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Pauliina Juola

OUTCOMES AND THEIR PREDICTORS IN SCHIZOPHRENIA IN THE NORTHERN FINLAND BIRTH COHORT 1966

UNIVERSITY OF OULU GRADUATE SCHOOL;
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OUTCOMES AND THEIR PREDICTORS IN SCHIZOPHRENIA IN THE NORTHERN FINLAND BIRTH COHORT 1966

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Abstract

The aim of this dissertation was to study outcomes in schizophrenia and their predictors in a meta-analysis and in the Northern Finland Birth Cohort 1966 (NFBC 1966).

The NFBC 1966 is an unselected, population-based cohort consisting of 12,068 pregnant women and their 12,058 live-born children. This dissertation utilises data that has been collected from medical records, national registers and from two extensive psychiatric studies conducted when the cohort members were 34 and 43 years old, including interview, neurocognitive and brain magnetic resonance imaging data, and questionnaires. Depending on the topic investigated, the sample size ranges between 43 and 103 individuals with schizophrenia.

The meta-analysis found that approximately 13.5% of subjects with schizophrenia recovered both clinically and socially, and the recovery rate has not increased in recent decades. Studies from countries with poorer economic indices had higher recovery estimates.

In the NFBC 1966, individuals with schizophrenia who were young and single at illness onset, who experienced an insidious onset, and who had more hospital treatment days early on, were at greater risk of a poor outcome in terms of later psychiatric hospitalisations and lack of remission. A novel finding was an association between suicidal ideations at onset and higher number of later psychiatric hospitalisations. Associations were detected between decreased gray matter density in the left frontal and limbic areas and decreased total white matter volume, and concurrent poor outcomes at 34 years. Concerning neurocognitive functioning at 34 years, better long-term verbal memory predicted a better global outcome (symptoms, hospital treatments, social relationships and working combined) and better visual memory predicted a better vocational outcome nine years later.

The results of this study show that recovery is possible, but not very common in schizophrenia. Though outcomes are relatively difficult to predict, many clinically relevant predictors were observed that can be used in predicting outcome in a nearly 20-year follow-up. However, more research is needed in order to explore predictors that could possibly be modified via early interventions so as to enhance outcomes.

Keywords: birth cohort, brain, cognition, epidemiology, longitudinal, meta-analysis, MRI, outcome, prediction, prognosis, psychosis, schizophrenia

Juola, Pauliina, Skitsofrenian ennuste ja ennustetekijät Pohjois-Suomen vuoden 1966 syntymäkohortissa.
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Tiivistelmä

Tämän väitöstutkimuksen tarkoituksena oli tutkia skitsofrenian ennustetta ja ennustetekijöitä meta-analyysin ja Pohjois-Suomen vuoden 1966 syntymäkohortin avulla.

Pohjois-Suomen vuoden 1966 syntymäkohortti on valikoitumaton, yleisväestöpohjainen kohortti, johon kuuluu 12 068 raskaana olevaa naista ja heidän 12 058 elävänä syntynyttä lastaan. Tässä väitöstutkimuksessa hyödynnetiin sairauskertomuksia, kansallisia rekistereitä sekä kahdessa laajassa kenttätutkimuksessa (34- ja 43-vuotistutkimukset) kerättyjä tietoja, jotka koostuvat haastatteluista, useista kyselyistä, neuropsykologisesta tutkimuksesta sekä aivojen magneettikuvauksesta. Tutkimuksen aiheesta riippuen aineiston koko eri osajulkaisuissa vaihteli 43:n ja 103:n välillä.

Meta-analyysin perusteella 13,5 % skitsofreniaa sairastavista toipuu sekä kliinisesti että sosiaalisesti, eikä toipuminen ole viime vuosikymmeninä yleistynyt. Toipuneiden osuus oli suurempi köyhissä maissa.

Pohjois-Suomen vuoden 1966 syntymäkohorttitutkimuksissa todettiin, että huonompi ennuste myöhempien sairaalahoitojen ja remission suhteen oli niillä, jotka olivat sairastuessaan nuoria ja naimattomia, joiden psykoosisairaus alkoi hitaasti ja joilla oli sairauden alkuvaiheissa enemmän sairaalahoitoja. Uusi löydös oli yhteys itsetuhoisten ajatusten ja myöhempien sairaalahoitojen välillä. Tiettyjen aivoalueiden tilavuuden ja rakenteen muutokset liittyivät monella tavoin samanhetkiseen taudinkuvaan 34-vuotiaana. Neurokognitiivisessa testauksessa parempi viivästetty kielellinen muisti 34-vuotiaana ennusti parempaa kokonaisvaltaista vointia (oireet, sairaalahoidot, sosiaaliset suhteet ja työssäkäynti yhdistettynä) ja parempi näönvarainen muisti ennusti työssäoloa 9 vuoden seurannassa.

Tämän väitöstutkimuksen tulokset osoittavat, että skitsofreniasta toipuminen on mahdollista, vaikkakaan ei kovin yleistä. Vaikka taudinkulun ennustaminen on haastavaa, tutkimuksessa havaittiin useita kliinisesti merkittäviä tekijöitä, joilla on ennustearvoa jopa 20 vuoden seurannassa. Lisätutkimuksia kuitenkin tarvitaan, jotta löydettäisiin sellaisia ennustetekijöitä, joihin kohdistuvalla varhaisella interventiolla voitaisiin parantaa skitsofrenian ennustetta.

Asiasanat: aivot, ennuste, epidemiologia, kognitio, magneettitutkimus, meta-analyysi, pitkittäistutkimus, psykoosit, skitsofrenia, syntymäkohortti, taudinkulku

This thesis is dedicated to the memory of my dear mother-in-law

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I want to express my warmest gratitude to the late Professor Paula Rantakallio and to Professor Marjo-Riitta Järvelin for making it possible to use the Northern Finland Birth Cohort 1966 as study material. I acknowledge the work done by many in collecting and managing the data of the NFBC 1966.

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Oulu, February 2015 Pauliina Juola

Main definitions in this doctoral thesis

Long-term follow-up – Usually defined as follow-up period exceeding five years. In this study, long-term follow-up means the time period of approximately ten years from the onset of the illness up to the age of 34 years.

Neurocognitive functioning – Neurocognitive functioning assessed with neuropsychological tests.

Onset of illness – The onset of schizophrenic psychosis defined as the age when the first positive symptoms occurred, based on a review of the medical records.

Outcome – The end-point of a measure investigated. The outcome measures used in this study include clinical (symptoms, remission, hospitalisations), functional (occupational outcome, functioning), and global outcomes (clinical and social outcomes combined).

Recovery – The term refers to levels of social and vocational functioning that are within the normal range, together with a remission of psychiatric symptoms. The definition used in this study includes the combined social and clinical recovery with at least one of these lasting for a minimum of two years.

Remission – A period of time when an individual experiences solely low-level symptoms that do not influence his or her behaviour. The remission criteria by Andreasen *et al.* (2005) are used in this study.

Schizophrenia – Diagnosis of schizophrenia according to the DSM-III-R criteria.

Schizophrenic psychosis – Diagnosis of schizophrenia spectrum disorder according to the DSM-III-R criteria, including the diagnoses of schizophrenia, schizophreniform disorder, schizoaffective disorder, and delusional disorder.

Short-term follow-up – Usually defined as a follow-up period from six months to two years. In this study, short-term follow-up means the two-year time period from the discharge from the first hospitalisation due to psychosis.

Very long-term follow-up – In this study, follow-up from the onset of the illness up to the age12 of 43 years, a period of approximately 19 years.

Abbreviations

95% CI	95% Confidence Interval
AIM	Abstraction and Working Memory Test
APA	American Psychiatric Association
CGI	Clinical Global Impression
CSF	Cerebrospinal fluid
CVLT	California Verbal Learning Test
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICV	Intracranial volume
MRI	Magnetic resonance imaging
MCCB	MATRICS (Measurement and treatment to improve cognition in schizophrenia) Consensus Cognitive Battery
NFBC 1966	Northern Finland Birth Cohort 1966
OPCRIT	Operational Criteria Checklist for Psychotic Illness
OR	Odds Ratio
PANSS	Positive and Negative Syndrome Scale
SCID	The Structured Clinical Interview for DSM-III-R
SD	Standard Deviation
SOFAS	Social and Occupational Functioning Assessment Scale
VOLT	Visual Object Learning Test
WHO	World Health Organisation

List of original publications

This thesis is based on the following original publications, which are referred to throughout the text by their Roman numerals I–IV:

I Jääskeläinen E, Juola P, Hirvonen N, McGrath J.J, Saha S, Isohanni M, Veijola J & Miettunen J (2013) A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull 39(6): 1296–1306.

II Juola P, Miettunen J, Veijola J, Isohanni M & Jääskeläinen E (2013) Predictors of short- and long-term clinical outcome in schizophrenic psychosis – the Northern Finland 1966 Birth Cohort study. Eur Psychiatry 28: 263–268.

III Jääskeläinen E, Juola P, Kurtti J, Haapea M, Kyllönen M, Miettunen J, Tanskanen P, Murray G.K, Huhtaniska S, Barnes A, Veijola J & Isohanni M (2014) Associations between brain morphology and outcome in schizophrenia in a general population sample. Eur Psychiatry 29: 456–462.

IV Juola P, Miettunen J, Salo H, Murray GK, Ahmed AO, Veijola J, Isohanni M & Jääskeläinen E. Neurocognition as a predictor of outcome in schizophrenia in the Northern Finland Birth Cohort 1966. Manuscript.

In addition, unpublished data have been added to this doctoral thesis.

Table of contents

1 Introduction

The term *schizophrenia* was first introduced at the beginning of the 20th century by Swiss psychiatrist Eugen Bleuler (WHO 1996). Before that, this mental disorder was referred to as *dementia praecox*, a name invented by German psychiatrist Emil Kraepelin and referring to a mental state reminiscent of premature dementia. Ever since 1896 when Kraepelin first described the disorder as a disctinct disease entity, the course of schizophrenia has been a major focus in psychiatric research. (Häfner & an der Heiden 1999).

Kraepelin considered dementia praecox to be a chronic or progressive illness leading to severe and permanent impairments in cognitive and social functioning. Early treatments, such as the injection of adrenaline and inducing fever proved to be ineffective, and pessimistic prognostic views dominated the outcome literature for decades. Later, new treatments such as electroconvulsive therapy provided the first signs of the possible benefits of treatment, and the invention of antipsychotic medications in the 1950s and introduction of family and community treatment made a real break-through in the treatment of schizophrenia. (Hegarty *et al.* 1994).

The estimated lifetime prevalence of schizophrenia is about 1%. Schizophrenia is one of the leading causes of health burden in the world (Whiteford *et al.* 2013) and one of the costliest mental disorders in terms of both human suffering and societal expenditure (Potvin *et al.* 2008). The direct health care costs due to schizophrenia in year 2010 in Europe were estimated to be around 5,900€ per person. In comparison, the cost of unemployment in individuals with schizophrenia was about 25,000€ per person annually. (Gustavsson *et al.* 2011). Unemployment is very common among people with schizophrenia, mortality rates are high, and there is substantial family burden (Knapp *et al.* 2004). Schizophrenia is not only a mental health problem, as it is often associated with negative somatic health outcomes, and the life expectancy of subjects with schizophrenia is about 20 years shorter compared to the general population (Laursen *et al.* 2014). All in all, schizophrenia causes more loss of life than do most cancers and physical illnesses (van Os & Kapur 2009).

In this day and age, the outcome in schizophrenia is still heterogeneous and difficult to predict. Good outcome has been found in approximately 40% of patients (Hegarty *et al.* 1994, Menezes *et al.* 2006); however, the rate of recovery is unclear. Despite new treatments and modern treatment approach, the outcome has not markedly improved in recent decades (Hegarty *et al.* 1994, Warner 2004).

Even though outcome and its determinants have been a major focus of schizophrenia research for many decades, there are still no definite answers as to the

aetiology of the disease, let alone its cure or predictors of prognosis. Outcome studies are, to a great extent, based on clinical samples and employ a vast spectrum of study methodologies, making it difficult to compare and generalise the results. Schizophrenia needs to be studied not only in clinical samples, but also in epidemiologically sound samples with a longitudinal study design and a long follow-up. The Northern Finland Birth Cohort 1966 (NFBC 1966) is one of the first samples to have followed subjects from the prenatal period up to the present day, providing information approximately twenty years before and after the onset of illness.

The purpose of this doctoral thesis was to investigate – in the NFBC 1966 – whether some easily assessable sociodemographic and illness-related factors as well as brain morphology and neurocognitive functioning could be used to predict later outcome. Additionally, a meta-analysis was conducted in order to disentangle the rate of recovery in schizophrenia.

2 Schizophrenia

Schizophrenia is not a discrete illness with a single cause or course. Rather, it appears to be a syndrome with multiple interacting genetic and environmental causes, and an outcome that is widely heterogeneous. The onset of schizophrenia is typically in adolescence or early adulthood. (van Os & Kapur 2009). So far, no society anywhere in the world has been found to be free from schizophrenia, and this puzzling illness represents a serious public health problem (WHO 1996). In 2004 there were 26.3 million people suffering from schizophrenia worldwide (WHO 2008).

2.1 Epidemiology of schizophrenia

The incidence and prevalence of schizophrenia varies significantly, not only within a population but also between countries (Laursen *et al.* 2014). Incidence is about 15.2 per 100,000 persons per year (McGrath *et al.* 2004), and the lifetime morbid risk about 7.2 per 1,000 persons (Saha *et al.* 2005). Men have a slightly higher risk (1.4–fold) of schizophrenia than women. In other words, about seven individuals per 1,000 will be affected by schizophrenia during their lifetime, and for every three men two women develop schizophrenia. (McGrath *et al.* 2008). However, the prevalence estimates vary from 0.5% to 1.5% in different parts of the world, with higher rates in some population isolates (Cannon & Jones 1996). In Finland, the lifetime prevalence of schizophrenia is 1.0%, and 2.3% for any nonaffective psychotic disorder (Perälä *et al.* 2007). There is also prominent regional variation within Finland, with a higher risk of schizophrenia in the eastern and northern parts of the country (Perälä *et al.* 2008). The cumulative incidence of schizophrenia in the NFBC 1966 by the age of 44 years was 1.4% (Keskinen *et al.* 2013). According to a recent large register study including all Danish residents, the lifetime risk for schizophrenia was 1.9% for males and 1.6% for females (Pedersen *et al.* 2014).

Schizophrenia can occur at any age, but in men incidence peaks at age 15–25 years (Sutterland *et al.* 2013), in general 3–4 years earlier than in women (Saha *et al.* 2005). This same pattern occurs across countries, indicating that it is not caused by cultural factors (Jablensky *et al.* 1992). No satisfactory explanation yet exists for the sex differences in the prevalence of schizophrenia or for the earlier onset of illness in men, but there is evidence suggesting a protective effect of female sex hormones (Kulkarni 2009). A small proportion of individuals, especially women, develop schizophrenia after the age of 60, with an incidence rate in this age group of approximately 5 per 100,000 person-years (van der Werf *et al.* 2014). In the large

Danish study, the incidence peaked at the same age in both genders, at about 20 years of age, but males had a slightly higher incidence from 20 to 50 years, after which the incidence rate was slightly higher in women (Pedersen *et al.* 2014).

Schizophrenia is one of the leading causes of disability and disease burden worldwide (WHO 2008). People with schizophrenia have low rates of marriage (MacCabe *et al.* 2009) and low fertility (Bundy *et al.* 2011), and they experience a steep decline in socioeconomic status alongside the onset of illness (Aro *et al.* 1995). The lifetime risk of suicide is approximately 5% (Hor & Taylor 2010), and the overall mortality rate is two to three times as high for individuals with schizophrenia as for the general population (Saha *et al.* 2007, Bushe *et al.* 2010). High mortality is found in all age groups, resulting in a life expectancy of approximately 20 years below that of the general population (Laursen *et al.* 2014). Evidence suggests that the mortality gap between patients with schizophrenia and general population not only persists but may actually have increased during past decades (McGrath *et al.* 2008, Laursen *et al.* 2014). However, in the Nordic countries this gap has been shown to be narrowing slightly (Wahlbeck *et al.* 2011). Four main reasons have been identified for the excess mortality among individuals with schizophrenia: 1) somatic illnesses in individuals with schizophrenia are common but are diagnosed late and treated insufficiently, 2) antipsychotic medication has negative side effects, 3) individuals with schizophrenia tend to have an unhealthy lifestyle (poor diet, smoking, excess alcohol consumption, and lack of exercise), and 4) the risk of suicide and accidents among patients with schizophrenia is high (Laursen *et al.* 2012).

2.2 Risk factors of schizophrenia

The cause of schizophrenia is incompletely understood. Three key periods across the lifespan may influence the risk for schizophrenia: 1) conception, 2) early developmental, and 3) later developmental periods (Karlsgodt *et al.* 2011).

There is evidence for a substantial genetic contribution to the aetiology of schizophrenia, with heritability estimates up to 85% (Cardno *et al.* 1999) and a 10-fold increase in the risk to siblings of probands (McGlashan & Johannessen 1996). All kinds of psychiatric disorders in the family, i.e. those concerning any psychiatric diagnosis cause an increase in the risk of schizophrenia. Nearly 30% of schizophrenia in the population can be attributed to psychiatric family history in general, compared to 6% that is attributable to a family history of schizophrenia specifically. (Mortensen *et al.* 2010). Nevertheless, 85% of individuals with schizophrenia have no first-degree relative with schizophrenia (McGlashan & Johannessen 1996).

Due to its high heritability and strong familial associations, genetic approaches are critically important for the study of schizophrenia. No Mendelian forms of schizophrenia (i.e. rare mutations with deterministic effects) have been identified. The genetic architecture of schizophrenia is diverse and includes genetic loci across the allelic spectrum (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) with many common variants of subtle effect, rare but highly penetrant copy number variants, and possibly exome variants. (Giusti-Rodríguez & Sullivan 2013). The genes thus far identified only explain part of the genetic risk of schizophrenia, although many of them seem to be involved in neurodevelopmental processes, including neurotransmission and synaptic plasticity, dopamin receptor D2, and calcium channel function (Craddock *et al.* 2005, Howes & Murray 2014, Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

With the well-known heterogeneity of the clinical expression of schizophrenia and the marked variability in the genetic liability to schizophrenia, a similar heterogeneity in the risk-increasing environmental factors comes as no surprise (McGrath *et al.* 2008). Pre- and perinatal complications, including maternal infections and hypertension (Suvisaari *et al.* 2013), abnormal foetal development, and obstetric complications (Cannon *et al.* 2002b, Forsyth *et al.* 2013) are significantly associated with schizophrenia. Mothers with schizophrenia carry risk genes that, in part, explain the higher risk of schizophrenia in their offspring; in addition to this, they also show increased health-risk behaviour during pregnancy, such as substance abuse and smoking that are per se related to obstetric complications (Bennedsen 1998). Also, higher paternal age (Miller *et al.* 2011, McGrath *et al.* 2014), antenatal stress (van Os & Selten 1998, Selten *et al.* 1999), low maternal body weight (Wahlbeck *et al.* 2001), and an unwanted pregnancy (Myhrman *et al.* 1996) have been identified to increase the risk of schizophrenia.

Prospectively collected measures of premorbid function have consistently revealed impairments or delays in some developmental domains in subjects who later develop schizophrenia. Such factors include later achievement of developmental milestones concerning motor functions, such as learning to stand or walk, or language functions, such as learning to produce or understand language (Jones *et al.* 1994, Isohanni *et al.* 2001, Cannon *et al.* 2002a). Individuals who later develop schizophrenia have a premorbid IQ of around 0.4 standard deviations (SDs) below the average (Khandaker *et al.* 2011). Poor school performance and social and behavioural difficulties have also been identified as risk factors for later schizophrenia (Jones *et al.* 1994, Isohanni *et al.* 1998).

Migration (Morgan *et al.* 2010) and living in a city as a child (Vassos *et al.* 2012), as well as cannabis abuse (Giordano *et al.* 2015) and childhood adversities, whether of a physical or psychological nature (Rubino *et al.* 2009), have all been associated with the increased risk of schizophrenia.

2.3 Symptoms and diagnosis of schizophrenia

2.3.1 Symptoms of schizophrenia

Schizophrenia is characterised in general by fundamental distortions of thinking and perception, and affects that are inappropriate or blunted. Motivation, cognitive functions and social communication are all altered in schizophrenia (Shenton *et al.* 2010). Schizophrenia is described in the following way in the 10th International Classification of Diseases classifications guidelines (ICD-10) by the World Health Organization (WHO 1992).

> *The disturbance involves the most basic functions that give the normal person a feeling of individuality, uniqueness, and self-direction.*

Schizophrenia is a heterogeneous syndrome, not only in its core psychopathology but also in terms of the course of the disorder, the extent of cognitive defects, response to treatment, and the diverse needs it presents to health care (Henderson & Malhi 2014). There is no one symptom that is essential to schizophrenia, and variations in symptoms occur even in the same patient (Shenton *et al.* 2010). Nor is psychosis exclusive to schizophrenia, as it occurs in various diagnostic categories of psychotic disorders. The term schizophrenia is applied to a syndrome characterised by long duration, bizarre delusions, negative symptoms and few affective symptoms (non-affective psychosis). (van Os & Kapur 2009).

People who develop schizophrenia tend to show subtle cognitive, social, and motor impairments in childhood. These early signs are followed by anxiety and depressive symptoms, and social withdrawal in adolescence and early adulthood, and then by the emergence of prodromal symptoms of psychosis before the onset of the first actual psychotic episode. (Howes & Murray 2014).

The course of schizophrenia can either be continuous or episodic with progressive or stable deficit, or there can be one or more episodes with complete or incomplete remission (WHO 1992). The first psychotic episode is frequently followed

by a fluctuating course, with enduring residual positive and negative symptoms interspersed with acute exacerbations of positive symptoms (Howes & Murray 2014).

There are various ways to categorise the symptoms of schizophrenia, which in general fall into three broad categories: positive symptoms, negative symptoms, and cognitive symptoms. People with positive symptoms often "lose touch" with reality. These symptoms, which vary in duration and severity include delusions, thinking disorders, and hallucinations, which are most often auditory. Negative symptoms include social withdrawal, lack of motivation, and reduction of spontaneous speech. Cognitive symptoms include e.g. difficulties in memory, attention, and executive functioning. (van Os & Kapur 2009). The Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987) is the most widely used scale to assess symptoms in schizophrenia (van der Gaag *et al.* 2006a).

2.3.2 Diagnosis of schizophrenia

The diagnostic criteria of schizophrenia have varied considerably since the first recognition of the disease, and great differences have existed between continents. Whereas Scandinavian psychiatrists have traditionally tended to use a rather narrow definition of schizophrenia, in the United States the diagnostic approach to schizophrenia has changed over time. (Warner 2004).

The US-based 5th Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by the American Psychiatric Association (APA 2013) and the ICD-10 (WHO 1992) are currently used to diagnose schizophrenia. With time, the diagnostic criteria of the two systems have approached one another; however, one of the features differentiating between the two diagnostic systems is that the ICD-10 requires for the key symptoms to have been present for a significant portion of time over a one month period, whereas the DSM-5 requires that continuous signs of the disturbance persist for at least six months, including at least one month of active symptoms. Additionally, the diagnostic criteria of the DSM-5 no longer identify subtypes of schizophrenia, such as paranoid, disorganised, or catatonic schizophrenia. The diagnostic criteria for schizophrenia according to the DSM-5 are represented in Table 1. (APA 2013).

The diagnostic system employed in this doctoral thesis is the DSM-III-R, which is the revised version of the DSM-III introduced in 1987 (APA 1987). The main difference concerning the diagnosis of schizophrenia between the DSM-III-R and the currently used DSM-5 is that in the latter the duration of characteristic symptoms is extended to a minimum of one month compared to one week in the DSM-III-R,

negative symptoms are added to the characteristic symptoms and subtypes of schizophrenia are eliminated (Bhati 2013).

Table 1. Diagnostic criteria for schizophrenia according to the DSM-5 (APA 2013).

Diagnostic criteria	Description
Criterion A: Characteristic symptoms Two (or more) characteristic symptoms, at least one must be 1, 2, or 3 Each present for a significant portion of time during a one-month period	1. Delusions 2. Hallucinations 3. Disorganised speech 4. Grossly disorganised or catatonic behaviour 5. Negative symptoms
Criterion B	Disturbances for a significant proportion of the time in at least one major area of social/occupational functioning, such as work or interpersonal relations
Criterion C	Continuous signs of the disturbance persist for at least six months
Criterion D	Schizoaffective disorder and depressive or bipolar disorder with psychotic features must be ruled out
Criterion E	The disturbance is not attributed to the direct physiological effects of a substance or another medical condition
Criterion F	In relationship to Global Developmental Delay or Autism Spectrum Disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least one month

2.3.3 Other schizophrenic psychoses (i.e. schizophrenia spectrum psychotic disorders)

Schizophrenia together with schizophreniform, schizoaffective, delusional, and brief psychotic disorders forms the schizophrenia spectrum psychotic disorders (APA 2013). According to the DSM-5, the schizophreniform disorder is characterised by the same symptoms as schizophrenia, but the duration of symptoms is shorter, lasting longer than one month but less than six months, and the diagnosis does not require a decline in functioning (Bhati 2013). In the follow-up, many cases later fulfil the

diagnostic criteria of schizophrenia (Moilanen *et al.* 2003). Schizoaffective disorder is characterised by coexisting schizophrenic and mood symptoms, with delusions or hallucinations present for at least two weeks in the absence of major mood symptoms (depressive or manic) during the lifetime duration of the illness. Delusional disorder is defined by the presence of one or more delusions for at least one month with no other psychotic symptoms. However, some tactile and olfactory hallucinations may be present if they are related to the delusional theme. Brief psychotic disorder is a transient psychosis lasting longer than one day but less than one month and with a return to a premorbid level of functioning. (APA 2013). Delusional disorder and especially brief psychotic disorder are often not included in studies of outcome in schizophrenia as they, by definition, have a more positive outlook in outcome.

2.4 Brain morphology and schizophrenia

The neuropathology of schizophrenia is still largely unknown (Shenton *et al.* 2010). In general, two types of developmental processes affect brain volumes after birth: 1) progressive changes, such as cell proliferation and myelination, and 2) regressive changes, such as synaptic pruning and apoptosis (Pfefferbaum *et al.* 1994). Many of the genes associated with the risk of schizophrenia seem to be involved in these neurodevelopmental processes, thus suggesting that some of the genetic risk leading to the development of schizophrenia is expressed as abnormal brain development (van Haren *et al.* 2012). A neurodevelopmental hypothesis of schizophrenia argues that disturbed early development of the nervous system, caused by a combination of genetic and environmental factors, later interact with normal brain maturation processes eventually resulting in schizophrenia (Murray & Lewis 1987). The competing hypothesis – the neurodegenerative hypothesis – first introduced by Emil Kraepelin in 1919, focuses on schizophrenia as a chronic and progressive disorder of the nervous system resulting in biochemical changes that lead to different clinical syndromes, loss of neurological function and deterioration of behaviour (Gupta & Kulhara 2010, Pino *et al.* 2014).

2.4.1 Focal brain abnormalities associated with schizophrenia

Multiple focal brain regions that are abnormal compared to controls have been identified in schizophrenia using the magnetic resonance imaging (MRI) (Haijma *et al.* 2013). In fact, abnormal brain structures are one of the most robust biological features of schizophrenia (Wright *et al.* 2000). There are consistent findings

conserning gray matter volume reductions in the medial temporal lobe structures including the amygdala, hippocampus, parahippocampal gyrus, and in the frontal, temporal and parietal lobes, and the basal ganglia. There is also consistent evidence for the enlargement of the ventricles and cavum septum pellucidum, i.e. increase of the cerebrospinal fluid (CSF). (Shenton *et al.* 2010). Compared to grey matter and CSF volumes, white matter has received far less attention in MRI studies as it is more difficult to define and evaluate. However, fairly consistent findings in subjects with schizophrenia concern reductions in total white matter volume and in the volume of the corpus callosum. (Walterfang *et al.* 2006, Haijma *et al.* 2013). White matter is more accurately studied using diffusion tensor imaging (DTI) and these studies have shown abnormalities in patients with schizophrenia particularly in fiber bundles that connect the frontal and temporal lobes (Shenton *et al.* 2010).

The precise timing of these abnormalities is still largely unknown, although evidence suggest that at least some of the neuroanatomical alterations are present before the onset of full psychotic disease, i.e. in the prodromal period, reflecting at least in part the neurodevelopmental abnormalities (Pantelis *et al.* 2003, Fusar-Poli e*t al.* 2012, Haijma *et al.* 2013, Zipursky *et al.* 2013). One large study has suggested that the grey matter reductions may be linked to the pathophysiology of the onset of psychosis as the observed grey matter volume differences between clinical high risk subjects who had converted to psychosis and subjects who did not convert to psychosis (or healthy controls) were not yet apparent at the clinical high risk stage, i.e. prior to the onset of psychosis (Cannon *et al.* 2015). Abnormalities are also observed, albeit in a more attenuated form, in the non-affected family members of patients with schizophrenia (Boos *et al.* 2007).

Some of the morphological changes are found to be progressive (Ho *et al.* 2003, Andreasen *et al.* 2011, Vita *et al.* 2012), and there is some evidence for continuous progressive brain tissue decrease up to 20 years after first symptoms. The extent of brain tissue decrease in patients (−0.5−0.7% per year) is almost twice that of healthy controls. (Hulshoff Pol & Kahn 2008, Veijola *et al.* 2014). The cumulative loss of brain tissue results in about 3% overall brain volume loss after 20 years of illness (Hulshoff Pol & Kahn 2008).

In addition to the disorder itself, cannabis or alcohol use, smoking, stress-related hypercortisolemia, and low physical activity may also contribute to the changes in cortical and ventricular volumes observed over the course of schizophrenia (Zipursky *et al.* 2013). Some of the morphological changes may relate also to the severity or duration of the illness, or the use of antipsychotic medications (van Haren *et al.* 2011,

Ho *et al.* 2011, Haijma *et al.* 2013, Shepherd *et al.* 2012, Andreasen *et al.* 2013, Fusar-Poli *et al.* 2013, Veijola *et al.* 2014).

2.5 Neurocognitive functioning and schizophrenia

Cognitive impairments are common in schizophrenia and they are present in patients with schizophrenia across all phases of the illness (Palmer *et al.* 2009), already at the onset of the disorder (Hoff *et al.* 2005) and independently of treatment with antipsychotic medications (Gur *et al.* 2001). The average cognitive deficit associated with schizophrenia is approximately one to two standard deviations below the mean for healthy comparison subjects (Nielsen 2011). However, approximately 20 – 25% of schizophrenia patients have neuropsychological profiles in the normal range (Palmer *et al.* 2009). Individuals with an early onset of the illness express more severe cognitive deficits compared to later onset subjects (Rajji *et al.* 2009). There is no convincing evidence of the loss of acquired cognitive skills after the onset of psychosis; rather, the cognitive deficits seem to be best explained by problems in acquisition during neurodevelopment (Bora & Murray 2014).

While clinical symptoms fluctuate, cognitive deficits appear to be relatively stable during the course of the illness (Hoff *et al.* 2005, Szöke *et al.* 2008, Ekerholm *et al.* 2012). Thus, cognitive impairments are relatively independent of clinical state, although the severity of the impairment may fluctuate with a change in symptoms (Buchanan *et al.* 2005). More severe negative symptoms and a high dose of antipsychotics have been associated with the most severe cognitive impairments, whereas mood symptoms do not affect cognitive performance (Torniainen *et al.* 2012). Impairments have also been observed in the unaffected relatives of patients with schizophrenia (Snitz *et al.* 2006, Chen *et al.* 2009, Husted *et al.* 2010).

There is evidence to suggest that neurocognitive functioning is among the most important factors contributing to employment and vocational outcome (Green *et al.* 2000, Christensen *et al.* 2007). It is hoped that the ongoing development of cognition-enhancing medications will provide the next major advance in the treatment of patients with schizophrenia (van Os & Kapur 2009). However, the only currently available treatment showing alleviation of cognitive deficits is cognitive remediation (Nielsen 2011).

2.5.1 Neurocognitive domains related to schizophrenia

Neurocognitive dysfunction in schizophrenia is well established with neuropsychological batteries, which indicate diffuse deficits in multiple neurocognitive domains (Gur *et al.* 2001). Impairments are seen in all neurocognitive domains, including processing speed, sustained attention/vigilance, working memory, verbal learning, visual learning, and reasoning and problem-solving (Buchanan *et al.* 2005, Corigliano *et al.* 2014). At the core of the schizophrenic disorder is, however, a generalised deficit in cognitive functions (Dickinson & Harvey 2009, Tuulio-Henrikson *et al.* 2011). First-episode patients shown similar deficits compared to multi-episode patients, but multi-episode patients are often more impaired as regards sustained attention/vigilance (Corigliano *et al.* 2014).

2.6 Treatment of schizophrenia

2.6.1 Antipsychotic medication

Antipsychotic drugs, which block dopamine D2 receptors are the main treatment for schizophrenia; however, there is no permanent cure for the disorder. Antipsychotics were first discovered in the 1950s, and these first agents, called first-generation antipsychotics, included e.g. haloperidol and chlorpromazine. New antipsychotic drugs, known as the second-generation antipsychotics, such as risperidone, olanzapine and quetiapine, have later been introduced for treatment. (van Os & Kapur 2009). The use of antipsychotic medications has been associated with a reduced mortality risk (Tiihonen *et al.* 2009, Cullen *et al.* 2013), reduction of positive symptoms, and reduced risk of relapse (Leucht *et al.* 2012). However, they do not have much effect on negative symptoms or cognitive deficits (Tandon 2011). Clozapine is generally considered the most effective neuroleptic but due to the risk of agranulocytosis its use has been limited mainly to treatment-resistant schizophrenia (Javitt 2014). Also other antipsychotic drugs have troubling side-effects (Leucht *et al.* 2012): first-generation antipsychotics typically cause extrapyramidal symptoms, such as movement disorders, whereas second-generation antipsychotics tend to induce metabolic side-effects, such as weight gain, impaired glucose tolerance and lipid abnormalities (van Os & Kapur 2009, Rummel-Kluge *et al.* 2010).

2.6.2 Psychosocial treatments

In order to improve the efficacy of the treatment, pharmacological treatment should be used together with psychosocial interventions (Valencia *et al.* 2013). Specific vocational and psychological interventions can improve functional outcome (van Os & Kapur 2009). For patients with drug-resistant symptoms, cognitive-behavioural therapy can improve coping and especially reduce positive symptoms. Psychoeducation and intensive case management can increase treatment adherence and independent living, while cognitive remediation and integrated psychological therapy improve neurocognitive and social and global functioning. Vocational rehabilitation has been shown to improve competitive employment. (Matheson *et al.* 2014). Family intervention may decrease the risk of relapse, improve treatment adherence, and reduce re-hospitalisations (Pharoah *et al.* 2010).

3 Outcome in schizophrenia

For many years, schizophrenia was regarded as a chronic lifetime illness with little or no hope of recovery (Andreasen *et al.* 2005). In fact, many clinicians regarded dramatic improvement in a patient with schizophrenia as an indication of original misdiagnosis (Liberman *et al.* 2002). The course of the illness in schizophrenia is often lifelong, characterised by exacerbations, remissions, residual symptoms and functional impairment (Giusti-Rodríguez & Sullivan 2013). However, the outcome is highly heterogeneous and the deterioration experienced by many patients over the long-term is not an inevitable part of the illness (Zipursky *et al.* 2013).

Systematic reviews report that approximately 40% of subjects with schizophrenia experience a good outcome (Hegarty *et al.* 1994, Menezes *et al.* 2006), and 27% a poor outcome (Menezes *et al.* 2006). However, rates of relapse, defined as return of the disease after partial recovery (Lader 1998), are 28% at one year and up to 54% at three years (Matheson *et al.* 2014), and may be as frequent as 82% at 5 years for the first relapse and 78% for the second relapse among those showing initial improvement (Robinson *et al.* 1999). The relapse rate seems to relate to poor treatment adherence, as patients who cease to take antipsychotic medication have a relapse rate of 77% during the first year off medication, compared to only 3% in patients who continue their medication (Zipursky *et al.* 2014). Some, albeit a small proportion of patients, have no further episodes of psychosis after the first episode; conversely, having had a psychotic episode leaves the person at risk of further episodes for several years (Bosveld-van Haandel *et al.* 2001).

Despite rehabilitation projects, the employment rate among subjects with schizophrenia is low, mostly between 10 and 20% in European countries (Marwaha & Johnson 2004). In Finland as many as 80% of patients with schizophrenia are pensioned and only 7% are working (Perälä *et al.* 2008). However, despite the deficits in occupational capacity and day-to-day functioning, subjects with schizophrenia are not necessarily less happy than their peers (Agid *et al.* 2012).

3.1 Definitions of outcome

Terms to describe the outcome in schizophrenia include remission, functional remission and recovery. Definitions for each of them vary considerably (Liberman *et al.* 2002, Andreasen *et al.* 2005, Henry *et al.* 2010). Other commonly used measures of outcome include vocational functioning, quality of life, number of hospital treatments, and symptomatology, some of which can be measured with various scales,

such as PANSS, CGI (Clinical Global Impressions), SOFAS (Social and Occupational Functioning Scale), QOLS (Quality of Life Scale), and GAF (Global Assessment of Functioning) (Miettunen *et al.* 2009).

3.1.1 Remission

Remission is commonly used in clinical practice to describe the stable state of patients with schizophrenia. In earlier studies, remission criteria have typically required that positive symptoms be reduced to a mild level of severity, while required criteria vary for the severity of negative symptoms and duration required to meet the threshold for remission (Lieberman *et al.* 1993).

In 2005, the Remission in Schizophrenia Working Group led by Nancy Andreasen suggested standardised criteria for remission in schizophrenia (Andreasen *et al.* 2005), and these criteria have become widely adopted in schizophrenia research. Remission was defined by two factors: 1) maximum mild severity of core symptoms in schizophrenia, and 2) the duration criterion of at least six consecutive months. Remission criteria were proposed separately for the most commonly used symptoms scales, and the selected symptom items reflect the three distinct components of the schizophrenic disorder: reality distortion (positive symptoms), psychomotor poverty (negative symptoms) and disorganisation symptoms. The selected symptoms also incorporate the five characteristic (diagnostic) symptoms for schizophrenia (Mosolov *et al.* 2012). The correspondence between the DSM-5 diagnostic criteria and the remission criteria according to PANSS, which is the symptom scale used in this doctoral thesis, is presented in Table 2. The severity thresholds proposed are such that any remaining symptoms will not interfere significantly with day-to-day functioning (van Os *et al.* 2006a). The proposed remission criteria present the opportunity for cross-study comparisons (Henry *et al.* 2010), and they have been shown to be valid and suitable for use in research (van Os *et al.* 2006b).

The remission criteria are fulfilled by 22–66% of patients with schizophrenia, depending on the characteristics of the population investigated, duration of illness and follow-up, and type of medication (Emsley *et al.* 2011, Haro *et al.* 2011, ten Velden Hegelstad *et al.* 2013). According to a large ÆSOP-study with a 10-year follow-up, 40% of subjects with schizophrenia had remained in remission for the last two years of follow-up (Morgan *et al.* 2014a).

Table 2. The correspondence between the remission criteria by the Remission in Schizophrenia Working Group and the diagnostic symptoms of schizophrenia according to the DSM-5.

Diagnostic symptoms according to the DSM-5 (2 or more)	Remission criteria by Andreasen *et al.* (2005) (score 3 or less in all PANSS items)
1. Delusions	P1 Delusions; G9 unusual thought content
2. Hallucinations	P3 hallucinatory behaviour
3. Disorganised speech	P2 conceptual disorganisation
4. Grossly disorganised or catatonic behaviour	G5 mannerisms/ posturing
5. Negative symptoms	N1 blunted affect; N4 social withdrawal; N6 lack of spontaneity

The remission criteria define a clinical state that is associated with good social and occupational functioning (van Os *et al.* 2006b, Helldin *et al.* 2007, Wunderink *et al.* 2007), good subjective quality of life (Haro *et al.* 2014), and good cognitive performance (Helldin *et al.* 2006). Unfortunately, one cannot assume that all patients who are in symptomatic remission will be functioning well in the society (van Os *et al.* 2006a). Also, as shown in a study by Karow *et al.* (2012), these remission criteria do not reflect the perception of remission by patients and their family members in clinical practice, as only in 18% of the cases all three parties, i.e. the patient, his or her relatives and the psychiatrist, agreed on their assessment of the patient's remission status.

3.1.2 Functional remission

Restoration of social functions, such as resuming the activities of daily life, social interaction and work skills, is subsumed under the concept of functional remission. It requires a level of functioning comparable with the general population, regardless of the presence of schizophrenic symptoms. (Menezes *et al.* 2009). Achieving functional remission is important in reintegrating patients into the community and the workplace, and thus reducing the social burden and health-care costs (Helldin *et al.* 2007). In 2009, the "Functional Remission of General Schizophrenia" (FROGS) scale was published (Llorca *et al.* 2009). It is a 19-item scale defining five domains of social functioning, namely Daily Life, Activities, Quality of Adaptation, Relationships, and Health and Treatment. Unfortunately, it has not become widely used so far, and research continues to employ various measures and scales to define functional remission, e.g. GAF (Global Assessment of Functioning) (Frances *et al.*

1994) or SOFAS (Social and Occupational Functioning Assessment Scale) (Spitzer *et al.* 2000). The rate of functional remission in schizophrenia has been reported to be 20–45% (Warner 2004, Lambert *et al.* 2008, Menezes *et al.* 2009, Henry *et al.* 2010, Haro *et al.* 2011).

3.1.3 Recovery

The term "recovery" is used to refer to achieving levels of social and vocational functioning that are within the normal range, together with a remission of psychiatric symptoms (Liberman *et al.* 2002, Robinson *et al.* 2004). A range of definitions of the term "recovery" have been used in the schizophrenia literature, and its meaning varies considerably between researchers, clinicians and, in fact, clients of mental health services themselves (Liberman *et al.* 2002, Liberman & Kopelowicz 2005). For clients, recovery can mean the ability to re-join the mainstream and function again in the absence of antipsychotic medication (Liberman *et al.* 2002). In schizophrenia research, simultaneously fulfilled criteria of symptomatic and functional remission are a precondition for fulfilling the concept of recovery. Remission is thus a necessary but not a sufficient step toward recovery (Andreasen *et al.* 2005). Criteria for recovery often employed in schizophrenia research include the remission of positive and negative symptoms to such an extent that they do not interfere with everyday functioning, and the ability to live independently with respect to caring for oneself, one's work or school attendance and peer or family relations. The criterion for the duration of recovery is suggested to be at least two years, i.e. when an individual has sustained clinical and social remission for two years, he or she can be considered recovered (Faerden *et al.* 2008). The incidence of recovery in schizophrenia ranges between 4% and 20% (Warner 2004, Lieberman *et al.* 2008, Bertelsen *et al.* 2009, Lambert *et al.* 2010). In Finnish schizophrenia studies using a broad schizophrenia concept the rate of recovery ranges from 10 to 18% (Achté 1967, Lauronen *et al.* 2005).

3.1.4 Linkage between the outcome definitions

Remission, functional remission and recovery all describe important facets of outcome in schizophrenia and have distinct courses. Achieving remission gives, for instance, only a slight indication of the social or work functioning of the patient (van Os *et al.* 2006a, Helldin *et al.* 2007). Subjects considered to be remitted might experience major difficulties in social functioning, such as work life or social

relations. The same applies vice versa, that is, subjects might function adequately in society despite the presence of persisting symptoms. (Harding *et al.* 1987a, 1987b).

Follow-up studies have highlighted the difference in prevalence between clinical and functional remission. Clinical remission is achieved more often than functional remission, thus, lack of recovery is more often caused by functional than by clinical non-remission. Of the subjects in clinical remission, 31–51% are also in functional remission, and of the subjects in functional remission, 55–88% are also in clinical remission (Robinson *et al.* 2004, Wunderink *et al.* 2009, Henry *et al.* 2010, Wunderink *et al.* 2013).

3.2 Predictors of outcome

Several studies have examined the predictors of outcome in schizophrenia and many potential factors, both pre- and postmorbid, have been identified. There are difficulties in comparing results between studies, however, as the predictors and outcome measures employed vary considerably. Also, as several studies have failed to find any association between outcome and the factors mentioned below, the prognostic variables affecting outcome remain to some extent unclear (Jonsson & Nyman 1991, Harrison *et al.* 1996, Menezes *et al.* 2006). Potential explanations of the varying findings include differences in study design, diagnostic criteria, assessment methods, follow-up periods, and predictor and outcome variables employed.

3.2.1 Predictors of good outcome

Good outcome (defined in various ways) has been associated with many illness-related factors such as later onset age (Harrison *et al.* 1996), acute mode of onset (Ciompi 1980, Harrison *et al.* 1996, Bromet *et al.* 2005), more severe positive symptoms (Kanahara *et al.* 2013), and early response to treatment (AlAqeel & Margolese 2012). Also, having an obvious psychological stressor preceding illness onset (Jonsson & Nyman 1991) has been associated with a better outcome. The use of any antipsychotics, compared with non-use, is associated with a lower risk of relapse (Leucht *et al.* 2012) and in some studies with a lower mortality rate (Tiihonen *et al.* 2011, Cullen *et al.* 2013), whereas the use of antidepressants has been associated with a lower risk for suicide deaths (Tiihonen *et al.* 2012). Temperament traits have also been associated with outcome in schizophrenia, with low harm avoidance and high novelty-seeking before illness onset associating with a higher likelihood of remission (Miettunen *et al.* 2012).

Emsley *et al.* (2006) created a model incorporating predictor variables of remission including neurologic soft signs, early treatment response, duration of untreated psychosis (DUP), marital status, and baseline PANSS score. With these predictors, the model was able to correctly predict an outstanding 89% of remitters and 86% of non-remitters.

3.2.2 Predictors of poor outcome

Sociodemographic and premorbid factors related to poor outcome include male gender (Harrison *et al.* 1996, Häfner & an der Heiden 1999, Bertelsen *et al.* 2009), being single (Harrison *et al.* 1996, Emsley *et al.* 2008), having a family history of schizophrenia (Suvisaari *et al.* 1998, Ganev *et al.* 2000, Käkelä *et al.* 2014), poor functioning (McGlashan 1986, Bromet *et al.* 2005, Emsley *et al.* 2008), personality disorders (Ciompi 1980), and alcohol or drug abuse (van Os *et al.* 1997). Illness-related factors such as lack of insight (Bromet *et al.* 2005), severe negative symptoms (Häfner & an der Heiden 1999, Möller *et al.* 2000, Emsley *et al.* 2007, Whitty *et al.* 2008), suicidal behaviour (Emsley *et al.* 2007, Schennach-Wolff *et al.* 2010) and long DUP (Perkins *et al.* 2005, Marshall *et al.* 2005, Penttilä *et al.* 2013) have been connected to poorer outcome.

The risk of relapse after the first psychotic episode has been predicted by non-adherence to medication, substance use disorder, family criticism and hostility, and poor premorbid adjustment (Alvarez-Jimenez *et al.* 2012, Matheson *et al.* 2014). On the other hand, a long duration of maintenance antipsychotic treatment has been associated with a lower functional remission rate (Wunderink *et al.* 2013). Taking more than one antipsychotic concurrently has been associated with a risk of premature death (Waddington *et al.* 1998, Joukamaa *et al.* 2006), and benzodiazepine use with increase in mortality (Tiihonen *et al.* 2012). Certain genetic variants in schizophrenia may contribute to poor response to antipsychotics (Liu *et al.* 2012) and to more severe symptomatology (Tovilla-Zárate *et al.* 2014). Treatment nonadherence is a major problem in schizophrenia affecting more than one third of patients and having a negative effect on outcome (Haddad *et al.* 2014).

In general, the best predictors of the long-term course and outcome in schizophrenia seem to be the previous course and outcome of illness (Angst *et al.* 1988, Siegel *et al.* 2006, Hopper *et al.* 2007). Accordingly, people with prior hospitalisations are prone to be hospitalised later on (McGlashan 1988), and people with relapses in the past are more vulnerable to relapses in the future (Ascher-Svanum *et al.* 2010). There seems to be significant variability between studies in the relevant

predictors of outcome depending on the length of follow-up (McGlashan 1986, Penttilä *et al.* 2013).

Many meta-analyses and systematic reviews have studied different factors relating to outcome in schizophrenia, and these studies are presented in Table 3. Studies on specific treatments in schizophrenia that have previously been analysed in a meta-analysis by Matheson *et al.* (2014) are not included in this table.

Table 3. Meta-analyses and systematic reviews of outcomes and their predictors in psychotic disorders. Systematic reviews of specific treatment interventions are not included.

Author	Primary topic and patient group	Predictors of outcome	Outcomes	Studies included	Main results
AlAqeel & Margolese 2012	Remission and related factors in first-episode and in multiple-episode schizophrenia	Several (e.g. premorbid functioning, DUP, type of medication, baseline symptoms)	Remission according to criteria by the Remission in Schizophrenia Working Group (Andreasen *et al.* 2005)	27	Remission rate 17–78% (weighted mean 35.6%) in first-episode and 16– 62% (weighted mean 37%) in multiple-episode schizophrenia. Better premorbid function, milder baseline symptoms, early treatment response, and shorter DUP most frequently associated with remisson.
Allot *et al.* 2011	Cognition at illness onset as a predictor of later functional outcome in early psychosis	Cognitive domains classified according to MCCB, with Verbal Fluency and Global Cognition studied separately	Outcomes in community, vocational and social functioning	22	There were more null than significant associations between cognition and functional outcome across every cognitive domain. Study methodology, especially duration of follow-up or taking statistical power or attrition rates into account, affected the associations.
Archie *et al.* 2009	The effect of substance abuse on the outcome in FEP	Alcohol, cannabis, hallucinogens, opiates, cocaine, ecstasy, multiple drug abuse	Relapse, hospitalisations, symptoms, compliance, psychosocial outcomes	12	Substance abuse increased the number of relapses and positive symptoms, and reduced negative symptoms and treatment compliance.

Author	Primary topic and patient group	Predictors of outcome	Outcomes	Studies included	Main results
Clemmensen *et al.* 2012	The long-term outcome and prognosis of early onset schizophrenia	Drop-out rate, type of measures of functioning, duration of follow-up, sex, and time period of diagnosis	Good, moderate or poor outcome	21	Poorer outcomes reported for males, for early onset samples (vs. mixed samples), and in samples with high dropout rates. Based on included studies, the outcome was better in early onset patients diagnosed in more recent decades.
Esterberg *et al.* 2010	Relation of family history of psychosis to onset age and symptom presentation in schizophrenia	Family history of psychosis	Onset age, sex differences in onset age, symptoms	35	Positive family history of psychosis predicted earlier onset and more positive symptoms.
Farooq *et al.* 2009	Association between DUP and outcome in psychotic disorders in low- and middle-income countries	DUP	Symptoms, social disability, occupational outcome, mortality	11	Longer DUP associated with poorer response to treatment.
Fett *et al.* 2011	Associations between neuro- and social cognitive functioning and functional outcome in schizophrenia	Various variables of neuro- and social cognition	Community functioning, social behaviour, social problem solving and skills	52	Both neuro- and social cognition correlated positively with outcomes, social cognition more strongly overall.
Green *et al.* 2000	Neurocognition as a predictor of functional outcome in schizophrenia	Various neurocognitive variables	Success in rehabilitation programmes, social problem solving or skills, community outcome and activities of daily living	37	Certain aspects of neurocognition (e.g. verbal memory, vigilance, executive functioning and especially composite measures) are correlated positively with functional outcome.

Author	Primary topic and patient group	Predictors of outcome	Outcomes	Studies included	Main results
Gupta *et al.* 2013	Outcome in schizophrenia in former substance using subjects compared to nonusers	Any former psychoactive substance use (alcohol, cannabis, stimulants and other drugs)	Positive and negative symptoms, ratings of depression and global function	20	No significant differences were found between the groups.
Hegarty *et al.* 1994	Outcome and related factors in schizophrenia	Type of treatment, year of the study, diagnostic system, duration of follow-up	Improved vs. not. Improvement defined as attainment of substantial levels of functioning and freedom from psychotic symptoms	320	40% of patients were improved. Improvement was predicted by neuroleptic treatment and non-Kreapelinian diagnostic criteria, but not by length of follow-up. Since the 1970s the rate of improvement has declined.
Large *et al.* 2014	Effect of current substance abuse on outcome in psychotic disorder	Any current psychoactive substance use (alcohol, cannabis, stimulants and other drugs)	Positive and negative symptoms, depression, social function and three secondary outcomes: violence, self-harm and hospital admissions	22	Current substance users had higher ratings of positive symptoms and were more likely to have a history of violence.
Käkelä *et al.* 2014	Effect of family history of psychosis on outcomes in schizophrenia	Family history of psychosis	Occupational, social and global outcomes	14	A small association detected between family history of psychosis and poor long-term occupational and global outcomes.
Leung & Chue 2000	Sex differences in schizophrenia	Sex	Age at onset, symptoms, premorbid functioning, physical and neurological abnormalities, cognition, brain morphology, treatment response, course of illness, family attitudes	461	Males have earlier onset, more negative symptoms and cognitive deficits. Females display more affective symptoms, auditory hallucinations and persecutory delusions. Females have a more favourable short- and middle-term outcome.

Author	Primary topic and patient group	Predictors of outcome	Outcomes	Studies included	Main results
Lincoln *et al.* 2007	Insight and its impact on symptoms and functioning in schizophrenia	Insight	Treatment adherence, symptomatology, functioning, aggressive behaviour, depression, suicide	88	Insight is associated with better treatment adherence, and with better long-term functioning and depression.
Marshall *et al.* 2005	Associations between DUP and outcomes in FEP	DUP	Symptoms (positive, negative, total), depression/ anxiety, overall and social functioning	26	Longer DUP associated with worse outcome in terms of more positive and total symptoms, worse overall functioning and quality of life, and lack of remission.
Menezes *et al.* 2006	Outcome in FEP	Medication, country of origin, sample representativeness, study design, diagnosis, and duration of follow-up	Outcome (good/ intermediate/ poor), readmission, relapse, employment, functional recovery	37	42% of the studies reported good outcome, 27% poor outcome. Studies with non-representative samples, a developing country of origin or using psychosocial therapy in addition to pharmacotherapy showed better outcomes.
Mintz *et al.* 2003	Relationship between insight and symptomatology in schizophrenia	Insight	Negative, positive, depressive and global symptoms	40	Poor insight was associated with more severe global, positive and negative symptoms and with less severe depressive symptoms.
Mullin *et al.* 2012	Effect of giving up substance use on outcome in psychotic disorder	Use of all substances (alcohol, cannabis and other psychoactive drugs)	Positive and negative symptoms, ratings of depression and global function	23	There was a significant improvement in the ratings of positive symptoms, mood and global function among patients who stopped using substances during the first episode of psychosis but not at later stages.

Author	Primary topic and patient group	Predictors of outcome	Outcomes	Studies included	Main results
Penttilä *et al.* 2014	DUP as a predictor of long-term outcomes in schizophrenia	DUP	General symptomatic outcome, positive and negative symptoms, remission, social functioning, employment, global outcome, QOL and hospital treatment	39	Long DUP associated with poor general symptomatic outcome, more severe positive and negative symptoms and lack of remission, as well as decreased social functioning and global outcome. No association was found between DUP and employment, QOL or hospital treatment.
Perkins *et al.* 2005	Relationship between DUP and outcome in first-episode schizophrenia	DUP	Treatment response, relapse risk, functional outcome, neurocognition, symptomatology, brain morphology	43	Longer DUP associated with lower levels of symptomatic and functional recovery and more negative symptoms.
Potvin *et al.* 2008	Cognitive performance of substance-abusing patients with schizophrenia	Use of various substances (e.g. alcohol, amphetamine, cannabis, cocaine)	Positive and negative symptoms, cognitive functioning	23	Groups did not differ in symptomatology or global cognition. Substance abuse associated with better performance in speed-processing; cannabis with better performance in problem-solving, reasoning and visual memory; alcohol with lower scores on working memory tasks.
Potvin *et al.* 2007	Severity of depressive symptoms in substance-abusing subjects with schizophrenia	Use of various substances (e.g. alcohol, amphetamine, cannabis, cocaine)	Depressive symptoms	20	Modest evidence was found for the more severe depressive symptoms in substance-abusing subjects.

Author	Primary topic and patient group	Predictors of outcome	Outcomes	Studies included	Main results
Potvin *et al.* 2006	Severity of negative symptoms in substance-abusing subjects with schizophrenia	Use of various substances (e.g. alcohol, amphetamine, cannabis, cocaine)	Negative symptoms	11	Substance-abusing subjects experience fewer negative symptoms with no differences in positive/general psychopathology
Roy *et al.* 2001	Association between male gender and deficit schizophrenia	Male gender	Deficit schizophrenia	23	Strong support found for an association between male gender and deficit schizophrenia.
Schmidt *et al.* 2011	Social cognition as a mediator between neurocognition and functional outcome in schizophrenia	Various neuro- and social cognitive measures according to MCCB	Functional outcome: social skills, social problem solving, social behaviour in the milieu, and community functioning	15	All neuro- and social cognitive measures correlated positively with social and/or psychological functioning, but none correlated with vocational functioning. Evidence was found for the mediating role of social cognition.
Tolman & Kurtz 2012	Neurocognitive predictors of objective and subjective QOL in schizophrenia	Many neurocognitive measures and moderators, e.g. treatment setting, age, illness duration, and symptoms	Subjective and objective QOL measures	20	Neurocognitive measures were positively correlated with objective QOL but either unrelated or negatively correlated with subjective QOL.

Author	Primary topic and patient group	Predictors of outcome	Outcomes	Studies included	Main results
Tsang *et al.* 2010	Predictors of vocational outcomes in schizophrenia	Cognitive functioning, demographic characteristics, substance abuse, symptoms, social support and skills, work history, rehabilitation services, hospitalisation history and medical features (e.g. age of onset, medication).	Vocational outcome	62	Better cognitive functioning received support as a significant predictor of better vocational outcome according to the frequency count. According to the meta-analysis factors predicting positive outcome were work history, diagnosis, marital status, and male gender. Factors negatively affecting outcome were negative symptoms, younger age, education, public support, executive functions and general intelligence.
Ventura *et al.* 2009	Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia	Neurocognition, positive and negative symptoms	Functional outcome (community functioning, skills assessment, and functional capacity)	73	Better neurocognition and less negative symptoms are both associated with better functional outcome; however, negative symptoms at least partially mediates the relationship between neurocognition and functional outcome.

FEP = First-episode psychosis, DUP = Duration of untreated illness, MCCB = MATRICS (Measurement and treatment to improve cognition in schizophrenia) Consensus Cognitive Battery (Nuechterlein *et al.* 2004) includes seven domains of cognition: Speed of Processing, Attention and Vigilance, Working Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Social Cognition. QOL = Quality of life.

3.2.3 Brain morphology as a predictor of outcomes

Cross-sectional studies on associations between brain morphology and outcomes

Cross-sectional studies have found evidence for an association between brain structures and outcomes in schizophrenia. First-episode and mixed samples of schizophrenia subjects have shown an association between the lack of remission and a smaller volume of the tail of the left hippocampus (Bodnar *et al.* 2010), and between more severe psychopathology, and 1) decreased grey matter volume in the right anterior cingulate gyrus and the right temporal gyri (Lui *et al.* 2009), 2) grey matter reductions in the left para-hippocampus and right superior temporal gyrus (García-Martí *et al.* 2008), and 3) grey matter reductions in the right cortical surface of the insula (Pressler *et al.* 2005). However, not all studies have found any evidence for relationships between brain structures and outcomes (Ha *et al.* 2004).

Studies examining subjects with medium-term illness duration (mean 8–13 years) have shown patients with more severe illness to have a lower density of the corpus callosum and the right anterior commissure (Hulshoff Pol *et al.* 2004), decreased white matter volumes in cingulate regions bilaterally and in the right internal capsule region (Paillère-Martinot *et al.* 2001), as well as decreased volumes of basal ganglia and grey matter in the occipital regions (Molina *et al.* 2010) and the hippocampus (Brambilla *et al.* 2013). Patients with poor functioning have shown ventricular enlargement (Rossi *et al.* 2000), reduction of grey matter in the left inferior frontal gyrus and in inferior parietal lobule (Wilke *et al.* 2001) and the hippocampus (Brambilla *et al.* 2013).

In studies investigating individuals with a long duration of illness (on average 22 years), those with a poor global outcome showed decreased grey and white matter volumes especially in the temporal, parietal, occipital and frontal lobes (Mitelman *et al.* 2003, Mitelman *et al.* 2007), in dorsal parts of the cingulate gyrus (Mitelman *et al.* 2005), and smaller sizes of the thalamus (Brickman *et al.* 2004) and putamen (Buchsbaum *et al.* 2003).

Longitudinal studies on associations between brain morphology and outcomes

Longitudinal studies have shown that poor outcome patients exhibit a larger cerebral volume decrease (van Haren *et al.* 2008, van Haren *et al.* 2011), cortical thinning (van Haren *et al.* 2011), grey matter density loss in the frontal lobe (van Haren *et al.* 2007), and more extensive ventricular enlargement than good outcome patients (van Haren *et al.* 2008, Mitelman *et al.* 2010, Nesvåg *et al.* 2012).

Progressive brain change including reductions of both grey and especially white matter has been found to correlate with poor cognitive functioning but its association to symptom dimensions or remission status is only modest (Andreasen *et al.* 2011). On the other hand, longer total duration of relapse during the follow-up period has been associated with more extensive brain tissue loss, particularly in structures of the frontal lobes (Andreasen *et al.* 2013).

3.2.4 Neurocognitive functioning as a predictor of outcomes

Cross-sectional studies on associations between neurocognition and outcomes

It is generally accepted that cognitive deficits in schizophrenia are related to functional outcome (Green *et al.* 2004). This has been the result of meta-analyses and reviews of cross-sectional studies (Green 1996, Green *et al.* 2000, Fett *et al.* 2011). Green *et al.* (2000) found that especially verbal memory and executive functioning associate with functional outcome. However, global or composite (rather than domain-specific) measure of cognition explain the largest amount of variance (between 20 and 60 percent) in functional outcome in schizophrenia (Green *et al.* 2000) and it associates also with real-life functioning including work skills, activities and interpersonal functioning (Bowie *et al.* 2010). A meta-analysis found verbal fluency, followed by verbal learning and memory, to be the strongest predictors of community functioning (Fett *et al.* 2011).

The association between the level of neurocognitive performance and clinical outcomes is not equally well documented. Some cross-sectional studies have shown that patients with greater cognitive ability have a higher likelihood of achieving remission (Kopelowicz *et al.* 2005, Helldin *et al.* 2006), while others have found no association between neurocognitive ability and clinical outcome (e.g. Li *et al.* 2010).

Longitudinal studies on associations between neurocognition and outcomes

Neurocognitive functioning has been a relatively consistent predictor of functional outcomes in longitudinal studies, and this association has been established in both long-term and first episode patients (Green *et al.* 2004, Robinson *et al.* 2004, Milev *et al.* 2005, Holthausen *et al.* 2007, Lucas *et al.* 2008, González-Blanch *et al.* 2010, Ventura *et al.* 2011, Hoe *et al.* 2012). However, not all longitudinal studies have found an association between neurocognitive performance and functional outcome (Johnstone *et al.* 1990, Verdoux *et al.* 2002). Allot *et al.* (2011) concluded in a systematic review of early psychosis studies that there were more null than significant findings concerning the predictive value of each separate neurocognitive domain on functional outcomes.

Neurocognition has more often been studied as a predictor of functional outcomes than clinical outcomes. Cognitive impairments have been related to later clinical deterioration (Gråwe & Levander 2001), whereas patients with greater cognitive ability have a higher likelihood of remaining in remission (Holthausen *et al.* 2007). Some studies have not detected any associations between cognition and clinical outcomes (Robinson *et al.* 1999, Buckley *et al.* 2007).

Some studies with recent onset samples have measured neurocognitive functioning at different time points following psychosis onset, and have found that concurrent, but not earlier neurocognitive performance associates with functional (Malla *et al.* 2002, Addington *et al.* 2005) and clinical outcomes (Stirling *et al.* 2003). Hence, neuropsychological measures in the early stages of schizophrenia may not be reliable predictors of later outcome (van Winkel *et al.* 2007, Leeson *et al.* 2009), and this association might be more marked in subjects with long-term psychosis than in first-episode subjects (Verdoux *et al.* 2002, Milev *et al.* 2005).

3.3 Previous studies on outcome in schizophrenia in the NFBC 1966

The prospective study design with a long follow-up has enabled several clinically and epidemiologically important findings. Outcome has been assessed in the NFBC mainly at 34 years and 43 years. At the 34-year follow-up, 56% of the individuals with schizophrenia were on disability pension (Miettunen *et al.* 2007) and 9.9% were considered at least partially recovered (Lauronen *et al.* 2005). A total of 81% of subjects had been re-hospitalised (Miettunen *et al.* 2006). At the age of 43, the figures

were quite similar, showing an unfavourable prognosis for most subjects with narrow schizophrenia, but not for all: 64% of the participants were on disability pension, 22% were married of cohabiting, and only 19% were in remission (Nykänen *et al.* manuscript).

The suicide rate among people with schizophrenia before the age of 39 was 7% with 71% of suicides occurring during the first three years after the onset of illness (Alaräisänen *et al.* 2009). Good school performance at the age of 16 was associated with an increased risk of suicide in schizophrenia and other psychosis but reduced the suicide risk in other members of the cohort (Alaräisänen *et al.* 2006).

Several relevant predictors of outcome have been previously identified in the NFBC 1966. Family history of psychosis (Miettunen *et al.* 2006), father's high social class (Lauronen *et al.* 2007) and earlier age at learning to stand or walk (Jääskeläinen *et al.* 2008) have predicted more hospitalisations. Smoking and using alcohol at the age of 14 (Mäkinen *et al.* 2010), poorer school performance at the age of 16 (Lauronen *et al.* 2007) and the temperament traits lower reward dependence and persistence (Poustka *et al.* 2010) have predicted more severe symptomatology. Longer birth length and higher weight at one year of age have been associated with treatment resistance (Mäkikyrö *et al.* 1998). Lack of friends in childhood, poorer school performance at high school (Lauronen *et al.* 2007), and the temperament traits lower persistence and higher harm avoidance (Poustka *et al.* 2010) predicted poorer social outcome.

3.4 Methodological problems in schizophrenia outcome studies

Studies examining epidemiology and outcome in schizophrenia have suffered from two major difficulties: discrepancy in case definition and the relative rarity of schizophrenia cases in the population. As there are no physiological tests or clear physical manifestations that would confirm a diagnosis of schizophrenia, the diagnosis is based on evaluation of patients' self-reported, subjective experiences or observations made by family members or health care professionals. (Cannon & Jones 1996).

The diagnostic criteria of schizophrenia can vary from country to country, from time to time and from one psychiatrist to another (Warner 2004). Until the late 1960s, the definition of schizophrenia was relatively loose, especially in the United States (Warner 2004, Cannon & Jones 1996), whereas in Scandinavia psychiatrists have traditionally used a much narrower diagnostic concept (Warner 2004). Using a broader definition of schizophrenia usually means that more subjects with a reactive

psychosis and subjects with more affective symptoms are included in to the samples, causing the general outcome to appear more positive (Salokangas 1985). Stricter criteria were beginning to emerge in the 1970s (Hegarty *et al.* 1994), and with the publication of the DSM-III in 1980, American psychiatry switched from one of the world's broadest schizophrenia concepts to one of the narrowest – a diagnostic approach similar to the Scandinavian system (Warner 2004).

There is a relative lack of recent studies investigating long-term outcomes (or natural course) in schizophrenia, as such studies are more labour- and resource-intensive especially in recent times where the flow of people in the community is rather multidirectional and hard to trace (Suzuki *et al.* 2014). Due to the low prevalence of schizophrenia the research relies mainly on case-control study design. Until the mid-1980s the studies examining outcomes in schizophrenia represented predominantly multi-episodic, chronically ill patient cohorts that were mostly recruited from hospital wards, and were then compared with volunteer controls from the community. These patient samples were not well representative and they gave an overly pessimistic picture of the outcome in schizophrenia. The resulting problems of selection bias in the sample and the consequent efforts to control for confounders have often led to unreplicated and contradictory findings. (McGlashan *et al.* 1988, Cannon & Jones 1996, Henry *et al.* 2010). Also, because the same measures may have different predictive values depending on the stage of the illness, including patients with both first-episode schizophrenia as well as patients with chronic schizophrenia in the same sample could cause inconsistencies in the findings (McGlashan 1986, Siegel *et al.* 2006).

In addition to the problems caused by the study sampling there are inconsistencies and inadequacies in the definitions of different outcomes (e.g. "recovered" or "improved"), which make findings of different studies difficult to interpret and preclude comparisons across studies (Salokangas 1985, Harding *et al.* 1987b, McGlashan *et al.* 1988, Liberman *et al.* 2002, Warner 2004).

4 Aims and hypothesis of the study

4.1 Aims of the study

This doctoral thesis comprises four original publications that aim in general to identify relevant predictors of different outcomes in schizophrenia, and more specifically, to study recovery from schizophrenia. In addition to the four publications, some new analyses were carried out for the thesis so as to further clarify the nature of the predictors in a longer follow-up. Publication I is a meta-analysis and publications II-IV are original research reports based on the NFBC 1966. The aims of the original publications were:

I (a) To identify by means of a meta-analysis the proportion of individuals with schizophrenia who meet the recovery criteria, (b) to examine whether the recovery rate is associated with factors such as gender, economic index of sites, and selected design features of the study, and (c) to examine whether the recovery rate has changed over time.

II To examine whether certain, clinically relevant and easily assessable variables could be used to predict the clinical outcome (utilisation of care and symptoms) of schizophrenia, and whether the early course of the illness would predict the long-term outcome.

III To investigate whether the volumes of total grey and white matter, CSF and density of regional grey matter in the brain are associated with outcomes in schizophrenia around the age of 34 years.

IV To study (a) whether neurocognitive performance at age 34 predicts outcome at follow-up 9 years later, and (b) whether neurocognitive performance at follow-up at age 43 is associated with outcomes.

The aims of the additional analyses were to study whether variables studied in original publication II would predict outcomes after an additional 9-year follow-up (i.e. at age 43), and whether remission and neurocognitive functioning at 34 years would predict remission and neurocognitive functioning at 43 years.

4.2 Hypotheses of study

The hypotheses of the original publications were:

I A greater proportion of recovery is reached by women, in countries with poorer economic indices, and in studies including first-episode subjects, a non-Kreapelinian diagnostic system, a low quality score and a long follow-up.

II Sociodemographic and illness-related variables such as gender, age of onset, the mode of illness onset and the early course of illness are good predictors of later clinical outcome.

III Poor outcome associates with lower density of grey matter especially in the frontal and temporal lobes, and the subcortical nuclei in the brain, and also with an increased CSF volume.

IV Impairments in neurocognitive functions particularly in the domains of verbal memory and executive functions associate with poor occupational and global outcomes.

The hypotheses of the additional analysis for this thesis were that the same variables predicting outcome at 34 years would be predictive of outcomes at 43, and that remission and neurocognitive functioning at 34 would predict remission and neurocognitive functioning at 43 years.

5 Materials and methods

5.1 Meta-analysis (I)

5.1.1 Data-Collection

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses (Moher *et al.* 2009) were applied to this meta-analysis. Several searches were conducted using the following six electronic databases: PsycINFO (year 1840 onwards), Pubmed (year 1950 onwards), the ISI Web of Science (year 1900 onwards), Elsevier Science Direct (year 1823 onwards), EBSCOhostÅLs Academic Search Premier (year 1975 onwards), and CINAHL (year 1981 onwards). No language, publication date, or publication status restrictions were imposed. As a title search, the following search strategy was used: "schizo* or psychotic or psychos*s" and "recovery or remission or outcome* or course or prognosis or longitudinal or follow-up." The second search in abstracts included the keywords "schizophrenia" and "recovery or remission." The last searches were conducted in October 2011. Articles were also searched manually and, if required and when feasible, authors were contacted directly for unpublished data and additional information.

5.1.2 Criteria for recovery

The recovery criteria required that an individual should show both clinical and social recovery. Thus, the outcomes included measures for both clinical (e.g. symptom rating scales and use of hospital treatment) and social/functional dimensions (e.g. occupational capacity, scales measuring the level of functioning). Additionally, the improvements in at least one of the clinical or social outcomes should have persisted for at least two years, and there should currently be at most mild symptoms.

5.1.3 Study selection

Studies included into the analyses were required to meet the following pre-defined inclusion criteria: an observational (naturalistic) design based on a sample with a minimum of 15 subjects that were over 16 years of age, mostly (at least 80%) diagnosed with schizophrenia (broadly defined), and who were not selected a priori

for good or poor outcome. In addition, the included studies had to report sufficient information on both clinical and social outcome in order to determine recovery proportions. Where multiple papers were available on the same or overlapping cohorts, one representative paper with the largest sample size was selected.

5.1.4 Statistical analysis

Recovery estimates were summarised with mean, standard deviations (SD), median, and interquartile (25%–75%) range (IQR). The estimates of the recovery proportions were expected to vary substantially (Menezes *et al.* 2006). Thus, in order to pool overall estimates of proportions, random effects models were used, in which each study was weighted by the inverse of its variance and by the between studies variance (Borenstein *et al.* 2009). In order to describe recovery in studies with different durations of follow-up, the annual recovery rate was derived by dividing the proportion of those who met the recovery criteria by the number of years of follow-up (Saha *et al.* 2008).

Concerning the impact of gender on recovery, the pooled proportions for male-only vs. female-only estimates were first compared. In addition, for studies that presented male and female estimates separately, odds ratios were calculated from the recovery proportions. Standard meta-regression techniques (Sterne 2009) were used so as to explore the influence of the following variables on recovery estimates: 1) the change in recovery rate over time using the same year categories as Warner (2004), 2) the effect of the economic index of the study site based on per capita income statistics of World Bank for year 1988 (data.worldbank.org) as done by Cohen *et al.* (2008), 3) first-episode vs. not first-episode sample status, 4) length of follow-up, 5) diagnostic criteria (Kraepelinian vs. non-Kraepelinian), 6) WHO-study vs. non-WHO-study, and 7) quality score of the study, which was based on our own ad hoc quality score ratings (I).

By way of post-hoc analyses, the influence of the origin of the sample (discharge cohorts, admission cohorts, general population, or cohorts including both outpatients and inpatients) was examined. The heterogeneity of the studies was explored with the I^2 statistic (with 95% CI). The analyses were carried out with STATA 9 (Stata Corporation 2005).

5.2 The NFBC Studies 1966 (II, III, IV)

The NFBC 1966 cohort study was originally founded to study risk factors for perinatal deaths and low birth weight (Rantakallio 1969). It is an unselected, general population-based birth cohort collected from mid-pregnancy and based on 12,068 pregnant women who were living in the provinces of Lapland and Oulu with an expected delivery date during 1966. 12,058 children were born alive, representing 96.3% of all live births in the catchment area. Altogether 11,017 of these subjects were alive and living in Finland at the age of 16, and 83 of these subjects have forbidden the use of their data and have been excluded. Thus, the total population from which subjects with schizophrenic psychosis were drawn amounted to 10,934 individuals. Data on biological, socioeconomic and health conditions, living habits and family characteristics of the cohort members have been collected at several study points.

5.2.1 Ascertainment and sampling of individuals with psychosis (II, III, IV)

Data concerning psychiatric hospitalisations were collected from the nationwide Care Register for Health Care (continuation of the Finnish Hospital Discharge Register), a register maintained by the National Institute for Health and Welfare (THL), covering all mental and general hospitals and in-patient wards at local health centres and private hospitals. Until recent years, the vast majority of patients who experienced an episode of schizophrenic psychosis have been hospitalised in Finland (Perälä *et al.* 2008). All cohort members over 16 years of age appearing in the Care Register for Health Care up to the end of year 1997 for any mental disorder were identified, and all case records were scrutinized and diagnoses assessed using the DSM-III-R criteria, after which the diagnoses were re-checked by a professional panel. The validity of the diagnoses deriving from the Care Register for Health Care has been shown to be acceptable for studies in psychoses and schizophrenia. (Isohanni *et al.* 1997, Moilanen *et al.* 2003). The reliability of the schizophrenia diagnoses was good (kappa = 0.85). By the end of year 1997 there were 160 subjects with a known psychotic episode in their life.

5.2.2 Baseline and follow-up studies of the NFBC 1966

Baseline study in 1999-2001 (II, III)

A baseline field study was carried out in years 1999–2001 at the University Hospital of Oulu when the subjects were 34 years old (mean 33.7, SD 0.6, range 32.6–35.4 years). Of the 160 cohort members (95 men, 59%) with a history of at least one psychotic episode 14 (9%) had died and one subject was found to be ineligible because of a metal implant in the head, leaving 145 potential participants in the baseline study. A postal address was denied or missing for three subjects, thus 142 subjects could be invited to participate in the study. If necessary, the subjects were invited by a maximum of three letters and a maximum of three telephone calls. Of the 142 invited cohort members 91 participated, 30 declined to participate, 3 did not arrive at the appointment and 18 did not respond. Those on disability pension due to a psychosis and with more positive symptoms and more psychiatric hospitalisations were more likely to be non-participants. Age at onset of illness did not differ between non- participants and participants. (Haapea *et al.* 2007). Also, 187 controls were randomly selected from the NFBC 1966 members living in the Oulu area with no history of psychotic disorder, and 104 (56%) of them participated in the study.

In the baseline examination, information on brain MRI, diagnostic interviews, neurocognitive tests and questionnaires from the subjects of the NFBC 1966 were collected. Structured Clinical Interview for DSM-III-R Axis I disorders (SCID-I, Spitzer *et al.* 1989) was used for diagnostic assessment, together with other available information on illness history. The interviews and neuropsychological testing were done to all participants by three experienced psychiatrists who received training for the diagnostic interviews. Inter-rater reliability was not assessed. Altogether 61 individuals were diagnosed with schizophrenia and 12 with some other schizophrenic psychosis: seven with schizoaffective disorder, three with schizophreniform disorder, and two with delusional disorder. In addition to the interview data, nationwide health and social registers were used. These registers have been found to be reliable and suitable for scientific research (Miettunen *et al.* 2011).

Follow-up study in 2008–2010 (IV, additional analysis)

Follow-up examinations were conducted in 2008–2010 when the cohort members were 43 years old (mean 43.1, SD = 0.8, range 41.8–44.6). Brain MRI, diagnostic interviews and neurocognitive tests were performed and questionnaires collected

again. All those who had participated in the baseline study were invited for reassessment. Altogether 45 people with a schizophrenic psychosis (62%) and 77 (74%) controls participated again at this stage. Interviews were conducted mostly by experienced psychistric nurses and medical doctors who had undergone training by one of the three psychiatrists collecting the baseline data. The interviewers always had the opportunity to consult a psychiatrist or a group of psychiatrists about a difficult rating. Neurocognitive testing was carried out by psychologists and medical students trained by an experienced neuropsychologist. The tests were administered in a fixed order and repeated investigator meetings were held during the study in order to ensure uniform ratings and execution of the tests. Inter-raiter reliability for SCID interview or neurocognitive testing was not assessed.

5.2.3 Study populations

Original publications II–IV are all based on the NFBC 1966. Sample sizes vary as different longitudinal trajectories were studied and all predictor variables, such as neurocognitive ability and brain morphology could not be measured from all participants (Figure 1). Original publications II and IV include subjects with a diagnosis of schizophrenic psychosis (DSM-III-R diagnoses for schizophrenia: disorganised 295.1, catatonic 295.2, paranoid 295.3, undifferentiated 295.9; and other schizophrenic psychosis: schizophreniform disorder 295.4 and schizoaffective disorder 295.7), and publication III only individuals with a diagnosis of schizophrenia (DSM-III-R criteria 295.1–3, 295.9).

Original publication II

In order to be able to assess the long-term outcome, a minimum follow-up of 10 years after the onset of psychosis was required. The end of the follow-up was the end of year 2005 or time of death. Ten individuals with delusional disorder were excluded because of the more positive outlook in outcome of this disorder. A hundred and eighteen subjects were given the diagnosis of schizophrenic psychosis in the validation process in 1997 and 15 of them were excluded due to insufficient follow-up time. The final sample thus included 103 subjects: 84 with schizophrenia, 15 with schizophreniform disorder and 4 with schizoaffective disorder. Information on symptoms during the first hospitalisation was available only for 43 of the 103 subjects, and information from the PANSS from only one time point for 56 subjects.

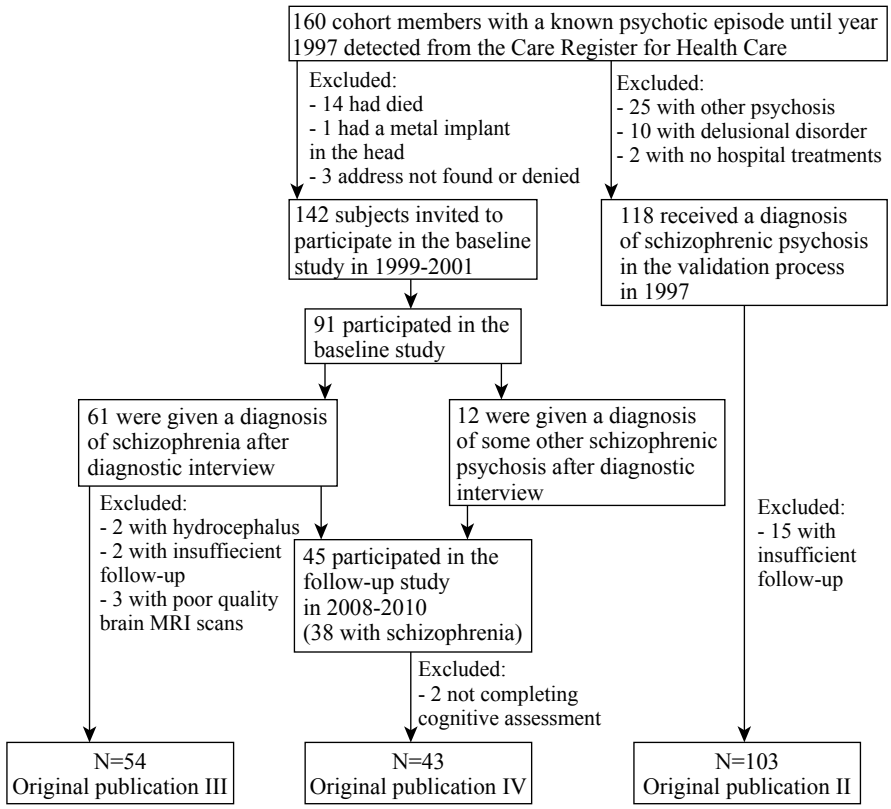

Fig. 1. Sample sizes of the original publications II-IV.

Original publication III

Of the 61 individuals diagnosed with schizophrenia after diagnostic interviews, two subjects were excluded because their illness had emerged less than two years prior to the baseline study, and they did not have adequate length of follow-up regarding outcomes (Lauronen *et al.* 2007). Three cases were excluded later due to poor quality brain MRI scans caused by motion artefacts, and two subjects because of gross structural lesions (hydrocephalus) in their scans. Thus, the final sample comprised 54 (61% male) subjects with schizophrenia.

Original publication IV

Forty-five individuals with schizophrenic psychosis and 77 controls who had participated in the baseline study participated again in the follow-up. Two cases and four controls did not complete any of the neurocognitive tests and were excluded. The study sample thus comprises 43 subjects with schizophrenic psychosis and 73 controls. The number of individuals in each neuropsychological test varies somewhat, as a few participants did not take part in all three tests. Subjects participating at both baseline and follow-up can be considered to be representative of all cohort members with schizophrenia and they did not differ statistically significantly from subjects participating only at baseline and not returning for follow-up investigations (Table 4).

Table 4. Attrition analysis of cohort members with schizophrenia spectrum psychosis who participated in the baseline[1] but not in the follow-up study.

Variables studied	Participants[2] (n=43)	Non-participants[3] (n=26)	Sig
Gender (male) n (%)	23 (53)	14 (54)	0.99
Age of onset mean (SD)	23.6 (4.4)	23.9 (3.8)	0.74
Variables assessed at 34 years			
Education secondary level[4] n (%)	12 (28)	6 (23)	0.78
On disability pension n (%)	21 (49)	12 (46)	0.99
Hospital care[5] mean (SD)	10.7 (8.7)	9.9 (8.9)	0.66
PANSS mean (SD)	53.0 (19.2)	53.2 (23.3)	0.97
CGI mean (SD)	4.7 (1.5)	4.6 (1.5)	0.87
SOFAS mean(SD)	50.7 (16.2)	47.8 (16.6)	0.48
CVLT (trials 1-5) mean (SD)	48.0 (13.6)	45.5 (14.7)	0.49
CVLT long delay mean (SD)	11.2 (3.6)	9.5 (4.3)	0.09
AIM (A+M) mean (SD)	20.8 (3.2)	22.0 (2.6)	0.14
AIM (A) mean (SD)	22.8 (3.1)	24.2 (1.9)	0.08
VOLT mean (SD)	59.3 (8.0)	61.7 (6.7)	0.25

[1] Altogether 73 subjects participated in the baseline study, and of them three had died and one denied the use of information before the follow-up study. [2] Participants = subjects who participated at both baseline and follow-up, [3] Non-participants = individuals who participated in the baseline but not in the follow-up study, [4] basic level of education (9 years), secondary education (9–12 years) and tertiary education (> 12 years), [5] Psychiatric hospital treatment times until 31.12.2010. PANSS = Positive and Negative Syndrome Scale, CGI = Global Clinical Impression, SOFAS = Social and Occupational Functioning Assessment Scale.

Additional analysis for the thesis

Additional analyses were completed so as to evaluate the predictive power of selected sociodemographic and illness-related factors on outcomes at 43 years. The variables used to predict outcome at 34 years in original publication II were now rerun with an additional 9 year follow-up. The sample consisted of all subjects included in original publication II who had participated in the follow-up examination in 2008–2010 (n=41). In addition, two subjects who were not part of the original publication II study sample participated in the follow-up examinations, had a diagnosis of schizophrenic psychosis and sufficient follow-up and were thus added to these additional analyses. The sample comprises 43 individuals with a schizophrenic psychosis.

5.3 Predictors of outcome

Predictor data were collected from hospital records, questionnaires, and interviews held during the baseline study. Also, brain MRI scans and neurocognitive tests were used to predict outcomes. Information on hospitalisations was derived from the Care Register for Health Care. The used variables are described in more detail in original publications II–IV. Data collection is presented in Figure 2.

5.3.1 Original publication II

Information on premorbid and illness-related factors was collected retrospectively from the medical records referring to the first hospitalisation after the onset of psychosis, using the Operational Criteria Checklist for Psychotic Illness (OPCRIT), version 3.3 (McGuffin *et al.* 1991). Predictors are described in Table 5.

Age of onset was dichotomised based on the observation by Panariello *et al.* (2010) of the existence of two homogeneous subgroups of schizophrenia patients, with the cut-off point at onset age of 22 years. In addition, measures of the short-term outcome, presence of suicidal ideation and symptoms during the first episode were used to predict the long-term outcome. Symptoms of the first episode were categorised with the five-factor symptom model by Matsuura *et al.* (2004) including manic, negative, depressive, vegetative, and positive symptoms. In this sample, no vegetative symptoms were reported.

Table 5. Predictor variables in original publication II and their definitions.

Predictor variable	Definition
Gender	Male vs. female
Age of onset	Age when first positive symptoms occurred; ≤ 22 years vs. > 22 years
Family history of psychosis	First-degree relative having a psychosis recorded in the cohort members medical records, reported in the follow-up interview, or a hospitalisation of the mother or father due to psychosis (Care Register for Health Care) between years 1972 and 2005.
Mode of onset	Acute/gradual (≤ 6 months) vs. insidious (> 6 months)
Marital status	Married/cohabiting vs. single
Premorbid personality disorder	Evidence of personality disorder present since adolescence and prior to the onset of psychosis
Alcohol abuse	Rated when the quantity of alcohol use was excessive (rater judgement) with alcohol related complications during the year prior to first psychiatric contact. None of the cohort members had cannabis use disorder.
Definite psychosocial stressor	Rated when a severely threatening event that was unlikely to have resulted from the subject's own behaviour had occurred prior to the onset of the disorder
Poor premorbid work adjustment	Scored 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 educational level or training. Also scored positively for a persistently very poor standard of housework (housewives) and badly failing to keep up with studies (students).
Poor premorbid social adjustment	Patient found difficulty entering or maintaining normal social relationships, showed persistent social isolation, withdrawal or maintained solitary interests

The variable information is mostly collected from the medical records using the Operational Criteria Checklist for Psychotic Illness (OPCRIT).

5.3.2 Original publication III – brain morphology

Structural MRI data were acquired from all participants in the 34 year follow-up at Oulu University Hospital using a GE Signa system (General Electric, Milwaukee, WI) operating at 1.5 T (III).

The MRI data were segmented and probabilistic maps of grey matter, white matter, and CSF were created for each subject using the BAMM (Brain Activation and Morphological Mapping) software (Brammer *et al.* 1997, Suckling *et al.* 1999a, Suckling *et al.* 1999b). Total grey matter, total white matter and intracranial volume (ICV) measures were calculated in native space. For each subject, the AAL (Automated Anatomical Labelling) regionally parcellated template image (Schmahmann *et al.* 1999, Tzourio-Mazoyer *et al.* 2002) was used to estimate regional mean grey matter densities in 116 cortical and subcortical structures. These structures were then combined into 17 larger regions so as to avoid problems posed by multiple testing. The regions were formed by dividing the cerebral grey matter in both hemispheres into eight regions: central, frontal, temporal, parietal, occipital, limbic, insular and subcortical grey matter regions (Tzourio-Mazoyer *et al.* 2002). Cerebellar grey matter formed a separate region analysed (Schmahmann *et al.* 1999). The method employed in this study in order to produce segmented brain tissue maps does not conserve the volume of the voxel occupied by a specific tissue. Therefore the voxel intensities represent grey matter density or concentration.

5.3.3 Original publication IV – neurocognitive assessment

Three identical neurocognitive tests were performed in both baseline and follow-up studies.

Verbal learning and memory

The California Verbal Learning Test (CVLT) is one of the most commonly used cognitive tests in schizophrenia research. It is an auditory verbal memory test using a 16-item shopping list from four semantic categories (the learning set) that is read to the subject five times (Delis *et al.* 1983). After each trial, subjects must repeat back as many items as they can remember. The two dependent variables used in this study are: 1) CVLT Trials 1–5 (summary score, reflects immediate verbal memory and learning) and 2) CVLT long delay (free recall, items remembered approximately 20 minutes later, reflects long-term memory).

Visual learning and memory

The Visual Object Learning Test (VOLT) is a computerised test of visual object learning and memory (Glahn *et al.* 1997). The VOLT is designed as a spatial analogue of California Verbal Learning Test (CVLT; Delis *et al.* 1983), and stimuli are complex and unfamiliar three-dimensional geometric designs that are unpronounceable. Participants are shown a learning set of 10 shapes as learning stimuli. In a forced choice paradigm, they are then required to recognize those stimuli within a group of 20 objects, of which 10 are distractors. There are 4 trials, each with novel distractors, and after each trial participants are shown the learning set again. The dependent variable is the total number of correct responses in the four trials. We excluded participants who performed below chance – i.e. who had less than 50% of correct answers – assuming that they had not understood the test assignment.

Subjects with schizophrenia have been shown to performe worse than healthy controls in VOLT. This test has not been frequently used in schizophrenia research but it has been shown to correlate with meaures from other visual memory tests (Glahn *et al.* 1997).

Executive functions

The Abstraction and Working Memory task (AIM) is a computerised rule-abstraction/category-learning task that requires subjects to use information on group stimuli in a meaningful way (Glahn *et al.* 2000). It was designed to allow abstraction and working memory to be analysed independently. Participants are shown five objects on the screen; two in the upper left corner and two in the upper right corner, with a fifth object, the target object, appearing in the centre of the screen below the other stimuli. Participants are required to group the target object with the left- or right-hand pair. In half the trials, there is an additional requirement for working memory maintenance (abstraction + memory) as a delay of 2.5 seconds is added between the presentation of the target and other objects. Stimuli vary in colour, being red, yellow or blue, and in shape, being modified circles, squares or triangles. The correct response for each trial is grouping on the most obvious, least complex set. Participants are given feedback from each trial. The dependent variable is the total number of correct answers. Participants performing below chance were excluded.

Subjects with schizophrenia have been shown to performe worse than healthy participants on the AIM tasks, especially in the abstraction plus memory subtest. This test has not been widely used in schizophrenia research but it has been shown to

correlate with other more commonly used test of executive functions, e.g. Wisconsin Card Sorting Test (Glahn *et al.* 2000).

Composite score of neurocognitive tests

The z-scores using means and standard deviations of the control group for neurocognitive test measures were averaged, unweighted, into a single composite score, as reported in earlier studies (Buckley *et al.* 2007, Emsley *et al.* 2007, Siegel *et al.* 2006). This measure provides an estimate of the total amount of variance in outcome that can be explained by the three neurocognitive test used in this study.

Cognitively impaired vs. cognitively normal

In order to assess whether having overall neurocognitive impairment would influence outcome, the differences in outcomes between cognitively normal and cognitively impaired individuals were analysed. A participant was considered to be cognitively impaired if he/she had a test score of 2 or more SDs below the control average in at least one of the tests. This criterion was chosen because it is used in clinical practice and has been used in previous studies of neurocognition in schizophrenia (Holthausen *et al.* 2007). It should be noted, however, that the impairment of 2 SD is severe and means performing worse that over 95% of the control subjects. On the other hand, a participant scoring e.g. 1.5 SD below the average still has severe cognitive deficits even though according to the categorisation used in this study he/she is considered cognitively normal for comparison purposes.

5.3.4 Additional analysis for the thesis

The predictors of outcome analysed in original publication II were re-analysed with a 9-years longer follow-up extending to age 43 years. It was also studied whether neurocognitive functioning at 34 years of age would predict neurocognitive functioning at 43 years, and whether symptoms and remission status at 34 years would predict clinical and functional outcomes at 43 years. To assess symptoms, the five-factor model by van der Gaag *et al.* (2006b) was employed. It covers all thirty items of the PANSS, subdivided into five factors: positive symptoms, negative symptoms, disorganisation, excitement, and emotional distress. A higher PANSS score indicates more severe symptoms.

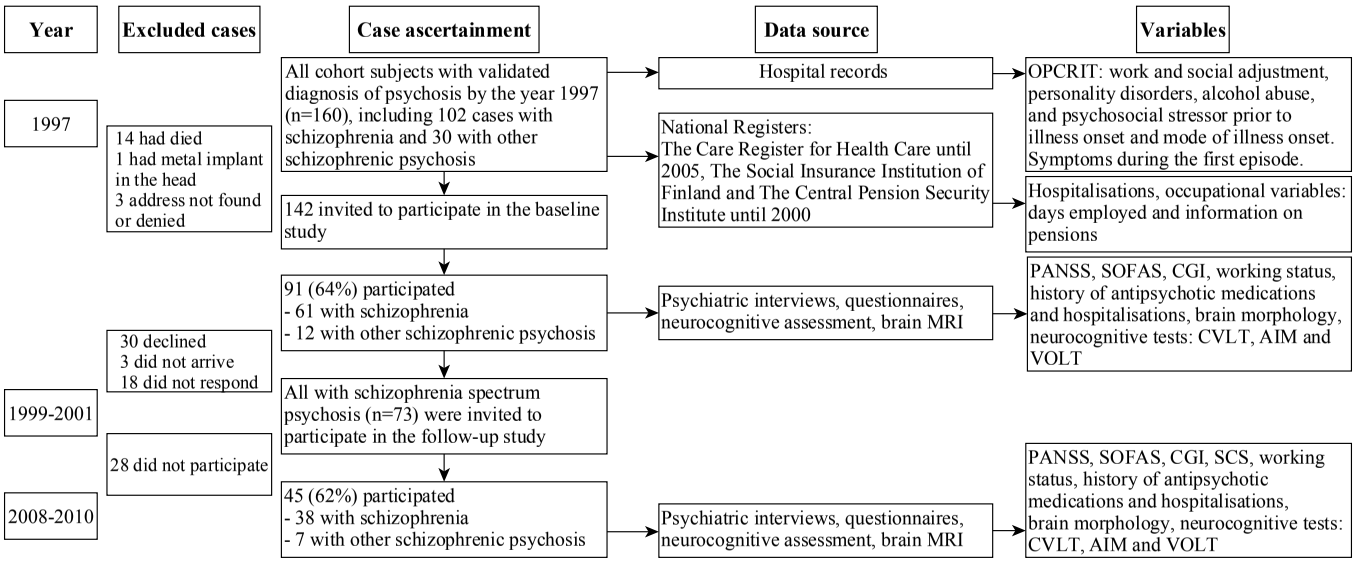

Fig. 2. Data collection in the NFBC 1966.

5.4 Measures of outcome

Data on outcome measures were derived from information gathered at baseline and follow-up studies (interviews, questionnaires) and from national registers. Information on hospitalisations was collected from the Care Register for Health Care. All original publications employ the remission criteria proposed by Andreasen *et al.* (2005), with the exception of the duration criterion, which could not be used as PANSS ratings were done only at one time point at both baseline and follow-up examinations (I, III, IV). Data collection is presented in Figure 2.

5.4.1 Original publication II

Measures of the short-term clinical outcome

The short-term clinical outcome was defined as the outcome up to two years after the discharge from the first hospitalisation due to psychosis. Outcome was assessed with two measures: 1) rehospitalisation due to psychosis during the two years after the discharge from the first hospitalisation (yes/no), and 2) cumulative number of treatment days due to psychosis during the same time period.

Measures of long-term clinical outcome

The minimum follow-up time for the long-term outcome was set at 10 years from the onset of the illness. Three measures were used to assess long-term clinical outcome: 1) the severity of symptoms at follow-up, 2) remission status, and 3) psychiatric hospitalisation (yes/no) during the last two years of follow-up. To assess the severity of symptoms, the five-factor model by van der Gaag *et al.* (2006b) was used.

5.4.2 Original publication III

The study focus was on both measures of clinical and functional outcomes and both cross-sectional and longitudinal course of illness.

Clinical outcomes

Clinical outcome was assessed with three measures: 1) remission status, 2) cumulative number of hospitalisations, and 2) cumulative number of days spent in hospital due to psychosis. Hospitalisations were assessed until the baseline study in 1999–2001.

Functional outcomes

Occupational status was assessed with two measures: disability pension status in year 2000, and 2) working at least 50% of the time during year 2000 vs. working less. The data was derived from the pension register of the Social Insurance Institution of Finland. In addition to this, information on all work periods contributing to pension was collected from the Central Pension Security Institute. In addition, the Social and Occupational Functioning Assessment Scale (SOFAS, Spitzer *et al.* 2000) was used to assess social activity and ability to work. The scores of SOFAS range from 0 to 100 points, higher points indicating better functioning.

5.4.3 Original publication IV and additional analysis for the thesis

Three outcome measures for the long-term outcome were used: 1) remission status, 2) global outcome, and 3) vocational outcome. Global outcome was measured with the Strauss-Carpenter Outcome Scale (SCS), which evaluates the following four items: need for hospitalisation, frequency of social contacts and useful employment during the past year, and symptom load during the past month (Strauss & Carpenter 1972). Each item is scored on a 5-point scale from 0 (very poor) to 4 (very good). The employment item from the SCS was analysed separately for its humane and economic importance. It was analysed as a dichotomised variable: no useful employment vs. employed at least 25% of the time during the past year. Being a housewife or student, or receiving supported employment were regarded as useful employment.

5.5 Adjustments of potential confounding variables

5.5.1 Original publication II

Gender was used as a confounder for all the predictors, and age at onset as a confounder in the prediction of the short-term outcome. Adjusting for onset age also largely implies an adjustment for the effect of changes in treatment policies during the period covered by the present data, including the notable decrease in the availability of hospital beds in Finland (Salokangas *et al.* 2000, Miettunen *et al.* 2006). Onset age was considered a potential confounder when predicting the short-term outcome, because – deriving from a birth cohort – the subjects had their illness onset at different times between the years 1980 and 1995. In this time period Finland experienced one of the world´s most rapid psychiatric deinstitutionalisation processes. No corresponding adjustment was necessary when predicting the long-term outcome, because the assessments were made at the same time point for all the subjects. Age at onset was used as a confounder when predicting the effect of marital status on the outcome, because the subjects who had fallen ill earlier were more likely to be single at the time of illness onset than older cohort members. Predictors, outcome variables and confounders of original publications II–IV have been summarised in Table 6.

5.5.2 Original publication III

Gender, duration of illness, ICV, and the use of antipsychotic medication were used as covariates in all analyses. ICV includes volumes of total grey and white matter and CSF, and is used to adjust for differences in the brain volumes of subjects of different heights. Duration of illness – defined as the period between the onset of first psychotic symptoms and the time of the MRI scan at age 34 years – also adjusts for the age of illness onset in a birth cohort setting. The use of antipsychotic medication was used as a covariate in order to exclude the possible protective or damaging effect of medication on the brain structures (Navari & Dazzan 2009, Ho *et al.* 2011). In the baseline study at 34 years, the subjects were asked about their current and lifetime use of antipsychotic medication. This information was divided into three subgroups: no long-term (over 1 year) use of antipsychotics; previous long-term use with a current low-dose, i.e. 300 mg or less in chlorpromazine equivalents daily, or no current use; long-term use with a current relatively high dose, i.e. more than 300 mg in chlorpromazine equivalents daily. Many sources of information were used to calculate the chlorpromazine equivalent doses, as altogether 27 different antipsychotic drugs

were used among the cohort members. Most drugs were computed into chlorpromazine equivalent as done in the paper by Kroken *et al.* (2009). For more information on the antipsychotic medication used in the NFBC 1966, see Husa *et al.* (2014).

5.5.3 Original publication IV

All results were adjusted for age of psychosis onset, which simultaneously adjusts for the duration of illness. Whenever statistical significance with any of neurocognitive performance test remained, other covariates were used, including gender, current antipsychotic medication, level of education, and symptoms and functioning at baseline. Baseline level of functioning variables were chosen as to best control for the baseline circumstances of each outcome investigated, i.e. baseline PANSS was used to control for remission status, prior occupational status to control for later occupational outcome and baseline CGI to control for later global outcome.

5.5.4 Additional analyses for the thesis

The only adjustment considered necessary was controlling for the age of onset when using marital status as a predictor of outcome.

5.6 Statistical analyses of the NFBC studies (II-IV)

Original publication II

Differences between the outcome groups were analysed using cross-tabulations with the chi-square test (or with the Fisher's exact test, as appropriate) and odds ratios (dichotomized variables), or with the Mann-Whitney U-test (continuous variables). Logistic regression analysis and analysis of covariance were used to adjust for confounders and to search for the model and variables that best predicted the individual outcome measures. Gender and all the predictors with $p < 0.1$ in the univariate analyses were used as covariates in the multivariate analyses. In addition, age at onset was used as a confounder when predicting the short-term outcome and in analyses where marital status was used as a predictor. Nagelkerke R^2 statistics were used to estimate the proportion of variability in a data set that is accounted for by the statistical model in logistic regression analyses. The limit for statistical significance

Table 6. Predictor and outcome variables and confounding variables used in original publications II–IV, and in the additional analyses.

Variables	Original publication II	Original publication III	Original publicationIV	Additional analyses
Age at outcome assessment	Outcome at 34 years	Outcome at 34 years	Outcome at 43 years	Outcome at 43 years
Predictor variables	Gender, age of onset, family history of psychosis, mode of onset, marital status, personality disorder, alcohol abuse, psychosocial stressor and premorbid work and social adjustment. In addition, symptoms of the first episode were used to predict the long-term outcome.	Total grey and white matter and intracranial volume (ICV). Cerebral grey matter density in 17 regions: central, frontal, temporal, parietal, occipital, limbic, insular and subcortical regions in both hemispheres, and cerebellar grey matter.	Neurocognitive tests: CVLT, AIM, VOLT, composite score and general neurocognitive impairment (yes/no).	All variables from original publication II, and neurocognition, symptoms and remissions status at 34 years.
Outcome variables	Short-term outcome: rehospitalisation due to psychosis (yes/no) and cumulative number of treatment days for psychosis. Long-term outcome: symptoms, remission and psychiatric hospitalisations in the last two years of follow-up (yes/no).	Clinical outcomes: number of hospitalisations and days in psychiatric hospitalisation, and remission. Functional outcomes: occupational status, SOFAS.	Remission, occupational outcome (unemployed vs. working at least 25% of the time), and global outcome measured with the Strauss-Carpenter Outcome Scale.	Same outcome variables as in original publication IV
Confounding variables	Gender, age of onset	Gender, duration of illness, ICV, antipsychotic medication, and remission status.	Age at onset, and additionally sex, antipsychotic medication, education, and baseline symptoms and functioning.	Age at onset when using marital status as predictor

was set at $p < 0.05$ in all the analyses. Spearman´s rho correlation coefficients were used to study correlations between the outcome measures. The statistical analyses were performed with PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.

Original publication III

The associations between brain density and continuous outcome variables (logarithmic transformations) were analysed with linear regression. The differences in brain density in categorical outcome variables were analysed with logistic regression. The results are presented as standardized beta- and p-values, and odds ratios (OR) with their 95% confidence intervals (CI). The p-values under 0.05 were considered statistically significant. The statistical analyses were performed with PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.

Original publication IV

Welch's t-test was used to compare neurocognitive test performance between subjects with schizophrenic psychoses and controls. Logistic regression was used for analysing the associations between neurocognitive tests and remission or vocational outcome, except for the unadjusted difference between cognitive impairment groups, where chi-square test was used. For analysing the associations between Strauss-Carpenter global outcome and the neurocognitive tests, linear regression was employed, except for the unadjusted differences between cognitive impairment groups where Student's t-test was used. A p-value under 0.05 was considered to be statistically significant. In addition, standardised odds ratios were calculated for the different neurocognitive tests so as to enable direct between-test comparisons. A similar method has been used previously with logistic regression (Nieminen *et al.* 2013). Data were analysed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Additional analysis for the thesis

Differences between the outcome groups were analysed using cross-tabulations with the chi-square test (or with the Fisher's exact test, as appropriate) and odds ratios. Marital status at illness onset was corrected for the age at illness onset using logistic regression. Spearman's rank correlation coefficients were used to test the statistical

dependence between the neurocognitive tests at two time points. Data were analysed using IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

6 Ethical considerations and personal involvement

6.1 Ethical considerations

Permission for gathering data for the entire NFBC 1966 was obtained from the Ministry of Social Welfare and Health Affairs in 1993. The Ethical Committee of the Northern Ostrobothnia Hospital District has approved the study and keeps the study design of the NFBC 1966 under review. The research plans for the 34-year follow-up of the NFBC 1966 study were accepted by the Ethical Committee of Oulu University, Faculty of Medicine, on March 30th 1998; and for the 43-year follow-up by the ethical committee of the Northern Ostrobothnia Hospital District on February 18th 2008. Data protection has been scrutinized by the Privacy Protection Agency, as well as by principles from the Ministry of Health and Social Affairs. Informed consent to the use of data has been obtained from all cohort members, and during baseline and follow-up field studies written informed consents were requested from all participants. Study participants have been assigned an ID-number and their identities will not be revealed. All cohort members have the right to decline the use of information concerning themselves at any time.

6.2 Personal involvement

I have planned my doctoral thesis in collaboration with my supervisors Adjunct Professor Erika Jääskeläinen and Professor Jouko Miettunen. I have been part of the NFBC 1966 research group since the spring of 2008, and have participated in collecting neurocognitive data in the follow-up study 2008–2011.

I planned original publication II, did all the literature searches, carried out all the statistical analyses, interpreted the results and wrote the first and final drafts of the manuscript. The same applies to original publication IV, except for the execution of statistical analyses, which were partly done by statistics student Henri Salo under my supervision. I personally planned and executed the additional analysis for the thesis. The work for original publication I was carried out in close collaboration between my supervisors and myself, as the study in question is a meta-analysis and its methodology requires the involvement of several researchers. I was in charge of verifying whether or not potential studies satisfied the inclusion criteria, which was a labour-intensive task as these studies included many articles and books in languages

other than English. Subsequently, I personally extracted salient data from the included studies. I also participated in assessing the methodological quality of the selected studies and strictness of the recovery criteria employed in them, and made a significant contribution to writing the final manuscript. In original publication III I was in charge of writing most of the manuscript, and I was also involved in interpreting the results and creating tables for the publication.

7 Results

7.1 A systematic review and meta-analysis of recovery in schizophrenia

The electronic database searches identified 5,647 unique records. From these, 37 articles or books met the inclusion criteria and were included in the systematic review. These 37 articles or books comprised altogether 50 discrete samples, including 13 samples from the WHO incidence and prevalence and 7 samples found through manual search. In total, these studies included 8,994 discrete individuals from 20 different countries.

50 estimates of the recovery rate were identified (males and females combined). The distribution of these estimates is shown in Figure 3. Based on this distribution, the median recovery estimate was 13.5% (mean 16.4%) with the IQR between 8.1% and 20.0%. The distribution was densely underpinned with estimates in its central 75% portion and was left-skewed (i.e. some studies reported very high estimates). As expected, the estimates from the studies included were highly heterogeneous ($I^2 = 99.8\%$; $Q = 38\ 000$, $p < 0.001$). The median annual recovery rate was 1.4% per year (IQR 0.7%–2.6%).

7.1.1 Factors related to the recovery rate

Associations between different variables and recovery estimates are presented in Table 7. Only an *economic index of the site* was found to affect recovery estimates to a statistically significant extent. Compared with countries with high or upper middle income, recovery estimate was significantly higher in low or lower middle-income countries (medians 13.0% in high income countries, 12.1% in upper-middle, and 36.4% in low or lower middle-income countries) ($t = 2.93$, $p = 0.005$). When this analysis was adjusted in meta-regression analysis with the midpoint (year) of the baseline data collection period, the difference remained statistically significant ($t = -3.86$, $p < 0.001$). When WHO studies were excluded from the crude analyses, the median recovery percentages were 15.0% (n = 34), 9.7% (n = 1), and 12.7% (n = 2), respectively, ($t = 0.48$, $p = 0.63$). There was no statistically significant difference between genders. When ranked according to the midpoint year of the data collection period, the median recovery estimate declined numerically from 1955 onwards, but the differences were not statistically significant.

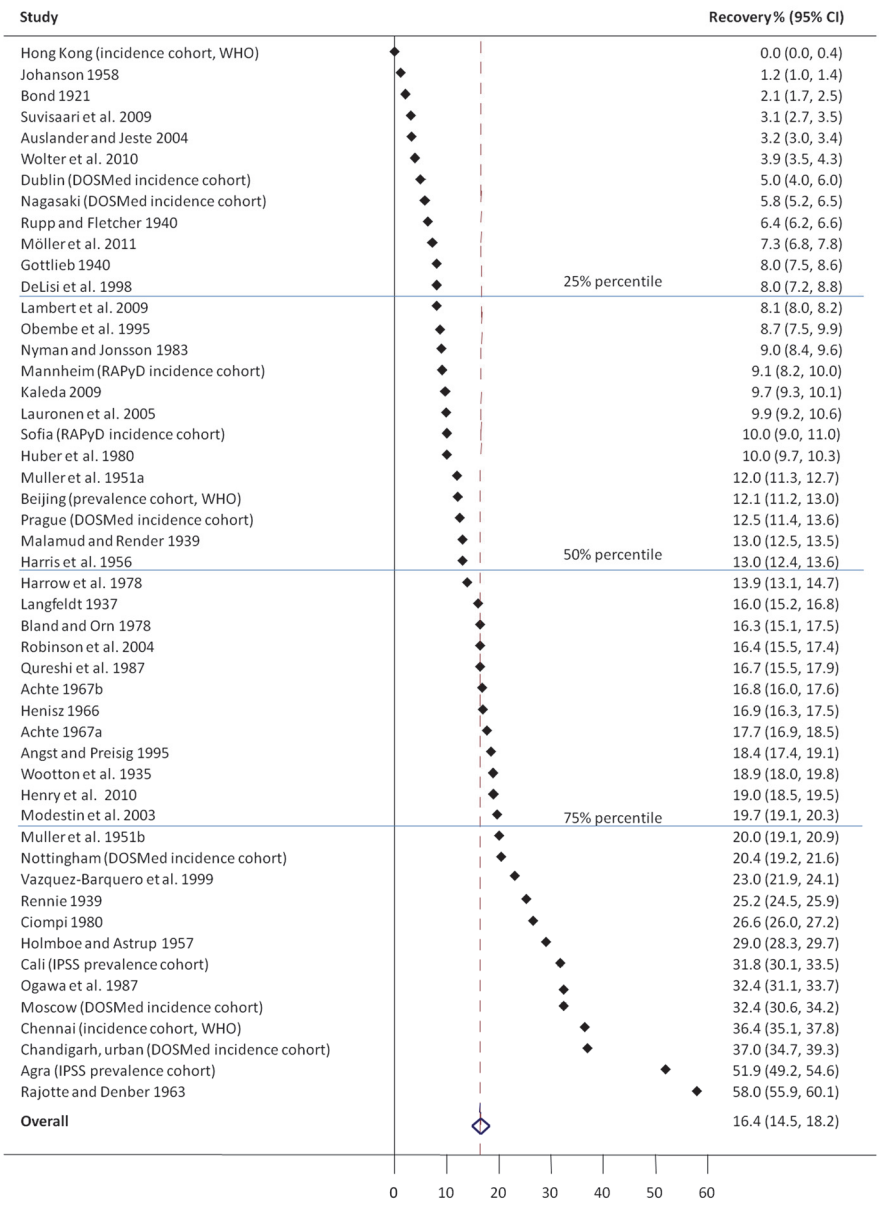

Fig. 3. Recovery percentage for the included studies.

Table 7. Recovery percentages in subpopulations.

Factors studied	Number of studies	Median%	IQR[1]	t-test (sig)[2]
Gender	24			1.08 (0.29)
Males	12	12.9	10.0–19.4	
Females	12	12.1	7.5–29.0	
Midpoint of the sample collection[3]	48			-0.38 (0.70)
before 1941	11	13.0	6.4–20.0	
1941–1955	5	17.7	13.0–19.7	
1956–1975	11	16.9	16.3–32.4	
1976–1995	19	9.9	5.8–19.0	
after 1996	2	6.0	3.9–8.1	
Economic index of the site[4]	50			**-2.93 (<0.01)**
Low or lower-middle	5	36.4	16.7–37.0	
Upper-middle	5	12.1	10.0–31.8	
High	40	13.0	7.7–19.0	
First-episode vs. not first-episode samples	46			-0.18 (0.86)
First-episode	30	16.6	9.0–20.4	
Not first-episode	16	11.1	6.0–22.5	
Length of follow-up	50			0.91 (0.37)
2–5 years	13	13.9	8.1–17.7	
>5–10 years	9	10.0	8.0–16.0	
>10–15 years	15	16.3	9.1–29.0	
>15 years	13	18.4	9.7–26.6	
Diagnostic criteria[5]	33			0.86 (0.40)
Kraepelinian	12	9.0	4.8–17.3	
Non-Kraepelinian	21	12.5	9.1–31.8	

[1] IQR = Inter Quartile range; [2] Meta-regression, t-test; [3] classified as in Warner (2004); [4] Income classes: Low-income economies ($1,005 or less) or Lower-middle-income economies ($1,006 to $3,975) versus Upper-middle-income economies ($3,976 to $12,275) versus High-income economies ($12,276 or more) (data.worldbank.org); [5] Kraepelinian: DSM-III, DSM-III-R, DSM-IV, Feighner, Kraepelin, Langfeldt, Statistical Manual of National Committee for Mental Hygiene; Non-Kraepelinian: Bleuler, DSM-II, ICD-8, ICD-9, ICD-10, Leonhard, Mayer-Gross, Research Diagnostic Criteria, Schneider. Statistically significant p-values are in bold.

There was no statistically significant difference between genders. When ranked according to the midpoint year of the data collection period, the median recovery estimate declined numerically from 1955 onwards, but the differences were not statistically significant.

There were no significant differences in recovery when studies were classified according to gender, Kreapelinian vs. non-Kraepelinian diagnostic system, first-episode studies vs. general intake, country of origin of the sample, duration of follow-up, being a WHO study vs. not, and studies methodological quality score.

7.2 Predictors of short- and long-term clinical outcome in schizophrenic psychosis (II)

7.2.1 Characteristics of the sample

The follow-up time from onset of illness until the end of the follow-up time (31.12.2005) or time of death was a minimum of 10 years (mean 16.4 years, SD 3.8 years, range 10–23 years). There were 59 (57%) males in the sample, 25 (24%) individuals with only a basic level of education (9 years), 69 (67%) with a secondary education (9–12 years) and 9 (9%) with a tertiary level of education (> 12 years). 34% were in remission and 66% received a disability pension by the end of the follow-up.

7.2.2 Predictors of short-term clinical outcome

The only statistically significant predictor for rehospitalisation in the first two years after discharge was the insidious mode of illness onset (OR 2.7, 95% CI 1.2–6.4). This statistically significant association remained after adjusting for gender and age at onset. None of the variables predicted the number of days in hospital treatment due to psychosis in the first two years after discharge.

7.2.3 Predictors of long-term clinical outcome

In the unadjusted analysis many significant associations occurred (Table 8), most of which remained significant after controlling for confounders. After adjustments, being single at onset predicted more negative ($p = 0.04$) and excitement symptoms ($p = 0.03$). Having more negative ($p = 0.04$) and depressive symptoms ($p = 0.02$) at onset was associated with more excitement symptoms at the end of the follow-up.

Poor premorbid work adjustment prior to the onset of the illness ($p = 0.01$) and depressive symptoms during the first hospitalisation ($p = 0.02$) predicted more emotional symptoms at the end of the follow-up. Illness onset at an early age was associated with lack of remission (OR 0.2, 95% CI 0.1–0.7). Insidious onset (OR 2.8, 1.1–7.05), suicidal ideations at onset (OR 4.9, 1.2–20.1), rehospitalisation (OR 4.3, 1.6–11.9) and more treatment days due to psychosis during the two years after index discharge (OR 1.4, 1.1–1.7) were all associated with having psychiatric hospital treatments during the last two years of follow-up.

Table 8. Predictors for long-term clinical outcome at the age of 34 in schizophrenic psychoses (n = 103) in the Northern Finland Birth Cohort 1966. Unadjusted analyses.

Predictors	Negative symptoms[1] median (IQR)	Positive symptoms[1] median (IQR)	Disorganisation symptoms[1] median (IQR)	Excitement symptoms[1] median (IQR)	Emotional symptoms[1] median (IQR)	Remission[2] n (%)	Psychiatric hospitalisations[3] n (%)
Sociodemographic and premorbid variables							
Gender							
female	10 (8–17)	14 (7–17)	13 (10–23)	11 (8–13)	12 (8–17)	10/25 (40%)	11/44 (25%)
male	11 (8–13)	10 (7–17)	15 (10–26)	10 (8–13)	11 (8–16)	9/31 (29%)	20/59 (34%)
Onset age							
<22 years	11 (8–25)	15 (7–19)	18 (11–30)	12 (8–17)	13 (8–18)	**4/26 (15%)**	19/54 (35%)
>22 years	11 (8–15)	10 (7–14)	13 (10–18)	10 (8–12)	11 (8–14)	**15/30 (50%)**	12/49 (25%)
Family history of psychosis							
yes	10 (8–16)	13 (8–19)	16 (10–21)	10 (8–13)	12 (8–17)	6/17 (35%)	10/29 (35%)
no	11 (8–20)	11 (7–17)	13 (10–25)	10 (8–13)	11 (8–17)	13/39 (33%)	21/74 (28%)
Mode of onset							
insidious	11 (8–20)	14 (7–19)	14 (11–23)	11 (8–14)	13 (8–18)	7/25 (28%)	**19/45 (42%)**
acute	10 (8–20)	9 (7–14)	10 (10–28)	10 (8–13)	11 (8–14)	10/25 (40%)	**10/47 (21%)**
Personality disorder							
yes	8 (8–16)	14 (7–18)	13 (10–21)	11 (8–13)	13 (8–19)	5/11 (46%)	5/16 (31%)
no	15 (8–26)	15 (7–17)	19 (12–30)	12 (10–18)	12 (8–17)	3/19 (16%)	15/44 (34%)
Single at onset[4]							
yes	**18 (8–31)**	13 (7–17)	**17 (13–31)**	**12 (10–18)**	**13 (10–17)**	**4/23 (17%)**	18/57 (32%)
no	**10 (8–13)**	12 (7–14)	**10 (10–18)**	**9 (8–12)**	**11 (8–13)**	**11/22 (50%)**	7/28 (25%)
Alcohol abuse							
yes	11 (8–19)	7 (7–13)	10 (10–17)	9 (8–11)	8 (8–13)	3/5 (60%)	3/10 (30%)
no	11 (8–20)	13 (7–17)	15 (10–26)	11 (8–14)	12 (8–17)	14/48 (29%)	27/89 (30%)

Predictors	Negative symptoms[1] median (IQR)	Positive symptoms[1] median (IQR)	Disorganisation symptoms[1] median (IQR)	Excitement symptoms[1] median (IQR)	Emotional symptoms[1] median (IQR)	Remission[2] n (%)	Psychiatric hospitalisations[3] n (%)
Psychosocial stressors							
yes	8 (5–19)	20 (7–24)	21 (10–26)	11 (9–18)	14 (8–17)	2/7 (29%)	1/9 (11%)
no	11 (8–20)	10 (7–17)	13 (10–23)	10 (8–13)	11 (8–17)	16/47 (34%)	30/92 (33%)
Poor work adjustment							
yes	12 (8–19)	14 (7–17)	14 (10–25)	11 (10–13)	**17 (11–19)**	5/14 (36%)	12/28 (43%)
no	10 (8–20)	11 (7–17)	13 (10–24)	11 (8–13)	**11 (8–14)**	11/34 (32%)	16/61 (26%)
Poor social adjustment							
yes	14 (8–19)	11 (7–17)	14 (10–27)	12 (9–13)	13 (10–20)	4/14 (29%)	10/31 (32%)
no	10 (8–13)	12 (7–16)	13 (10–19)	10 (8–11)	11 (8–12)	6/16 (38%)	8/30 (27%)
Symptoms at first hospitalisation due to psychocis							
Negative symptoms							
yes	13 (8–22)	14 (9–19)	19 (12–28)	**12 (10–18)**	13 (11–17)	3/23 (13%)	8/23 (35%)
no	11 (8–19)	10 (7–17)	16 (10–23)	**10 (8–12)**	10 (8–18)	7/19 (37%)	6/20 (30%)
Positive symptoms							
yes	11 (8–20)	14 (7–17)	17 (10–26)	12 (8–14)	12 (8–17)	8/27 (30%)	8/28 (29%)
no	13 (8–19)	13 (7–18)	16 (11–25)	11 (9–13)	13 (8–17)	2/15 (13%)	6/15 (40%)
Manic symptoms							
yes	13 (8–24)	12 (7–17)	16 (10–29)	11 (8–14)	13 (8–18)	7/24 (29%)	9/25 (36%)
no	11 (7–20)	15 (8–21)	20 (12–26)	12 (9–14)	12 (8–17)	3/18 (17%)	5/18 (28%)
Depressive symptoms							
yes	13 (8–23)	14 (7–18)	18 (10–27)	**12 (10–16)**	**13 (10–18)**	7/34 (21%)	11/35 (31%)
no	10 (7–14)	9 (7–13)	13 (11–23)	**9 (8–11)**	**8 (8–11)**	3/8 (38%)	3/8 (38%)
Suicidal ideations							
yes	8 (8–18)	16 (7–19)	17 (10–27)	11 (8–17)	12 (8–18)	4/16 (25%)	**9/17 (53%)**
no	15 (10–21)	12 (7–16)	17 (10–26)	12 (10–14)	13 (8–17)	6/26 (23%)	**5/26 (19%)**

Predictors	Negative symptoms[1] median (IQR)	Positive symptoms[1] median (IQR)	Disorganisation symptoms[1] median (IQR)	Excitement symptoms[1] median (IQR)	Emotional symptoms[1] median (IQR)	Remission[2] n (%)	Psychiatric hospitalisations[3] n (%)
Early outcome variables							
Rehospitalisation within first 2 years							
yes	11 (8–19)	14 (7–18)	17 (10–25)	11 (8–14)	13 (8–17)	9/31 (29%)	**25/60 (42%)**
no	11 (8–20)	10 (7–16)	12 (10–19)	10 (8–13)	11 (8–14)	10/25 (40%)	**6/43 (14%)**
Hospital days within first 2 years							
<13	11 (8–20)	13 (7–17)	12 (10–21)	10 (8–13)	11 (8–17)	10/29 (35%)	**10/51 (20%)**
≥13	10 (8–19)	10 (7–17)	16 (10–25)	10 (8–14)	13 (8–17)	9/27 (33%)	**21/52 (40%)**

[1] PANSS symptoms are continuous variables, other outcome measures are dichotomised, [2] Remission = ≤ 3 score on 8 PANSS items (P1, P2, P3, N1, N4, N6, G5, and G9), [3] Psychiatric hospital treatments in the last two years of follow-up (yes/no), [4] When being single was adjusted with gender and onset age, the only statistically significant associations remained with negative and excitement symptoms. All other associations remained statistically significant when adjusted for gender. **Bolding** of the values indicates a p-value < 0.05. Analyses were performed with Mann-Whitney U-tests or Chi-square tests.

7.2.4 Multivariate models for outcome

Models for predicting outcome were generated to test whether all predictors with an initial p-value of less than 0.1 would together make up a powerful model for predicting the individual outcome measures. Gender and age at onset were inserted into each model. The strongest model regarding short-term outcome was the one predicting rehospitalisation due to psychosis in the two years after discharge. This model included gender, age at onset and mode of onset. The Nagelkerke R^2 value for this model was 0.11, indicating that only 11% of the variance of rehospitalisation could be explained by this model.

The strongest model concerning long-term outcome was the one predicting remission (variables gender, onset age, being single, Nagelkerke $R^2 = 0.39$). Premorbid personality disorder and negative symptoms could not be included in the model due to the low frequencies of these factors. Age at onset was the only statistically significant variable in the model ($p < 0.01$). Of the variance of psychiatric hospital treatments at the end of the follow-up, 33% could be predicted with a model including gender, age at onset, mode of onset, suicidal ideations, rehospitalisation and number of days in hospital treatment due to psychosis in the two years after discharge. None of individual predictors remained statistically significant in this model. Other models predicted 4–20% of the long-term outcome measures.

7.3 Associations between brain morphology and outcome (III)

7.3.1 Characteristics of the sample

Participants were almost the same age at the time of MRI brain scanning (mean 33.8, years SD 0.7). The mean age of illness onset was 23.0 years (SD 4.2). Of the sample 31 (57%) were male, 12 (22%) subjects had only a basic level of education, 11 (20.4%) were in remission, and 28 (53%) were on disability pension. A diagnosis of alcohol abuse was received by 11 (20.4%) participants, but none had a diagnosis of drug abuse.

7.3.2 Associations between brain morphology and measures of clinical outcomes

All analyses were controlled for ICV, gender, duration of illness and use of antipsychotic medication. Increased grey matter density of the left limbic area was associated with a lower number of hospitalisations and increased volume of total white matter with being in remission. Significant results after adjustments are presented in Table 9. When we took handedness into account as well by excluding left-handed subjects (three left-handed subjects and one with no information), these results remained statistically significant.

7.3.3 Associations between brain morphology and measures of functional outcomes

When ICV, gender, duration of illness and antipsychotic medication were controlled for, higher grey matter density of the left frontal lobe and left limbic area related to better functioning, i.e. higher score on SOFAS. After excluding the three left-handed subjects and one with no information on handedness, left frontal lobe still predicted statistically significantly higher score on SOFAS, but left limbic area was rendered insignificant.

Table 9. Significant associations between brain morphology and outcomes in schizophrenia at age 34 (N=54). All results are adjusted for intracranial volume (ICV), gender, duration of illness and use of antipsychotic medication. Modified from online supplement Table 2 and 3 of the original publication III.

Brain area/matter	Days hospitalised due to psychosis Beta (B, SE)[1]	Times hospitalised due to psychosis Beta (B, SE)[1]	SOFAS score Beta (B, SE)[1]	Remission OR (95% CI)[2]	Not on disability pension OR (95% CI)[2]	Working at least 50% of time OR (95% CI)[2]
Total white matter	-0.29 (-0.003, 0.005)	-0.14 (-0.001, 0.002)	0.08 (0.02, 0.07)	**1.07 (1.01–1.14)**	1.02 (0.99–1.06)	0.99 (0.96–1.02)
Frontal left grey matter	-0.17 (-0.03, 0.03)	-0.26 (-0.02, 0.01)	**0.29 (0.78, 0.36)**	1.02 (0.86-1.21)	1.16 (1.00-1.34)	1.04 (0.90-1.20)
Limbic left grey matter	-0.19 (-0.09, 0.07)	**-0.39 (-0.08, 0.03)**	**0.28 (2.25, 1.06)**	1.05 (0.66–1.66)	1.53 (0.94–2.47)	1.55 (0.93–2.59)

[1] Linear regression, [2] Logistic regression. Beta = standardised coefficient, B = unstardardised coefficient, SE = standard error of B, OR = Odds ratio, 95% CI = 95% confidence interval, SOFAS = Social and Occupational Functioning Scale. **Bolding** indicates a p-value < 0.05. No statistically significant findings were observed in the adjusted analyses between outcomes and total brain volume, total grey matter, cerebrospinal fluid volume, and the following regional grey matter densities: central left and right, frontal right, temporal left and right, parietal left and right, occipital left and right, limbic right, insula left and right, subcortical grey nuclei left and right, and cerebellum.

7.4 Neurocognitive functioning and outcome (IV)

7.4.1 Characteristics of the sample

Of the sample, 23 (54%) were male and 21 (50%) had only a low level of education. 12 (28%) cases were in remission at follow-up, 21 (49%) had been employed at least 25% during the previous year, and the mean SCS score was 10.5 (SD 3.7). Neurocognitive test scores of the subjects with schizophrenia and the controls are presented in Table 10. Cases differed statistically significantly from controls in all of the neurocognitive tests.

7.4.2 Neurocognitive functioning as a predictor of outcomes – longitudinal analyses

In the unadjusted analyses, better verbal memory (CVLT Trials 1–5) at age 34 predicted a better global outcome at age 43 ($p = 0.02$), and better long-term verbal memory (CVLT long delay) predicted remission (OR 1.33, 95% CI 1.00–1.76) and a better global outcome ($p = 0.003$). Better performance on visual memory (VOLT) predicted better vocational (OR 1.14, 1.03–1.27) and global outcomes ($p = 0.02$). Higher composite score predicted a better global outcome ($p = 0.026$).

After adjusting for onset age, the only statistically significant results remained between long-term verbal memory and global outcome ($p = 0.027$), and between visual memory and vocational outcome (OR 1.14, 1.03–1.27). For these associations, several other potential confounders in addition to onset age were analysed (IV). Gender and education had no great effect on the results, as opposed to negative symptoms, which markedly reduced the predictive significance of neurocognitive performance. For a comparison of the effects of different cognitive tests, please see standardised effect measures in Table 11.

Table 10. Cognitive performance of subjects with schizophrenic psychosis (cases) and controls at age 34 and 43.

Cognitive tests	At age 34 years							At age 43 years						
	Cases			Controls				Cases			Controls			
	n	Mean	SD	n	Mean	SD	Sig	n	Mean	SD	n	Mean	SD	Sig
CVLT trials 1-5[1]	42	47.98	13.59	74	59.81	7.31	<0.001	43	44.30	15.54	76	54.83	8.32	0.001
CVLT long delay[2]	42	11.21	3.61	74	13.64	2.17	<0.001	43	10.12	3.87	76	12.47	2.48	<0.001
AIM (A+M)[3]	40	20.78	3.16	71	23.63	3.36	<0.001	32	20.81	3.49	77	23.92	2.94	<0.001
AIM (A)[4]	41	22.78	3.11	72	24.13	2.52	0.021	38	22.89	2.87	77	24.66	2.56	0.002
VOLT[5]	39	59.33	8.01	76	68.59	5.38	<0.001	36	60.92	8.24	75	68.79	5.24	<0.001
Composite score[6]	43	-1.23	1.21	77	-0.02	0.67	<0.001	43	-1.23	1.21	77	0.00	0.67	<0.001

[1] California Verbal Learning Test (CVLT), immediate free recall, summary score, [2] CVLT, long delay free recall, [3] Abstraction and Working Memory task (AIM), abstraction and memory subtest, [4] AIM, abstraction subtest, [5] Visual Object Learning Test (VOLT), [6] Mean of z-scores standardised for control group. SD = Standard deviation, Sig = difference between cases and controls with Welch's t-test (p-value).

Table 11. Standardised effect measures of cognitive tests as predictors of outcomes in schizophrenia: comparable effects between different cognitive tests. Unadjusted and adjusted longitudinal analyses; cognitive tests performed at 34 years, outcomes assessed at 43 years.

Cognitive tests	Remission				Vocational outcome				Global outcome			
	Unadjusted		Adjusted [1]		Unadjusted		Adjusted [1]		Unadjusted		Adjusted [1]	
	OR_s	95% CI	OR_s	95% CI	OR_s	95% CI	OR_s	95% CI	β	Sig	β	Sig
CVLT trials 1-5 (n = 42)[2]	1.44	0.69–3.02	1.13	0.49–2.60	1.94	0.97–3.88	1.58	0.73–3.39	**0.36**	**0.020**	0.26	0.102
CVLT long delay (n = 42)[3]	**2.78**	**1.01–7.67**	2.49	0.81–7.62	1.87	0.94–3.73	1.45	0.67–3.13	**0.45**	**0.003**	**0.35**	**0.027**
AIM (A+M) (n = 40)[4]	1.30	0.65–2.58	1.16	0.39–2.06	1.37	0.72–2.62	1.17	0.57–2.42	0.02	0.925	-0.07	0.671
AIM (A) (n = 41)[5]	1.15	0.58–2.31	1.07	0.49–2.31	1.41	0.74–2.69	1.34	0.63–2.84	0.12	0.457	0.07	0.634
VOLT (n = 39)[6]	1.50	0.72–3.13	1.28	0.56–2.89	**2.90**	**1.27–6.64**	**2.55**	**1.07–6.10**	**0.37**	**0.020**	0.29	0.069
Composite score[7]	1.87	0.82–4.26	1.52	0.61–3.78	1.90	0.95–3.83	1.47	0.68–3.21	**0.34**	**0.026**	0.22	0.162

[1] Adjusted for onset age, [2] California Verbal Learning Test, immediate free recall, [3] CVLT, long delay free recall, [4] Abstraction and Working Memory task; abstraction and memory subtest, 3 participants excluded due to below chance score, [5] AIM abstraction subtest, 2 participants excluded due to below chance score. [6] Visual Object Learning Test, [7] Mean of z-scores standardised for control group. 95% CI = 95% confidence interval, OR_s = standardised odds ratio, i.e. OR for outcome when predictor variable changes by one standard deviation. (Interpretation: When the predictor variable increases by one SD, odds of having the outcome are multiplied by the amount indicated by the ORs. This way the statistic does not depend on the scale of the measure used and the different cognitive tests can be directly compared with one another.) β = standardised coefficient. **Bolding** indicates a p-value < 0.05.

7.4.3 Associations between neurocognitive functioning and outcome – cross-sectional analyses

In the unadjusted cross-sectional analysis, better long-term verbal memory was associated with remission (OR 1.27, 95% CI 1.00–1.62), and better executive functioning (AIM abstraction subtest) with remission (OR 1.35, 1.00–1.82) and a better global outcome (p = 0.025). Better performance on visual learning was associated with a better vocational (OR 1.14, 1.02–1.26) and global outcome (p = 0.006). A higher composite score associated with remission (OR 2.43, 1.08–5.50) and a better global outcome (p = 0.008).

After adjusting for onset age, the only statistically significant findings remained between *visual memory* and global outcome (p = 0.035), and *composite score* and global outcome (p = 0.036).

7.4.4 Additional adjustments

The statistically significant results were adjusted for additional potential confounders including gender, antipsychotic medication, level of education, baseline symptoms (PANSS positive, negative and total score), and a corresponding outcome at baseline. All adjustments were performed in combination with onset age. In the longitudinal analysis, the statistical significance between VOLT and vocational outcome remained when adjusting for onset age and gender or baseline positive symptoms. With respect to CVLT long delay and global outcome, the association remained significant when adjusted for onset age and, alternately with gender, educational level, or positive symptoms. All other adjustments rendered the results non-significant. Especially negative symptoms were relevant as confounders as controlling for them rendered all statistically significant results non-significant.

In the cross-sectional analysis, the statistical significance between VOLT and global outcome remained when adjusted for current antipsychotic medication, gender and education. The association between composite score and global outcome remained statistically significant when adjusting for education. All other adjustments rendered the results non-significant.

7.5 Additional analysis for the thesis

7.5.1 Socio-demographic and illness-related predictors of very long-term outcomes at 43 years

The predictors used for original publication II were employed to predict the very long-term outcome in schizophrenia (a minimum follow-up of 19 years) until the cohort subjects were approximately 43 years old. The only statistically significant predictors were young age of illness onset (OR 0.12, 95% CI 0.02–0.67) and being single at illness onset (OR 0.10, 0.02–0.63) both predicting a lack of remission (Table 12). When inserted in the same model, neither of the variables remained statistically significant ($p = 0.054$ for early onset age, $p = 0.142$ for being single). Together they explained 45% of the total variance in remission (Nagelkerke $R^2 = 0.448$). 52% of subjects with later onset compared to 81% of early onset subjects were single at the onset of illness.

Mode of onset, family history of psychosis, premorbid personality disorder, poor premorbid work or social adjustment, or rehospitalisation in the first two first years after discharge did not associate with any of the outcome dimensions (Table 12).

Of the predictors investigated in the analyses of original publication II, alcohol abuse, premorbid psychosocial stressor and symptoms during first episode were not re-analysed due to the low frequency counts.

7.5.2 Variables assessed at 34 years as predictors of outcomes at 43 years

The symptoms at 34 years, categorised according to the five-factor model by van der Gaag *et al.* (2006b), proved to be relatively consistent predictors of later outcomes (Table 13). They all had an effect on the expected direction, i.e. more symptoms at 34 years predicting poorer outcomes at 43 years. Disorganisation symptoms in particular were relevant in predicting all outcome dimensions. More positive and excitement symptoms predicted lack of remission, and more negative and emotional symptoms poorer vocational outcome.

Consistent with these results concerning the five symptom factors, remission status at 34 years was predictive of all outcome dimensions at 43 years with being in remission predicting better outcomes (Table 13).

Table 12. Additional analysis for the thesis. Predictors of very long-term outcome (at 43 years) in schizophrenia (n = 43) in the Northern Finland Birth Cohort 1966.

Predictors	In remission n (%)	Employed n (%)	Good global outcome n (%)
Gender			
Female (n = 18)	7 (38.9)	7 (43.8)	11 (61.1)
Male (n = 25)	4 (16.7)	10 (41.7)	9 (39.1)
Onset age ≤ 22 years			
Yes (n = 23)	**2 (9.1)**[1]	7 (33.3)	8 (38.1)
No (n = 20)	**9 (45.0)**	10 (52.6)	12 (60.0)
Family history of psychosis			
Yes (n = 12)	2 (16.7)	4 (44.4)	5 (41.7)
No (n = 31)	9 (30.0)	13 (41.9)	15 (51.7)
Insidious onset			
Yes (n = 15)	2 (13.3)	7 (46.7)	9 (64.3)
No (n = 21)	7 (35.0)	8 (44.4)	8 (40.0)
Personality disorder			
Yes (n = 9)	2 (22.2)	3 (37.5)	5 (55.6)
No (n = 14)	2 (14.3)	5 (38.5)	6 (42.9)
Single at onset			
Yes (n = 20)	**2 (10.5)** [2]	6 (33.3)	7 (36.8)
No (n = 13)	**7 (53.8)**	6 (50.0)	8 (61.5)
Poor work adjustment			
Yes (n = 12)	3 (25.0)	4 (33.3)	6 (50.0)
No (n = 24)	7 (30.4)	10 (47.6)	10 (45.5)
Poor social adjustment			
Yes (n = 11)	2 (18.2)	3 (30.0)	6 (54.5)
No (n = 12)	6 (54.5)	6 (54.5)	6 (54.5)
Rehospitalisation in 2 years			
yes (n = 22)	5 (23.8)	9 (42.9)	11 (52.4)
No (n = 19)	4 (21.1)	7 (41.2)	7 (38.9)

All predictor variables were dichotomised (yes/no). Information on some variables was not available to all. [1] Pearson Chi-Square test p = 0.008, [2] Fisher`s Exact Test p = 0.015. When adjusted for age of onset: Odds ratio 0.22, 95% confidence interval 0.03–1.67). **Bolding** indicates a p-value < 0.05. Bonferroni correction (with level of significance p < 0.005) would render all results statistically insignificant.

Table 13. Additional analysis for the thesis. Symptoms at 34 years as predictors of very long-term outcome (at 43 years) in schizophrenia in the Northern Finland Birth Cohort 1966. PANSS ratings were available for 36 participants.

Predictors	In remission n (%)	Employed n (%)	Good global outcome n (%)
Negative symptoms			
Yes (n = 20)	2 (10.0)	**6 (30)[1]**	8 (40.0)
No (n = 16)	6 (37.5)	**9 (64.3)**	8 (57.1)
Positive symptoms			
Yes (n = 19)	**0 (0.0)[2]**	5 (29.4)	7 (38.9)
No (n = 17)	**8 (47.1)**	10 (58.8)	9 (56.2)
Disorg. symptoms[3]			
Yes (n = 21)	**1 (4.8)[2]**	**4 (20.0)[2]**	**5 (23.8)[2]**
No (n = 15)	**7 (46.7)**	**11 (78.6)**	**11 (84.6)**
Excitement symptoms			
Yes (n = 18)	**1 (5.6)[1]**	5 (29.4)	6 (35.3)
No (n = 18)	**7 (38.9)**	10 (58.8)	10 (58.8)
Emotional symptoms			
Yes (n = 18)	2 (11.1)	**5 (27.8)[1]**	7 (41.2)
No (n = 18)	6 (33.3)	**10 (62.5)**	9 (52.9)
Remission at 34 years			
Yes (n = 12)	**7 (58.3)[2]**	**10 (83.3)[2]**	**9 (81.8)[2]**
No (n = 24)	**1 (4.2)**	**5 (22.7)**	**7 (30.4)**

Symptoms were divided into factors based on the five-factor model by van der Gaag et al. (2006b) and dichotomised with the median as cut-off point (yes = above median score). Statistical testing was performed with chi-square test (or with the Fisher's exact test, as appropriate) and statistically significant results ($p < 0.05$) are **in bold**. [1] $p < 0.05$, [2] $p < 0.01$, [3] disorganisation symptoms.

Neurocognitive test performance at 34 years correlated, as hypothesised, with the same variables at 43 years (Table 14). Accordingly, having a neurocognitive impairment at 34 years predicted neurocognitive impairment at 43 years ($p = 0.001$).

Table 14. Correlations between neurocognitive test scores at 34 years and at 43 years with Spearman´s rank correlation coefficients.

	Neurocognitive tests at age 43						
Neurocognitive tests at age 34	CVLT trials 1-5 (n = 43)	CVLT delayed (n = 43)	AIM (A+M) (n = 32)[5]	AIM (A) (n = 38)[6]	VOLT (n = 36)[7]	Composite score	Cognitive impairment[8]
CVLT trials 1-5 (n = 42)	**0.45**[10]	**0.46**[10]	0.23	**0.36**[9]	**0.43**[10]	**0.50**[11]	**-0.52**[11]
CVLT delayed (n = 42)	**0.44**[10]	**0.55**[11]	0.17	0.23	**0.34**[10]	**0.46**[10]	**-0.51**[11]
AIM (A+M) (n = 40)[1]	0.05	0.11	-0.01	0.24	0.25	0.13	-0.22
AIM (A) (n = 41)[2]	0.04	0.17	-0.08	0.01	**0.44**[10]	0.13	**-0.34**[9]
VOLT (n = 39)	**0.38**[9]	**0.45**[10]	0.20	0.15	**0.58**[11]	**0.47**[10]	**-0.53**[10]
Composite score[3]	**0.44**[10]	**0.53**[11]	0.18	0.28	**0.51**[10]	**0.51**[11]	**-0.57**[11]
Cognitive impairment[4]	**-0.38**[9]	**-0.45**[10]	-0.35	-0.31	**-0.35**[9]	**-0.47**[11]	**0.48**[11]

[1] Abstraction and Working Memory task (AIM) abstraction and memory subtest, 2 participants excluded due to below chance score, [2] AIM abstraction subtest, 2 participants excluded due to below chance score, [3] Mean of z-scores standardised for control group, [4] 23 cases (53% of total 43) were cognitively disabled at 34 years, [5] 8 participants excluded due to below chance score, [6] 2 participants excluded due to below chance score, [7] Visual Object Learning Test (VOLT), 2 participants excluded due to below chance score, [8] 24 cases (56% of total 43) were cognitively disabled at 43 years. [9] $p < 0.05$, [10] $p < 0.01$, [11] $p \leq 0.001$. CVLT = California Verbal Learning Test. **Bolding** indicates a p-value < 0.05. After Bonferroni correction, $p < 0.007$ can be considered statistically significant, i.e. values marked with a superscript number 11 in this table.

8 Discussion

8.1 Main findings

The main findings of this doctoral thesis corresponding with the aims presented in original publications I–IV and additional analyses were:

I Studies meeting the inclusion criteria (n=50) showed heterogeneous recovery estimates. Approximately 13.5% of subjects with schizophrenia recovered both clinically and socially. The recovery estimate was relatively stable; factors such as gender, first-episode sample status, diagnostic system, duration of follow-up or the methodological quality of the studies did not significantly affect the recovery estimate. However, poorer economic indices of the study countries related to higher recovery estimates. The recovery rate has not increased in the last decades.
II Schizophrenia patients who were young and single at onset and experienced an insidious mode of illness onset were at greater risk of having a poor outcome in terms of later psychiatric hospitalisations and a lack of remission. A greater number of days in hospital treatment due to psychosis in the early stages of the illness predicted a greater likelihood of hospitalisations 10 years later. A novel finding was the association between suicidal ideations at onset and a greater risk for future psychiatric hospitalisations.
III A greater total white matter volume associated with greater likelihood of remission, and increased grey matter density of the left limbic area with lower cumulative number of hospitalisations. Higher grey matter density of the left frontal lobe and left limbic area related to better level of functioning. CSF and total grey matter did not associate with any of the outcomes studied.
IV Better long-term verbal memory at 34 years predicted better global outcome at 43 years of age and better visual memory predicted better vocational outcome. In the cross-sectional analyses at 43 years, better visual memory and higher composite neurocognitive score associated with better global outcome. Remission status did not relate to neurocognitive performance.

The main finding from the additional analysis for the thesis was that younger onset age increased the likelihood for symptomatic course of illness, i.e. lack of remission, even after almost 20 years since illness onset. Vocational or global outcome could not be predicted with the variables selected. Remission status and good neurocognitive performance at 34 years predicted remission and good neurocognitive functioning at 43 years.

8.2 Recovery in schizophrenia (I)

Based on the meta-analysis, the median proportion of individuals with schizophrenia who recover both clinically and socially for a minimum of two years is 13.5%. Contrary to the hypothesis, no difference was found in recovery rates based on gender, diagnostic system, length of follow-up, methodological rigour of the study, or in studies with first-episode subjects versus general intake. However, as hypothesised, recovery rates related to the economic index of the country, with poorer countries showing more recoveries. It should be noted that these characteristics would be more efficiently examined in meta-analyses studying these variables in particular. Despite reasonable concerns about how to best assess recovery, and the well-appreciated heterogeneity in the recovery estimates, the median values for recovery appeared to be stable, with estimates for each of the different comparisons ranging only from 6.0% to 18.4%.

The recovery estimates found in this study are lower than those reported for "good outcome" in previous reviews (Hegarty *et al.* 1994, Warner 2004, Menezes *et al.* 2006). This probably reflects the more stringent criteria for recovery used in this study including both clinical and functional dimensions and the requirement that the recovery should have lasted for at least two years. This study reports for the first time data on the annual recovery rate for schizophrenia with the median recovery estimate of 1.4% per year. Put simply, this suggests that for every 100 individuals with schizophrenia, one or two of them would meet the recovery criteria per year, and approximately 14 would be expected to recover over 10 years.

Concerning the finding that low-income nations have higher recovery rates, it should be noted that only five recovery estimates from lower income sites were available, and three of these were based on the influential WHO studies that underpinned the earlier hypotheses related to developed-nation status and outcome (Leff *et al.* 1992, Harrison *et al.* 2001, Jablensky & Sartorius 2008). If, as expected, treatment influences clinical outcomes, and if access to treatment varies between nations favouring higher income countries, it seems reasonable to expect different outcomes between these sites. However, results of large international studies show just the opposite – outcome has been shown to be better in low-income countries (Jablensky *et al.* 1992). However, concerns have been raised about the interpretation of the WHO studies, relating, for instance, to the high dropout and mortality rates in studies conducted in developing countries (Cohen *et al.* 2008). A more recent report from SOHO (Schizophrenia Outpatient Health Outcome) suggests that clinical remission was significantly lower in Europe compared with other regions, namely

East Asia, North Africa, Middle East, and Latin America. This difference was not found for functional remission. (Haro *et al.* 2011). These results put together challenge the notion that better treatment automatically results in better outcomes. Even though the study design and methodology in the WHO studies is strictly controlled and no bias should relate to those factors, other factors that were not cotrolled for may have influenced the results. These could relate especially to occupational outcome, as the labour markets in different continents are difficult to compare.

In the meta-analysis of Hegarty *et al.* (1994) studies using broad, non-Kraepelinian criteria showed better outcomes than those using narrow Kraepelinian criteria. This study found no clear support for this finding. Somewhat surprisingly, there was also no statistically significant difference in the recovery estimates between males and females. This issue has not been a subject in the earlier meta-analyses (Hegarty *et al.* 1994, Warner 2004, Menezes *et al.* 2006), while a better prognosis for females has long been a general assumption supported by many studies (e.g. Leung & Chue 2000, Bertelsen *et al.* 2009). It may be that there are gender differences in other, perhaps less strict outcomes than recovery.

8.2.1 Why is the recovery rate not increasing?

Consistent with the previous reviews (Hegarty *et al.* 1994, Warner 2004), no evidence was found to suggest that recovery rates would have improved over time. On the contrary, recent decades had lower proportions of individuals meeting the recovery criteria, but this finding did not reach statistical significance. However, this is a sobering finding; despite major changes in the delivery of care to people with schizophrenia (e.g. deinstitutionalisation, antipsychotic medications, psychosocial interventions, and early psychosis services), the recovery rates seem not to have improved over time. It is, however, important to notice that the studies in this meta-analysis were naturalistic and the type of treatments received and information on treatment adherence were unknown. Thus, conclusions about the effect of treatment cannot be drawn. In Finnish schizophrenia studies the rate of recovery ranges from 10% in the NFBC 1966 (Lauronen *et al.* 2005) to 17–18% in studies where subjects were diagnosed with schizophrenic psychoses in the 1950s and 1960s (Achté 1967). Also in a study comparing patient cohorts from consecutive decades from 1950s to 1970s from the Helsinki area no significant improvement in the outcome of schizophrenia was detected. Hospital treatments were less frequently required with

every cohort, whereas the number of subjects in pension increased. (Achté *et al.* 1986).

Possible explanations for the finding that recoveries have not become more frequent with time include factors concerning patients, society, mental health services, and possibly also the nature of the schizophrenic disorder. Patients with schizophrenia are known to often have poor treatment adherence, which can affect treatment results. It should also be pointed out that some patients do not have optimal non-pharmacological care. (Davidson *et al.* 2008, Zipursky *et al.* 2013). It can also be discussed whether, among the range of schizophrenic disorders with subjects with very heterogeneous outcomes, there are in fact different disease entities, of which some may be less sensitive to treatment effect, or even treatment-resistant. There is strong evidence for the positive effects of antipsychotic treatment in schizophrenia. However, studies providing this evidence have a short-term follow-up of 2 years or less (Leucht *et al.* 2012). There is very little evidence for the long-term benefits of antipsychotics, and even some longitudinal data suggesting the opposite (Harrow & Jobe 2013, Wunderink *et al.* 2013).

Strong emphasis has been laid on early intervensions in schizophrenia in order to improve outcomes. So far, no convincing evidence exists for the long-term effects of early intervention services on later outcomes in schizophrenia (ten Velden Hegelstad *et al.* 2013, Nordentoft *et al.* 2014, Secher *et al.* 2014).

It is difficult to cope with social and cognitive impairment in todays demanding social environment. According to the large ÆSOP-study with a fairly recent cohort and a 10-year follow-up, only 16% of individuals with non-affective psychosis were employed at follow-up and 25% were in a relationship. These are rather modest numbers compared to the fact that, of the same individuals, 40% were considered symptomatically recovered, meaning that they had been symptom-free for the past two years. Only a small minory of the subjects moved into employment or relationship during the follow-up period, indicating a persistence of social exclusion that is evident already at first presentation (Morgan *et al.* 2014a).

The findings from the large national survey conducted in Australia in 1997–98 and again in 2010 support the findings of the ÆSOP-study. The results indicate that in some respects things have improved for people with psychotic illness, but some major problems still persist. These problems relate mostly to employment and social contacts as well as to mental and physical health issues, whereas the proportion of subjects experiencing the most severe and chronic forms of the illness has been reduced by half. (Morgan *et al.* 2012, Morgan *et al.* 2014b).

In light of the present thesis and other studies of the matter, it seems that even though the recovery (clinical and social aspects combined) from schizophrenia seems not to have become more frequent with the modern treatment approach, clinical outcomes have improved and the most severe outcomes and long in-patient stays have become less common (Morgan *et al.* 2014a, Morgan *et al.* 2014b). The social outcome, however, has not improved, and there is a lot more to be done in order to enhance the social recovery and reintegration of individuals suffering from schizophrenia. Social recovery, especially when measured by occupational success, is the limiting factor when assessing recovery rate.

8.3 Predictors of outcomes in schizophrenia (II-IV)

8.3.1 Predictors of early clinical outcomes in schizophrenia (II)

In accordance with the hypotheses, a connection was found between insidious onset and the risk for rehospitalisation due to psychosis during the two years after the first admission, which is in line with some previous observations (Sartorius *et al.* 1978, Westermeyer & Harrow 1984, Jablensky *et al.* 1992). Unlike some other authors (Menezes *et al.* 2006, Selten *et al.* 2007), no association was detected between early onset age and poorer *early* outcome. This indicates that age, at least in this sample, is not a clinically relevant predictor of early clinical outcome.

All in all, the prognosis of schizophrenia is most difficult to be assessed during the earliest stages of the illness (Carpenter *et al.* 1978), as was also indicated by the current results. No relationship was found between gender or family history of psychosis and early outcome, even though gender has been a fairly consistent predictor of outcome in many previous studies (Sartorius *et al.* 1978, Jablensky *et al.* 1992, Vazquez-Barquero *et al.* 1999), though not in all (Emsley *et al.* 2006). Familial risk has often been associated with more severe negative symptoms (Esterberg *et al.* 2010), but in this sample it did not predict the severity of any of the symptom domains or number of hospitalisations. Nor was there a connection between any of the early outcome measures and marital status, which is in accordance with some previous findings (Westermeyer & Harrow 1984), though not all (Bromet *et al.* 1974). Sartorius *et al.* (1978) found a connection between marital status and a better outcome, but only in the developing countries. In a large Finnish study, single men had the poorest quality of life, whereas in women the quality of life was more independent of the marital status (Salokangas *et al.* 2001).

As in previous studies, it was quite difficult to find satisfying models to predict outcome. The best early outcome model in this study predicted 28% of the variance in the negative symptom domain. Correspondingly, Sartorius *et al.* (1978) were able to predict 8–22% of the early course with a model consisting of their five best predictors.

8.3.2 Predictors of long-term clinical outcomes (II)

In accordance with the hypotheses, some sociodemographic and illness-related variables, such as age of onset, mode of illness onset and the early course of illness, predicted later clinical outcomes after approximately 10 years since illness onset. However, both gender and a family history of psychosis proved to have no predictive value for the long-term outcomes. Meta-analyses have found small but significant associations between family history of psychosis and poorer social (Käkelä *et al.* 2014) and clinical outcomes (Esterberg *et al.* 2010). Female gender has often been associated with a better outcome (Harrison *et al.* 1996, Grossman *et al.* 2008).

Early age at onset predicted difficulty in achieving symptomatic remission, but there was no association with later psychiatric hospital treatments. Early onset has previously been connected with a poorer outcome (Jonsson & Nyman 1991, Suvisaari *et al.* 1998), although a systematic review found no relationship between age at onset and outcome (Menezes *et al.* 2006).

Insidious onset predicted psychiatric treatments at the end of the follow-up. Previously insidious onset has been associated with a poorer outcome in some studies (Ciompi 1980, Bromet *et al.* 2005), but not in all (Siegel *et al.* 2007).

Being married has predicted better outcome in many studies (e.g. Harrison *et al.* 1996, Emsley *et al.* 2008), and consistently in the present study, being single at onset predicted more symptoms in most symptom domains in the follow-up, and accordingly, lack of clinical remission. However, after adjusting for onset age the predictive power of marital status diminished markedly indicating, as expected, that age of onset and marital status are associated to one another.

An association has been found between the number and severity of negative symptoms and poorer outcome (Häfner & an der Heiden 1999, Möller *et al.* 2000). No statistically significant relationship was found in this study, possibly due to the small sample size, although the subjects with no negative symptoms at the initial hospitalisation did achieve remission almost three times as often as those with negative symptoms (37% vs. 13%). Some studies have found that positive symptoms predict a better outcome (Ciompi 1980), but as in the case of some other authors

(Jonsson & Nyman 1991, Whitty *et al.* 2008), no association between positive symptoms and outcome emerged in this study. In a large early intervention study more severe positive symptoms at baseline predicted non-remission (ten Velden Hegelstad *et al.* 2013).

Fairly little is known about the effect of suicidal ideations on the outcome in schizophrenia. A connection has been found between suicidality and negative and depressive symptoms, but not between suicidality and remission (Emsley *et al.* 2007, Schennach-Wolff *et al.* 2010) or recovery (Shrivastava *et al.* 2010). In the current data, suicidal ideations during the first hospitalisation predicted psychiatric hospitalisations at the end of the follow-up but, as in previous studies, were not associated with remission. It should be noted that hospitalisations are an indirect measure of outcome, and that this finding may relate to service utilisation as well as to the severity of illness. Individuals with suicidal ideations at one point may also be prone to suicidality later on, which might result in hospital admissions and explain our finding. Suicidal ideations might also relate to schizoaffective disorder.

There have been discrepancies regarding the significance of depressive symptoms manifested in the early stages of illness. According to some studies, depressed mood at the index admission or before is predictive of a better outcome (Ciompi 1980, McGlashan 1986), while others have not found any such association (Carpenter *et al.* 1978). In this study, depressive symptoms at the first hospitalisation predicted more excitement and emotional symptoms in the long-term follow-up. This association between affective symptoms might also relate to schizoaffective disorder.

In this study, the best model predicting a long-term outcome measure predicted 39% of remission. Similarly, Harrison *et al.* (1996) were able to explain over 30% of the variance in global outcomes by the early illness course combined with basic demographic variables. However, the model presented in this study seems rather modest in comparison to the model created by Emsley *et al.* (2006), which was able to predict an outstanding 89% of remitters and 86% of non-remitters correctly. Emsley *et al.* (2006) had a first-episode psychosis sample, a short follow-up of two years, and they used e.g. early treatment response as a predictor of early outcome. These differences in the samples and study methodologies could account for the differences in the results between the two studies.

8.3.3 Association between early and long-term clinical outcomes (II)

Previous studies have shown that the best predictors of the long-term course and outcome of schizophrenia are the previous course and outcome (Siegel *et al.* 2007).

Accordingly, the best predictors of subsequent hospitalisations are prior hospitalisations, not the degree of psychopathology (McGlashan 1988). Similarly, this study showed that the best predictor of psychiatric hospital treatment at the long-term follow-up was the number of treatment days during the earlier phase of the illness. The connection between early and long-term symptomatology, on the other hand, remained somewhat inconclusive. This could in part relate to the use of different symptom categories at the two time points and the small sample size. The symptoms at illness onset were analysed using Matsuura *et al.* (2004) symptom division (manic, negative, depressive, and positive symptoms) and symptoms at 34 years were categorised according to van der Gaag *et al.* (2006b) assessing positive, negative, and disorganisation symptoms, and excitement and emotional distress.

Experiencing more relapses in the first treatment year has been associated with lack of remission (ten Velden Hegelstad *et al.* 2013). This study did not study relapses, per se, but hospitalisations in the first two years of illness did not associate with remission.

It seems that some of the typical factors associated with outcome in schizophrenia (e.g. marital status and onset age) only related to the long-term illness course and not at all to the early clinical outcomes.

8.3.4 Predictors of very long-term functional and clinical outcomes (additional analyses)

The symptoms at 34 years of age that were categorised into five factors according to the five-factor model by van der Gaag *et al.* (2006b) proved relatively consistent predictors of a 20-year outcome. The symptoms had an effect on the expected direction, i.e. more symptoms at 34 years predicted poorer outcomes at 43 years. Especially the disorganisation symptoms were relevant as they predicted all outcome dimensions statistically significantly. This finding is in accordance with previous literature indicating that subjects with disorganisation symptoms are prone to early illness onset (Salokangas *et al.* 2002), antipsychotic treatment resistance (Rodriguez *et al.* 1998), and more pronounced brain volume decrease (Collin *et al.* 2012), i.e. factors that have been associated with poorer outcome. Also, symptomatic remission at 34 years was predictive of both clinical and functional outcomes at 43 years. However, because of the small sample size and the high number of statistical tests conducted, the nature of these analyses should be considered exprolative and the results interpreted with caution.

The symptoms at first hospitalisations did not predict outcomes nearly 20 years later, but it should be noted, that the sample size was fairly small and not all analyses could be performed.

8.3.5 Brain morphology and outcomes (III)

Grey matter volumes and outcome in schizophrenia

In accordance with the hypothesis, grey matter deficits in the frontal lobe and limbic area associated with poorer outcome. The association between lower grey matter density in the subcortical nuclei and poorer functional outcome remained somewhat unclear, as it reached statistical significance only when adjusted for antipsychotic medication or remission status (III, online supplement Table 3).

This study offers support for the already existing evidence of the association between poor outcomes and grey matter deficits in the frontal lobe (Wilke *et al.* 2001, Mitelman *et al.* 2007, van Haren *et al.* 2007) and the limbic area of the brain (Mitelman *et al.* 2005, Lui *et al.* 2009, Bodnar *et al.* 2010, van Haren *et al.* 2011). However, not all studies have found associations between frontal lobe grey matter and outcome (Mitelman *et al.* 2003, Mitelman *et al.* 2007) and others did not find associations between any regional grey matter volumes and outcome (Staal *et al.* 2001, Ha *et al.* 2004). Unfortunately, in most previous studies the clinical and social outcomes have not been analysed separately within same samples.

In addition, earlier studies have found poor outcome patients to display decreased volumes of the whole cerebrum (van Haren *et al.* 2008), and more specifically of brain areas including temporal lobe (Mitelman *et al.* 2003, Mitelman *et al.* 2007, Lui *et al.* 2009), occipital lobe (Molina *et al.* 2010), and parietal lobe (Wilke *et al.* 2001), as well as subcortical grey matter nuclei (Buchsbaum *et al.* 2003, Brickman *et al.* 2004, Molina *et al.* 2010). After controlling for potential confounders, these findings could not be not replicated in this study.

Few previous studies have investigated the associations between brain morphology and remission. A first-episode study by Bodnar *et al.* (2010) found that subjects in remission had larger hippocampal tail volumes on the left. In a study by Andreasen *et al.* (2011) with a long follow-up, symptoms or remission status were only modestly associated with progressive brain tissue loss. In this study, there was no relationship between subcortical grey matter density and remission.

Ventricular/CSF volumes and outcome in schizophrenia

This study found no evidence of a relationship between increased CSF volume and poor outcome. Previously, more extensive ventricular enlargement has been detected in subjects with poor outcome (Mitelman *et al.* 2010, Nesvåg *et al.* 2012, van Haren *et al.* 2008), and longer periods of remission have been associated with less CSF expansion (Andreasen *et al.* 2011).

White matter volumes and outcome in schizophrenia

In this study increased total white matter volume was associated with being in remission. However, the results of volumetric MRI studies of white matter in schizophrenia have been rather inconclusive (Mitelman *et al.* 2007, Kanaan *et al.* 2009). A greater increase in cerebral white matter volume has predicted more positive psychotic symptoms in one study (Cahn *et al.* 2006), and more hospitalisations in another study (van Haren *et al.* 2008). However, there is also evidence for increased white matter volumes in subjects with good outcomes in the temporal, parietal, and occipital lobes (Mitelman *et al.* 2007), and in the cingulate regions (Paillère-Martinot *et al.* 2001, Mitelman *et al.* 2007). Mitelman *et al.* (2006) have previously suggested, based on a diffusion tensor imaging study, that the larger white matter volumes detected in good outcome patients may compensate for the lower regional anisotropy (i.e. lower fibre directionality). This reasoning could also explain the larger white matter volumes found in remitted individuals in this study.

Temporality of the morphological abnormalities

A study by Andreasen *et al.* (2011) showed that the greater brain loss in schizophrenia patients compared to controls occurs mainly during the first two years of illness. Longitudinal studies with first or recent onset samples have shown that brain structures measured early in the illness predict later outcome, at least to some extent (Ho *et al.* 2003, Milev *et al.* 2003, Kasparek *et al.* 2009). Since the subjects in this study had been ill for quite a long time before the brain scanning, it is not possible to draw conclusions concerning the temporality of the morphological differences. Van Haren *et al.* (2011) found the pattern of progressive tissue loss to be similar in patients with recent onset illness compared to those who had been ill for many years, and found significantly more pronounced decreases in cortical thickness in patients with poor outcomes. It is possible that already in the early stage of illness, brain

morphological abnormalities or factors causing the abnormalities indicate who will have good or poor outcomes later on. The differences in brain morphology between outcome groups might be most pronounced in the earlier stages of the illness, but some outcome related differences can be detected even after years of illness onset.

The results of this study indicate very heterogeneous courses of illness and differences in brain morphology between patients with good and poor outcomes. These phenomena could be due to a number of different pathological mechanisms and varying aetiologies behind schizophrenia. However, the differences in brain morphology detected between subjects with good and poor outcomes were relatively small and their role in clinical practice in predicting outcome is of minor importance. Based on this and previous studies, we are still a long way from employing morphological analysis as a biological marker in prognostics.

Methodological considerations

The differences between the results of this and other studies may be partly due to differences in study methodology. Studies have analysed, in part, different brain regions employing different MRI techniques, and used varying outcome measures, which all make between-study comparisons difficult. In addition, the study samples are often not comparable and generalisable. The advantage of the current study is the use of an epidemiologically sound population-based sample with no illicit drug users included. Compared to other studies, more specific outcome measures were used indicating social and clinical outcomes separately, as well as measures indicating both longer-term and more recent outcomes, whereas many earlier studies have analysed only cross-sectional or global outcomes (social and clinical outcome combined).

Different studies have used different variables when controlling for potential confounders, which is likely to have caused varying findings. According to Bodnar *et al.* (2010), the use of antipsychotic medication did not affect the associations between brain morphology and outcome. Most studies investigating brain morphology and outcomes have not controlled in their analyses for the use of antipsychotic medication. However, recent studies have suggested more influence of antipsychotics on brain structures than was previously known (Ho *et al.* 2011, van Haren *et al.* 2011, Fusar-Poli *et al.* 2013), including a study from the NFBC 1966 (Veijola *et al.* 2014). Thus, in this present study, all results were controlled for the use of antipsychotic medication, and additionally for ICV, gender, and duration of illness. The analyses were also re-run with the left-handed subjects excluded, and most results remained unchanged.

It should be noted that the MRI techniques have improved greatly in recent years in terms of field strength and corresponding resolution. This makes it possible to detect smaller differences among individuals.

8.3.6 Neurocognitive functioning and outcomes (IV)

Supporting the hypothesis, verbal memory was found to predict global outcome, and contrary to the hypothesis, executive functions did not relate to functional outcome. Visual memory predicted vocational outcome, whereas remission could not be predicted by neurocognitive performance in the tests used in this study. In the cross-sectional analysis at 43 years of age, visual memory and cognitive composite score were associated with global outcome.

Neurocognitive predictors of occupational outcome

Neurocognitive domains that have been associated with occupational outcome are, for instance, working memory (Hofer *et al.* 2011, Shamsi *et al.* 2011, August *et al.* 2012), verbal memory (Dickerson *et al.* 2007, Hofer *et al.* 2011), processing speed and attention (Milev *et al.* 2005, Kern *et al.* 2011, August *et al.* 2012) and visual memory (Hofer *et al.* 2005, Kern *et al.* 2011). Nuecterlein *et al.* (2011) found that all these domains predicted occupational outcome, except for visual memory, which they did not study. In a meta-analysis, Tsang *et al.* (2010) found that executive functions and general intelligence predicted occupational outcome, but that attention and working memory, and verbal and visual memory did not. Patients with cognitive abilities within the normal range have been shown to have a better occupational outcome than cognitively impaired subjects (Holthausen *et al.* 2007). However, in many prior studies the controlling for potential confounders has not been done (e.g. August *et al.* 2012, Holthausen *et al.* 2007, Nuechterlein *et al.* 2011), which could results in biased estimation of causal associations.

It has been suggested that the association between neurocognitive ability and occupational or global functional outcome might be more marked in subjects with long-term psychotic illness than in first-episode subjects (Verdoux *et al.* 2002, Stirling *et al.* 2003, González-Blanch *et al.* 2010). In this sample consisting of participants who were in different phases of the illness, only visual memory predicted vocational outcome in the longitudinal analysis after adjusting for onset age/duration of illness.

Neurocognitive predictors of remission

Most studies using the remission criteria by the Remission in Schizophrenia Working Group have found no association between neurocognitive functioning and remission (e.g. Buckley *et al.* 2007, Emsley *et al.* 2007, Eberhard *et al.* 2009, Brissos *et al.* 2011). However, marked neurocognitive differences have been shown between the remission and non-remission groups in some cross-sectional (Helldin *et al.* 2006, Hofer *et al.* 2011) and in one longitudinal study with a 6-month follow-up (Torgalsbøen *et al.* 2014), but only in the study by Hofer *et al.* (2011) the adjusting for confounders was done. In the present study, after adjusting for onset age, no individual neurocognitive test or composite score predicted the remission status.

Neurocognitive predictors of global outcome

When predicting the global outcome, the only significant results remaining after adjusting for onset age were with long-term verbal memory in the longitudinal analysis and with visual memory and composite score in the cross-sectional analysis. Eberhard *et al.* (2009) found that most of their neurocognitive tests associated with the 5-year global outcome. In first-episode studies, after adjusting for confounders, better global outcome has been predicted by better global neurocognitive functioning (Robinson *et al.* 2004) and better performance on many specific neurocognitive domains, but not on verbal memory (Faber *et al.* 2011). Poor global outcome, on the other hand, has been predicted by impaired attention and memory (Keshavan *et al.* 2003). Siegel *et al.* (2006) studied both first-episode and previously treated subjects separately, and found, using only a composite score, no cognitive contribution to the 3-year global outcome after controlling for possible confounders.

Methodological considerations

There are many possible explanations for the varying findings in studies examining the relationship between cognitive functions and outcomes in schizophrenia. These include the heterogeneity of the samples and course of illness, varying methods and analytical tools used to measure neurocognitive performance, and the large variability of outcome measures (Addington *et al.* 2005, Siegel *et al.* 2006, Allott *et al.* 2011, Pino *et al.* 2014). Also, different studies have assessed different confounding variables, and in many of them no adjustments have been done (Addington *et al.* 2005, Allot *et al.* 2011). One of the major problems that have prevented a clearer

understanding of the cognitive functions and their role in predicting outcomes in schizophrenia has been the paucity of large longitudinal studies. Much of the evidence has been extrapolated from cross-sectional studies, which do not allow causal conclusions (Smith *et al.* 2002). In fact, there are only a few studies with a follow-up time of ten years or more (Fujii & Wylie 2003, Stirling *et al.* 2003). Other problematic issues include collecting the neurocognitive data during or soon after acute psychosis (Norman *et al.* 1999) and assessing outcome concurrently or soon after neurocognitive testing (Fujii & Wylie 2003). Because follow-up studies of neurocognition are money- and time-consuming investigations, the sample sizes are often small resulting in low statistical power, which in some cases could explain the lack of statistically significant findings (Emsley *et al.* 2007). These factors taken together result in difficulties in drawing conclusions regarding the relationship between cognitive ability and outcomes.

Because same measures may have different predictive values depending on the stage of the illness, some inconsistencies in findings may relate to some samples including both first-episode as well as long-term schizophrenia patients (Siegel *et al.* 2006). In this study, most of the findings were rendered insignificant after adjusting for onset age/duration of the illness, which is in line with a meta-analysis concluding that onset age represents a surrogate measure for severity of neurocognitive deficits, as early-onset patients express more severe impairment in many neurocognitive domains (Rajji *et al.* 2009). Also, adjusting for negative symptoms rendered all associations non-significant, whereas gender and education were less important confounders. The confounding effect of negative symptoms on neurocognitive functioning has previously been recognised in the literature (Ventura *et al.* 2009). The adjustments notwithstanding, it is still possible that there is a true and clinically relevant connection between neurocognitive functioning and functional outcome, despite the fact that other disease related factors partly explain this association.

Studies have used differing methods and assessment tools. The MATRICS consensus conference lead to the identification of the following seven cognitive domains suggested to be used to assess cognition in schizophrenia: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Social Cognition (Neuchterlein *et al.* 2004). These recommendations were made to create standardised methods by which to measure cognitive performance in clinical trials of cognition-enhancing drugs, but they have been used in other studies of cognition as well. Hopefully, the MCCB or another generally excepted cognitive battery will help to unify the cognitive test used and thus enable better between-study comparison. The

cognitive domains proposed in the MCCB could not be used in this doctoral thesis, as the cognitive assessment had been carried out before such recommendations were made.

8.4 Outcome measures used in the study

8.4.1 Remission

At 34 years, 34% of the sample was in cross-sectional remission, and at 43 years the remission rate was very similar, 32%. Considering that 80% of subjects maintained their previous remission status (remitted or not-remitted) during a 9-year follow-up, remission status can, at least at the midlife stage of the illness, be regarded as a relatively stable construct. Previously the stability of remission based on the same criteria has been found to be 90% in a 1-year follow-up study including subjects who had a long illness duration (mean 15 years) and were remitted at baseline (Ciudad *et al.* 2009). In another sample of subjects with a mean illness duration of 11 years and a 5-year follow-up, the rate of remission changed during follow-up from 41% to just less than 60%, with 50% of subjects maintaining the same remission status of either remission or non-remission throughout the follow-up (Eberhard *et al.* 2009). The difference between this study and the study by Eberhard *et al.* (2009) was that in the latter the remission status was investigated annually for five years, compared to only two checks during the whole follow-up in this study. Thus, the study by Eberhard *et al.* (2009) gives a more precise estimate of the stability of remission.

In the Danish–Norwegian early psychosis detection study, 50.5% of the participants were in symptomatic remission after 10 years of illness with no difference between the early and usual detection groups (ten Velden Hegelstad *et al.* 2013). Their sample represents a slightly younger cohort than the NFBC 1966 and it is possible that the higher remission rate compared to our one-third reflects better treatment outcome.

In original publications II and III, categorisation of remission relies solely on the severity of symptom requirements. In original publication IV and in the additional analyses for the thesis, an attempt was made to fulfil both the severity and duration requirements of the remission criteria proposed by Andreasen *et al.* (2005). For this analysis, I checked that the subjects considered as remitted according to the symptom severity criteria had not been hospitalised during the past 6 months and had reported no psychotic symptoms in the SCS or SCID-interview (assessment of symptoms

during the past month). Of the subjects considered remitted by the PANSS symptom criteria, two had been hospitalised during the past 6 months and they were thus considered not-remitted in the original publication IV and in the additional analysis for the thesis.

From a researcher's perspective, it is wonderful to have such unequivocal and easily assessable criteria for remission, which is considered an important outcome measure both in measuring treatment response and as an essential step on the road to recovery in schizophrenia. The research community still lacks analogical criteria for other important outcomes, such as functional remission and recovery, even though attempts to create these have been made in recent years (e.g. Faerden *et al.* 2008, Llorca *et al.* 2009, Barak *et al.* 2010).

8.4.2 Vocational outcome

In original publication III, the vocational status was assessed using national registers and the information was summarised into two dichotomised variables: 1) not on disability pension in year 2000 vs. on disability pension, and 2) working at least 50% of time during 2000 vs. working less. In original publication IV, vocational outcome was defined as working at least 25% of time during the past year versus working less or not working. The type of work was not specified, i.e. some of it was not competitive but of a supportive nature. The information was gathered from the Strauss-Carpenter Outcome Scale, which is one of the questionnaires completed at the follow-up interview. Register information could not be used for this variable as it was not available concerning the last years of follow-up. Questions can be raised as to the reliability of the SCS as well as the implication of studying vocational outcome on the whole. The reason it was studied so extensively in this doctoral thesis was because of its significance for both the public economy and, above all, human wellbeing. This being said, it is also critical to take into account the multifaceted nature of vocational outcome in a disorder such as schizophrenia. One can ask what the possible reasons are for a person suffering from schizophrenia to be unemployed in follow-up. Warner (2004) showed that social recovery is clearly dependent on the overall employment rate among the target population; thus, the national unemployment rate needs to be taken into account. The high rates of unemployment in the society are likely to keep most of the patients with schizophrenia out from the job market despite their abilities to work. The unemployment rate in Finland was 6.4–8.4% during the years 2008–2010 when the follow-up study took place (Statistics

Finland). This general unemployment rate does not explain the low activity in work life among the individuals with schizophrenia.

There are signs that the employment rate among subjects with schizophrenia has, on the whole, decreased in recent decades in Finland (Jääskeläinen *et al.* 2010). One factor definitely affecting this is the present-day demanding work environment with no "easy jobs" available any longer. A worker needs to cope in vast social networks and handle stress, busy schedules, deadlines, conflicts and insecurity. Subjects with impairments in social skills or neurocognition are highly disadvantaged in the modern work environment, and experience difficulties and discrimination in receiving and maintaining work (Thornicroft *et al.* 2009).

Subjects with schizophrenia are often on a disability pension. Even though it is sometimes used as an indicator of occupational outcome, disability pension seems not to be a reliable measure of occupational capacity. In the NFBC 1966, 44% of the schizophrenia subjects were not on disability pension at the age of 34, but only 20% were working at least half of the days during the last two years of the follow-up (Miettunen *et al.* 2007). In Finnish studies the rate of pensioning among individuals with schizophrenia varies according to study decades, ranging from 40–68% in older cohorts to 86–94% in younger cohorts. These increasing numbers may reflect the changes in the social security system in Finland since the 1970s, which have made it easier for subjects with chronic incapacitating disorders to receive pension. (Jääskeläinen *et al.* 2010). According to a Finnish general population study, approximately 14% of individuals with schizophrenic psychoses (schizophrenia and other non-affective psychosis) were employed and 74% were on pension, most on disability pension (Perälä *et al.* 2008). Receiving social benefits has been shown to affect occupational outcome negatively. Thus, it is not surprising that with the higher rate of pensioning there come lower rates of employment.

As social security systems vary between countries, between-country comparisons of disability pension rates are difficult to make. In a register-based study of first episode schizophrenia subjects in Finland, the median number of days from the onset of first hospitalisation to disability pension for schizophrenia was 370 days. Being awarded a disability pension was associated with decreased mortality and other beneficial factors in schizophrenia, possibly because individuals on pension no longer have to make an effort to cope at work and can, instead, focus on managing the mental disorder. (Kiviniemi *et al.* 2011).

8.4.3 Recovery

Recovery from schizophrenia is possible, albeit still relatively rare. It is a very challenging issue to investigate, as a relapse can occur many years after the initial episode has subsided. Therefore, if a definite recovery rate was to be determined, subjects with schizophrenia should be thoroughly evaluated at regular intervals throughout their entire lives. This would understandably be an extremely time- and money-consuming task and, no matter how sophisticated the study design, would inevitably include many potential factors of bias, the effect of attrition being among the most important. Therefore, investigators have mostly reported recovery estimates based on a duration of recovery of between two to five years.

8.4.4 Hospitalisations

Hospitalisations have been one of the most studied indicators of outcome in schizophrenia research. This is, however, a complicated measure in many ways and it can at best be seen as a surrogate measure of the severity of illness, indicating a relapse and exacerbations of positive symptoms. It might, however, also reflect service utilisation, and it is largely determined by the number of available hospital beds, in which large differences exist between different countries and even regionally within countries. The number of hospital treatments can also, to some extent, depend on the treatment policy selected and it is not necessarily closely related to changes in the clinical status of the patients (Salokangas 1985). Trying to keep hospital stays as short as possible means that the actual number of hospital treatment days might not correspond solely to the clinical state of the patient.

Finland experienced one of the world´s most rapid psychiatric deinstitutionalisation processes in the 1980s. A large study was conducted to investigate the effects of this process on schizophrenia outcomes. Discharge cohorts from 1982, 1986 and 1990 were studied and followed up for three years. Residential outpatient care became more frequent with every cohort but the number of readmissions was found to increase as well. Patients discharged into the community in the later cohort had more severe symptoms and received more psychotropic drugs than those discharged in the early 1980s. (Salokangas & Saarinen 1998). They were also more impaired in terms of social functioning (Honkonen et al. 1999).

Despite the cut down on hospital beds, the proportions of hospitalisations seem to have been rather stable from the 1980s to 2000s ranging from 10% to 13% of the follow-up period (Salokangas *et al.* 1991, 2000, 2009). In more recent years, there has

been a 33% decline in hospital treatment days and 31% decline in hospital treatment periods due to schizophrenia from year 2001 to 2012, whereas outpatient visits to specialised psychiatric care due to schizophrenia have increased by 27% since 2006 (THL 2014).

8.4.5 Symptomatology

Symptomatology in schizophrenia is most often assessed with symptom scales such as the PANSS, which was used in this study. The first construction of the PANSS by Kay *et al.* (1987) included three factors: positive syndrome, negative syndrome and general psychopathology. Many studies have later established models with five-factors, which have better psychometric properties compared to the original three. However, as it has been unclear which of the many published five-factor models is the best, researchers continue mainly to use the original three-factor model (van der Gaag *et al.* 2006a). It should be noted that in this study the PANSS procedure differed between the two follow-ups. The actual PANSS interview took place only at the follow-up study at 43 years of age, and at the 34-year study the PANSS items were rated by the interviewers based on information obtained during the interview.

The symptoms during the first hospitalisation, on the other hand, were gathered retrospectively from medical records using the OPCRIT (McGuffin *et al.* 1991). Although OPCRIT is a commonly used method, it is possible that some information related to the variables has not been presented well enough in some hospital notes. It is, however, unlikely that there were incorrect positive recordings. This study found no strong correlations between symptom occurrences between the follow-up points. This could relate to the fluctuating nature of symptoms in schizophrenia, but also to the use of differently categorised symptoms.

8.5 Other important aspects of recovery and other outcomes in schizophrenia

8.5.1 Personal recovery

Beginning in the 1980s, the exclusively pessimistic view of outcome in schizophrenia began to change, as several long-term outcome studies demonstrated a much more variable illness course than previously thought, with many individuals experiencing rather good outcomes (e.g Harding *et al.* 1987a and 1987b, Harrison *et al.* 2001).

Encouraged by this evidence of hope for recovery, a growing consumer movement among people with schizophrenia begun to promote the view that people with a psychotic illness can live a productive and satisfying life (Bellack 2006) and to advocate a recovery-oriented rehabilitation environment (Andresen *et al.* 2003).

With regard to the assessment of recovery, there is a need for appropriate measures of both clinical and personal aspects of recovery (Mausbach *et al.* 2009). The "clinical recovery" assumes that schizophrenia is a physical illness and sees recovery primarily as a return to a premorbid state of health. In most cases, the clinical recovery definition is used in outcome studies of schizophrenia. The view of "personal recovery" is driven by the consumer movement and it defines recovery as an individual process leading to regaining a self-determined and meaningful life (Cavelti *et al.* 2012). Based on experimental accounts of recovery by people with schizophrenia, recovery is identified as an active process with four key elements: 1) finding hope, 2) re-establishment of identity, 3) finding meaning in life, and 4) taking responsibility for recovery (Andresen *et al.* 2003). Perception of personal recovery is very important, and it associates with a better quality of life, even in the presence of substantial psychotic symptoms (Kukla *et al.* 2014).

In the survey conducted by the Schizophrenia Commission, people with schizophrenia highlighted the following factors as important for recovery: support from family, stable housing, self-management strategies, support from friends, and help finding or keeping a job (Schizophrenia Commission 2012).

8.5.2 Somatic health aspects

Even though some improvements have been achieved concerning the mental health aspects of schizophrenia, there are still major challenges to be addressed in both mental and somatic health issues. According to the Australian survey, 58% of subjects with schizophrenia had metabolic syndrome and 86% had a low or very low level of physical activity. Substance abuse was frequent, as 67% were currently smoking, and the rates for lifetime alcohol, cannabis or other drug abuse/dependence were 51%, 54% and 32% respectively (Morgan *et al*. 2014b). In the NFBC 1966, 7.7% of individuals with a diagnosis of schizophrenia had died from causes other than suicide before the end of year 2011, whereas in the whole cohort this rate was significantly lower, 2.5%. These facts highlight the urgent need for physical health interventions. In addition to often having unhealthy lifestyles, individuals with psychotic disorders might also encounter discrimination in somatic health care, which could explain some variance in excess mortality and morbidity. For example a large Finnish register study

showed poor access to coronary care among persons with psychotic disorders (Manderbacka *et al.* 2012).

8.5.3 Suicide

Suicide can rightly be considered the worst outcome in schizophrenia. It has been studied in the NFBC 1966 (e.g. Alaräisänen *et al.* 2006, Riala *et al.* 2007, Alaräisänen *et al.* 2009) but was not studied as an outcome of schizophrenia in this thesis. A large Australian national survey in 2010 showed that 43% of subjects with schizophrenia had attempted suicide at some point in their life, and the figure was even higher for schizoaffective disorder (61%). One fifth of the subjects with schizophrenia and one third of subjects with schizoaffective disorder had attempted suicide over the past year. (Morgan *et al.* 2014b). In the NFBC 1966, 6.6% of subjects with schizophrenia had committed suicide before the end of year 2011. The suicide rate in the whole cohort was 0.7%. In order to further improve outcomes among individuals with schizophrenia, this sad and irrevocable outcome deserves ongoing research efforts.

8.5.4 Stigma

The term stigma refers to problems of knowledge (ignorance), attitudes (prejudice) and behavior (discrimination) (Thornicroft *et al.* 2007). Stigma and self-stigma related to serious mental illnesses such as schizophrenia are considered as barriers to recovery from mental illness (Wahl 2012). Thus, the diagnosis of schizophrenia as such can for many be as debilitating as the symptoms associated with it (Brabban *et al.* 2013). Mental health users and health care professionals around the world have started calling for a change of name, as "schizophrenia" is considered as stigmatizing and harmful. Nevertheless, renaming schizophrenia will not be useful unless accompanied by changes in legislation, services and, above all, the education of professionals and the public. In some Asian countries, the name schizophrenia has been officially replaced, in Japan to "integration dysregulation syndrome", whereas in European and North American countries the debate is still open. (Lasalvia *et al.* 2015). What really needs to be changed is the public perception of schizophrenia, rather than the name itself (Brabban *et al.* 2013).

Stigma can lead to conscious or unintentional discrimination. A recent Swedish study found that about half of the patients with schizophrenia experienced discrimination by their families, in intimate relationships, and regarding employment. Most patients (88%) wanted to conceal their mental health problems from others.

Anticipated discrimination resulted in avoidance of close personal relationships and isolation from work and studies. (Brain *et al.* 2014).

Individuals with schizophrenia encounter discrimination also from medical staff when seeking medical attention for physical or mental health issues (Manderbacka *et al.* 2012, Brain *et al.* 2014, Welch *et al.* 2014). Despite the accumulation of longitudinal data suggesting that for a substantial part of the patients the outcome in schizophrenia is good and recovery is even possible, many mental health professionals still retain their traditionally narrow and negative view of outcome in schizophrenia. This has been called ‘‘clinician’s illusion’’, a notion introduced by Cohen and Cohen (1984) suggesting that mental health professionals only seeing and treating patients with poorer outcomes, as these understandably accumulate in clinical care, are prone to pessimistic attitudes concerning prognosis.

8.6 Strengths and limitations

8.6.1 Meta-analysis

Meta-analyses in general have been criticised for being prone to publication bias as well as other biases inherent in the primary studies, and for ignoring single important studies. Criticism has also been directed against meta-analyses for statistically combining the effect sizes of different samples and outcomes. However, a well-conducted meta-analysis has the ability to make robust, generalisable conclusions exceeding those usually possible from a single study and, thus, provide the closest estimate of the true effect size.

The studies in this meta-analysis included a wide variety of methods and results, and this heterogeneity made pooling of the results challenging. Instead of the mean, the median recovery rate was used to pool the original studies. The median recovery rate was quite stable, as indicated also by the results of the meta-regression.

The strength of this review was the comprehensive search strategy with no language restrictions attached. However, as the search language was English, some older publications may have been missed. It should be noted that the inclusion criteria resulted in the exclusion of studies that may still be informative with respect to recovery (e.g. treatment studies).

The primary aim of this meta-analysis was to clarify the recovery rate in schizophrenia, and thus studies investigating recovery were searched. Some study characteristics that could possibly have an effect on recovery rate were studied in this

meta-analysis. Among those, gender was the only one that could be directly analysed, i.e. the comparison included original studies that specifically looked for gender differences concerning recovery. Other variables affecting the recovery rate were investigated indirectly, i.e. they were analysed more as potential confounders of the recovery rate.

8.6.2 The NFBC 1966 studies

The NFBC 1966 is a unique sample providing information on its members approximately twenty years before and after the onset of illness. As the sample is population-based and the study setting naturalistic, these findings are generalisable to the general population and can be made use of in clinical practice. The recovery, course of illness and predictors of outcome in schizophrenia have been scarcely studied in a birth cohort setting, and especially longitudinal brain imaging and cognition studies in population-based samples are rare, which make these results valuable.

An important strength is the possibility to control for some potentially important variables, such as the long-term use of antipsychotic medication. In addition, attrition analyses have been conducted, which is critically important in such long-term follow-up studies. Non-participants generally had more severe illness regarding the first follow-up, whereas subjects participating at both baseline and follow-up did not differ statistically significantly from subjects participating only at baseline and not returning for follow-up investigations (III, IV).

The outcome measures were received from personal interviews, questionnaires or national registers, which have been found to be reliable and suitable for scientific research (Miettunen *et al.* 2011). All these sources of information, albeit valuable and partly complementary, have some limitations. When using register information, the amount of missing information is low, whereas the content may be relatively superficial and scarce. Hospital notes, on the other hand, may vary in quality and content, whereas interview data may contain recall bias.

When investigating brain morphology (III), it should be pointed out that the cohort members are still relatively young, and different associations between brain morphology and course of illness might emerge later on. The method employed in this study in order to produce segmented brain tissue maps does not conserve the volume of the voxel occupied by a specific tissue. Therefore the voxel intensities represent grey matter density, or concentration. In recognition of this, comparisons with other studies that have used different techniques that account for volume changes

in grey matter after processing, should be interpreted with these methodological differences in mind. It should also be pointed out that the MRI techniques have improved since this study was conducted and some studies are now using equipment with much higher resolution.

In original publication IV addressing neurocognition, identical neurocognitive tests at two-time points were performed so as to maximise retest comparability. Of the three test employed, CVLT has often been used in schizophrenia research and its psychometric properties have been shown to be very good (Spreen & Strauss 1998). AIM and VOLT, on the other hand, are less known tests but they have been shown to generate scores that are sensitive to the presence of schizophrenia and show differential deficits with high levels of significance (Glahn *et al.* 1997, Glahn *et al.* 2000, Gur *et al.* 2001). However, the selection of tests was very limited and only a few cognitive domains were assessed. Thus, the overall neurocognition could not be evaluated. AIM, the test of executive functions, differs from the more common card sorting/vigilance tests used in previous studies, which could have contributed to the lack of findings. Unlike the other tests employed, AIM did not correlate significantly with other tests, or even with subsequent AIM performance at follow-up. Also, it seemed to be a rather difficult test as 20% of the participants with schizophrenia scored below chance (less than 50%) at the age of 43.

One general limitation concerning this study is the relatively small sample size, which may have resulted in a lack of statistical power, and in not being able to detect all the true positive associations in the data. Also, as the number of analyses conducted in this thesis is rather large, chance findings are possible.

With a birth cohort sample, it is possible to study subjects with schizophrenia who are all of the same age, which is a strength in many ways. However, the duration of illness varies as individuals have been diagnosed at different ages, and in a birth cohort setting, duration of illness cannot be separated from onset age. This raises questions about the role of onset age as a confounder. Early and late onset schizophrenia are different in many respects and can to some extent even be considered as different disease entities. By simply adjusting for onset age, this difference might be overlooked.

9 Conclusions

9.1 Main conclusions

This doctoral thesis provided the scientific community with new information on the outcomes on schizophrenia. Adding value to its findings are the epidemiologically sound, unselected population and the long follow-up period up to 30 years. For the first time, the recovery rate was reliably assessed with a meta-analysis, showing that approximately 13.5% of individuals with schizophrenia recover. Also, this study supported prior knowledge that the rate of recovery has not increased despite the modern treatment approach.

A novel finding was the association between suicidal ideations at first hospitalisations and later hospital treatments. This study strengthens prior observations of the predictive importance of early age at illness onset, insidious mode of onset and marital status on later outcomes, and confirms that prior outcome is often the best predictor of subsequent outcome. Remission status and neurocognitive functioning were found to be relatively stable in midlife schizophrenia. Defects in some brain areas were confirmed to associate with outcomes in schizophrenia. The role of neurocognitive functioning in the domains of verbal and visual memory in predicting functional outcome also found supporting evidence in this study. However, a substantial proportion of the variance in outcomes were not explained by the variables investigated in this thesis.

9.2 Future research

Despite having been a major research focus of psychiatric research for decades, a large proportion of the variance in presentation of schizophrenic illness still remains to be explained, and a full understanding of predictors of clinical heterogeneity in schizophrenia remains to be realised. The knowledge of determinant factors and predictors of different outcomes would allow mental health professionals to plan appropriate interventions. Therefore the influence of other factors warrants further investigation. According to this doctoral thesis, age of onset is among the most important factors affecting the outcome in individuals with schizophrenia. This observation leads to the conclusion that in order to improve the outcome in schizophrenia, we need a greater insight into what determines the age of onset and how, if possible, to affect those determinants. This could very well be studied in

samples such as the NFBC 1966, which offers a vast and reliable amount of information on the individuals approximately 20 years before and after the onset of illness. Thus, factors potentially affecting the age of onset could be explored, and these factors, if found modifiable, could possibly be targeted with planned interventions.

Age of onset has been studied in the NFBC 1966 by Luoma *et al.* (2008). They found associations between the age of onset and the clinical picture of schizophrenia. Inappropriate affect, positive thought disorder and deterioration from the premorbid level of function associated with very early-onset schizophrenia, while slowed activity and dysphoria related to later onset. These findings, and also the results obtained in this doctoral thesis, confirm the impression that early- and later onset schizophrenia might actually represent phenomenologically and even etiologically different disease entities.

A few authors have studied factors related to the age of onset. Verdoux *et al.* (1997) studied, using a meta-analysis, whether there was an association between the age of onset and birth complications. They found that, indeed, individuals with an early onset were much more likely to have experienced complications at birth compared to individuals with later onset, and they concluded that this was evidence of neurodevelopmental impairment involved in the pathophysiology of early-onset schizophrenia. Individuals with a family history of psychosis have also been shown to experience an earlier onset (Suvisaari *et al.* 1998, Esterberg *et al.* 2010).

More research is also needed into other potentially important predictors of outcome that may be modifiable with the help of interventions. Negative symptoms and cognitive functioning represent features of illness that directly affect current functioning and they are currently being investigated as targets for novel medications and remediation strategies. These factors have been and are being investigated in the NFBC 1966.

Another important aspect of schizophrenic illness that could be studied in more detail in the NFBC 1966 is the effect of therapeutic interventions on long-term outcomes in schizophrenia. There is a birth cohort of subjects born in Northern Finland in 1986, similar to the NFBC 1966, and comparing these two cohorts could offer important insights into the development of outcome in schizophrenia.

9.3 Clinical implications of outcome studies

Finding out more about the risk factors, course and outcome of schizophrenia will help develop better treatments and ways of perhaps even preventing future relapses.

Identifying variables that can be used to predict individual outcomes is important in clinical practice as people with schizophrenia and their families want to gain knowledge about the prognosis and future course of the illness. Determining specific predictors of outcome would allow more specific and individual treatments to be developed. As schizophrenia is a fairly common disease with an undesirable prognosis, achieving even a slight improvement in its outcome by using more specific interventions would be significant.

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