline for schizophrenia (Finnish Psychiatric Association 2001), short hospitalisation is recommended. However, the length of hospitalisation should not be an end in itself, but should be planned according to the patient's individual needs and severity of illness. The clinical recommendation based on the current thesis study is that the maximal short-stay policy is not always the best alternative for all patients during the first hospitalisation in schizophrenic psychoses.

Finding developmental pathways may provide informative endophenotypes for future genetic analysis, or subtypes to help unravel psychoses. The lack of association with early development good outcome has implications especially for researchers. It seems that the causation between early development and the course of schizophrenia is very complex and needs further exploring, for example about temporal changes of development.

## 7.3 Future research

During the work on this doctoral thesis, a few questions remained, and some new ones were raised. What would be the number of recovered subjects, if it had been possible to assess all the missing cases face to face? How different would the results of outcomes be

if the patients' opinion of their well-being had been asked? What is the outcome for these individuals after 5 or 10 years; are individuals who are now experiencing good outcome or recovery still in good condition? If the earlier outcome studies had studied "true" recovery, what would have been the result? Is the association between short first hospitalisation and poor outcome in schizophrenic psychosis causal or confounded by some unknown factors? This is a predictor that could be prevented.

In addition, what would be the association between early developmental milestones and outcome in schizophrenia when studied in a larger sample of general population? If there really is an association between early learning and poor outcome, at what point of life does the change or hit leading to poor prognosis happen, and what exactly would this hit be? In addition, the results about an association between later learning and somewhat better outcome (and early learning and worse outcome), albeit weak, give rise to a question: maybe schizophrenia cases that learn early have a different subtype of illness? The associations between development, age of illness onset and subsequent course of illness should be studied further.

Concerning the outcome and its predictors in schizophrenia, more epidemiological, representative studies with long enough follow-up, large data sets (also pooling of data sets), and validated diagnoses are needed. Special consideration should be used when defining and assessing good and poor outcomes and recovery. It would be ideal to have a structured, so-called golden standard definition or measure for recovery and other outcomes, which would help to compare the results from different samples. This kind of measure for remission has been developed (Andreasen *et al.* 2005), but there is a need for operationalised measures for other outcomes as well. In addition, in present studies, the significance of missing cases is undeniable, and future studies should try to minimise the amount of cases lost to follow-up, in addition to including subjects treated solely as outpatients.

The interest in the life-course epidemiology of schizophrenia is increasing. Although a great deal has been discovered, there is still an enormous amount to be solved - the causes, development and natural course of severe mental disorders are still minimally known. The course and consequences of schizophrenic psychoses is of great scientific and public health importance, but clarification of the mechanism responsible has been hindered by the lack of cohorts providing both foetal and later life phenotypic data and genetic information, as well as prospective follow-up. For the research of life-course and prognosis of schizophrenia, the advantages of birth cohort data are of major importance. Utilising international collaboration and combining several birth cohorts would help us understand better the genetic and environmental components in the evolution and course of schizophrenia.

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- I Lauronen E, Miettunen J, Veijola J, Karhu M, Jones PB & Isohanni M (2006) Outcome and its predictors in schizophrenia within the Northern Finland 1966 Birth Cohort. *Eur Psychiatry* (in press).
- II Lauronen E, Miettunen J, Veijola J, McGrath JJ, Murray G, Jones PB & Isohanni M. Associations between early development and outcome schizophrenia – A 35-year follow-up of the Northern Finland 1966 Birth Cohort. (manuscript).
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