

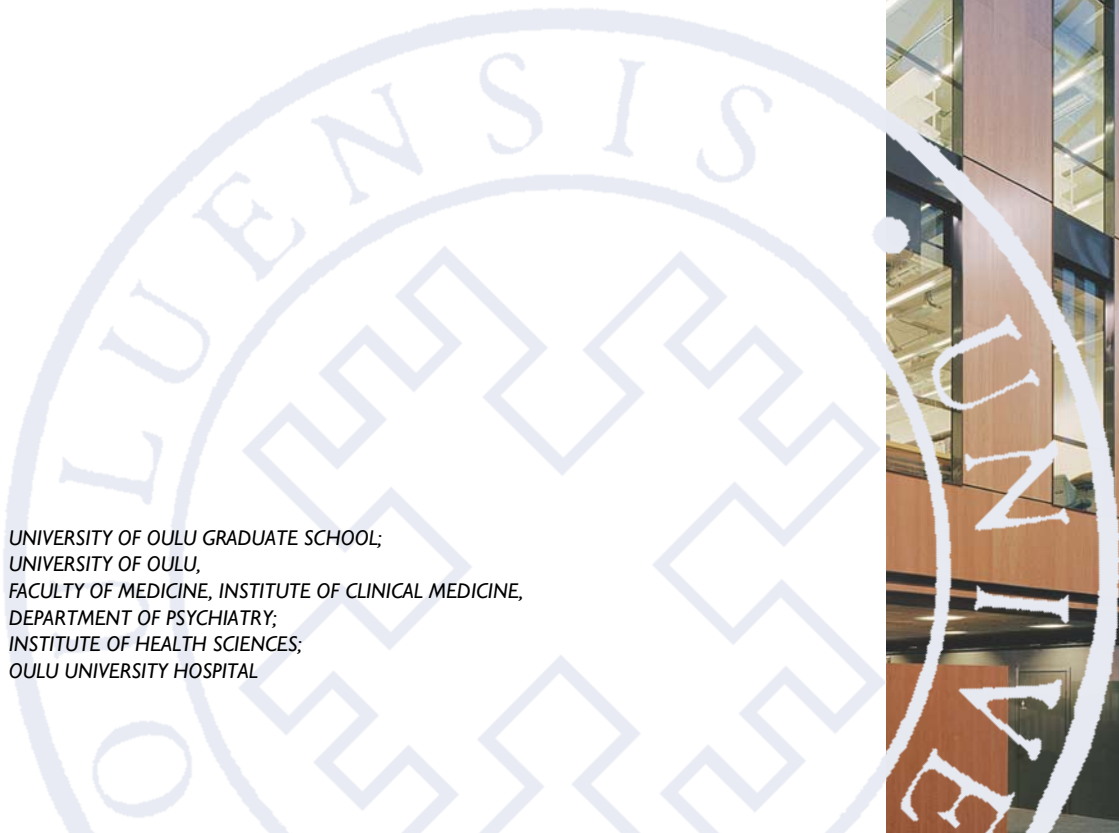
Matti Penttilä

DURATION OF UNTREATED PSYCHOSIS

*ASSOCIATION WITH CLINICAL AND SOCIAL
OUTCOMES AND BRAIN MORPHOLOGY
IN SCHIZOPHRENIA*

UNIVERSITY OF OULU GRADUATE SCHOOL;
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MATTI PENTTILÄ

**DURATION OF UNTREATED
PSYCHOSIS**

Association with clinical and social outcomes and brain
morphology in schizophrenia

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Abstract

The duration of untreated psychosis (DUP) and its association with the course of illness in schizophrenia has been widely addressed, but the conclusions still remain essentially unclear. The studies with unselected samples and longitudinal data are few and needed. The aim of this dissertation was to study DUP and the long-term course of illness in schizophrenia in a meta-analysis and in the Northern Finland 1966 Birth Cohort (NFBC 1966).

A meta-analysis of 31 original studies on the long-term association between DUP and clinical and social outcomes showed that long DUP had a small but statistically significant association with poor symptomatic, social, and global outcomes. However, there was no significant correlation between DUP and use of treatment, employment, and quality of life.

In the NFBC 1966, the associations between DUP and the outcomes (n=89) were assessed with several measurements of mental and psychical state, treatment factors, education, and ability to work. In the short-term outcome, long DUP was associated with longer first hospitalization and increased risk of re-hospitalization. In the long-term, long DUP was associated only with a decreased rate of disability pension. When the association between DUP and brain structures using magnetic resonance imaging (MRI) was analyzed (n=46), long DUP correlated with decreased gray-matter density in the right hippocampus. DUP may be a modest marker of a more severe clinical phenotype regarding early outcome, but in the NFBC 1966, longer DUP seems to associate with better clinical and occupational outcomes.

The relatively modest effect of DUP on outcomes indicates that shortening DUP may have positive effects on the long-term clinical course. However, it is unlikely that early intervention alone could significantly improve the overall long-term outcome of schizophrenia. Early detection of psychosis is one of the possibilities to achieve the improvement, especially in the short-term outcome of schizophrenia.

Keywords: birth cohort, brain morphology, course of illness, duration of untreated psychosis, meta-analysis, MRI, outcome, prognosis, schizophrenia

Penttilä, Matti, Hoitamattoman psykoosin kesto. Yhteys kliiniseen ja sosiaaliseen ennusteeseen ja aivojen rakenteeseen skitsofreniassa

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Tiivistelmä

Hoitamattoman psykoosin kestoja ja sen yhteyttä skitsofrenian taudinkulkuun on tutkittu laajasti, mutta johtopäätökset asiasta ovat jääneet olennaisilta osilta epävarmoiksi. Aihetta koskevia valikoitumattomien aineistojen pitkittäisseurantoja on olemassa vain vähän. Tämän osajulkaisuväitöskirjan tavoitteena oli tutkia hoitamattoman psykoosin keston ja skitsofrenian taudinkulun pitkäaikaista yhteyttä meta-analyysin sekä Pohjois-Suomen vuoden 1966 syntymäkohorttiaineiston avulla.

Meta-analyysi hoitamattoman psykoosin keston ja kliinisen ja sosiaalisen ennusteen välillä osoitti, että pidentynyt hoitamattomuus on tilastollisesti merkitsevästi yhteydessä vakavampiin oireisiin ja huonompaan sosiaaliseen toimintakykyyn sekä kokonaisennusteeseen pitkäaikaisseurannoissa. Merkitsevää yhteyttä ei ollut hoitamattoman psykoosin keston ja sairaalahoidon määrän, työllistymisen tai elämänlaadun välillä.

Pohjois-Suomen vuoden 1966 syntymäkohortissa tutkittiin hoitamattoman psykoosin yhteyttä taudinkulkuun ja ennusteeseen (n=89) ja aivojen rakenteeseen (n=46). Kahden ensimmäisen vuoden seurannassa pitkä hoitamattomuus oli yhteydessä pidempään ensimmäiseen sairaalahoittoon ja uuden sairaalahoidon kohonneeseen riskiin. Pitkäaikaisseurannassa pidentynyt hoitamattomuus oli merkitsevästi yhteydessä vähäisempään työkyvyttömyyseläkkeellä olemiseen. Kun aivojen rakennetta tutkittiin magneettikuvantamisen (MRI) avulla, löytyi yhteys pidentyneen hoitamattomuuden ja harmaan aineen pienemmän tiheyden välillä oikean hippokampuksen alueella.

Hoitamattoman psykoosin keston tilastollisesti merkitsevä yhteys taudin eri ennusteisiin viittaa siihen, että psykoosin varhaisella tunnistamisella voi olla myönteisiä vaikutuksia. Muut mahdollisuudet parantaa skitsofrenian pitkäaikaissennustetta lienevät keskeisiä ja voivat tehostaa varhaisen tunnistamisen vaikutuksia.

Asiasanat: ennuste, hoitamattoman psykoosin kesto, kuvantaminen, meta-analyysi, skitsofrenia, syntymäkohortti

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I dedicate this work to my dear friend and to the memory of his late wife. Her tragic death could not be prevented by psychiatry. The burden of mental disorder is too often too much to bear. By studying the factors that lead to these disorders and their different outcomes, it is hoped that it will be possible to have more success in decreasing the burden of psychiatric disorders.

Cambridge, April 2013

Matti Penttilä

Abbreviations

AAL	Automated Anatomical Labelling
APA	American Psychiatric Association
ARMS	At Risk Mental State
BAMM	Brain Activation and Morphological Mapping
CBT	Cognitive Behavioral Therapy
CGI	Clinical Global Impression
CI	Confidence Interval
CSF	Cerebrospinal fluid
D2	D2 subtype of dopamine receptor
DIPT	Delay in intensive psychosocial treatment
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders. 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders. 4th edition
DUI	Duration of untreated illness
DUP	Duration of untreated psychosis
FHDR	Finnish Hospital Discharge Register
GAS	Global Assessment Scale
ICD-10	International Statistical Classification of Diseases, Injuries and Causes of Death, 10th edition
ICV	Intracranial volume
MRI	Magnetic resonance imaging
NFBC 1966	Northern Finland 1966 Birth Cohort
OPCRIT	Operational Criteria Checklist for Psychotic Illness
PANSS	Positive and Negative Syndrome Scale
ROI	Region of Interest
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SOFAS	Social and Occupational Functioning Scale
UHR	Ultra-high risk of psychosis
VBM	Voxel-based morphometry
WHO	World Health Organization

List of original publications

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

- I Penttilä M, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. The association between duration of untreated psychosis (DUP) and long-term outcome in schizophrenia. A systematic review and meta-analysis. Manuscript.
- II Penttilä M, Miettunen J, Koponen H, Kyllönen M, Vejjola J, Isohanni M, Jääskeläinen E (2013) Association between duration of untreated psychosis and short- and long-term outcome in schizophrenia within the Northern Finland 1966 Birth Cohort. *Schizophrenia Research* 143:3–10.
- III Penttilä M, Jääskeläinen E, Haapea M, Tanskanen P, Vejjola J, Ridler K, Murray GK, Barnes A, Jones PB, Isohanni M, Koponen H, Miettunen J (2010) Association between duration of untreated psychosis and brain morphology in schizophrenia within the Northern Finland 1966 Birth Cohort. *Schizophrenia Research* 123:145–152.

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1 Introduction

Psychosis is defined as a state of mind where a person loses their sense of reality. It is usually a very severe form of psychiatric disorder. Psychotic symptoms include, for example, hallucinations, delusions, and disorganization. Schizophrenia is a disorder in which psychotic symptoms exist for a long period of time. Schizophrenic psychoses are some of the most disabling disorders (WHO 2004) and schizophrenia is diagnosed in an estimated 0.7% of the population worldwide during their lifetime (Saha *et al.* 2005), but estimates of the incidence of schizophrenia in Finland have been bit higher (Perälä *et al.* 2007, 2008).

The prognosis of schizophrenia is heterogeneous (Jobe & Harrow 2005) and depends on the criteria of the outcome (Hegarty *et al.* 1994, Lauronen *et al.* 2007). A systematic review reveals that about 40% of the patients are doing well, 35% moderately well, and 27% poorly after the first episode of psychosis (Menezes *et al.* 2006). A recent meta-analysis estimated that 13.5% of subjects diagnosed with schizophrenia recover, but this number has not increased during the development of treatments (Jääskeläinen *et al.* in press). Comparing affective psychoses such as psychotic mania and schizoaffective disorder to schizophrenia, the treatment outcome of schizophrenia is more unfavorable (Harrow *et al.* 2000, Benabarre *et al.* 2001).

Treatment of schizophrenia has changed remarkably in the last century. The innovation of typical antipsychotics in the latter half of the 20th century made it possible to effectively treat positive symptoms of psychosis. Before that, treatment was based on different methods such as insulin shocks and electroconvulsive therapy. Electroconvulsive therapy is also used nowadays for psychosis with severe symptoms, when treatment response is not achieved by using medication (Sommer *et al.* 2012, Zervas *et al.* 2012). Atypical antipsychotics have become the choice for first-line treatment of psychosis widely, due to their relatively better tolerance of long-term use compared to typical antipsychotics. Psychosocial support and treatment also has a major role in the treatment of schizophrenia and psychotherapies are being studied, especially in the treatment of first-episode psychosis and possible prevention of psychosis.

The previous and current treatment options have not come without unwanted effects. Even the latest atypical antipsychotics can have severe side-effects such as extrapyramidal symptoms, metabolic disorders like diabetes, and high serum cholesterol, which may be one cause of shortened life-expectancy in

schizophrenia. With antipsychotics, it is possible to achieve remission in positive symptoms, but they do not have much effect on negative symptoms of schizophrenia or on the decline of the cognitive functioning that is common in schizophrenia (Tandon 2011).

Schizophrenia has been studied intensively, but the definitive cause of it is still unknown, although it is thought that biological and psychosocial factors both play a part in the etiology and course of the illness. The development of technology has provided new methods for schizophrenia research. Magnetic resonance imaging (MRI) has given new information on the changes in structure and functioning of the brains of persons diagnosed with schizophrenia. Many other factors from pregnancy to early adulthood, when the onset of illness most commonly happens, have also been linked to schizophrenia, but it is generally thought that schizophrenia is a complex psychiatric disorder that cannot be explained by one or two, but by several factors. It has even been suggested that diagnosis of schizophrenia may include many different disorders that have their own etiological causes and different prognostic features.

One of the aspects that make treatment of schizophrenia very challenging is the part of the illness that makes a person impaired in recognizing that they have the illness and the symptoms that are part of the illness. This is called as poor insight and it is often prominent at the very beginning of the disease, and it may be one reason for the common delay in treatment. A person may have psychotic symptoms for a long time before contacting the psychiatric services, with the mean delay of treatment estimated to be 1-2 years (Marshall *et al.* 2005). The period between the onset of psychosis and the beginning of treatment is called *duration of untreated psychosis (DUP)*, and it has been studied widely as one of the potentially modifiable predictors of outcome in schizophrenia (Marshall *et al.* 2005, Perkins *et al.* 2005), and it is the focus and main concept, exposure, and predictor studied in this thesis.

This complex and severe disorder of schizophrenia needs to be studied not only in clinical samples, where subjects are detected and followed up based on the need for treatment, but also in epidemiologically sound and longitudinal samples. The Northern Finland 1966 Birth Cohort (NFBC 1966) is one of the first samples to have followed subjects from the prenatal period to date, providing information approximately from the twenty years before and after illness onset. Thus, the NFBC 1966 provides an opportunity to study factors related to early phases of schizophrenia, such as DUP.

2 Schizophrenia

Schizophrenia usually starts in early adulthood, lasting for a long period of time or even for life. The severe and complex symptoms of the disorder affect the person's life remarkably and cause disability in social and occupational life. Schizophrenia is an illness with various negative characteristics and WHO estimated in 2004 that schizophrenia is one of the leading causes of disability worldwide (WHO 2004).

The difference in standardized mortality ratio for all causes of death between subjects diagnosed with schizophrenia and controls has been stated to have increased over recent decades, although in the Nordic countries, the gap has been shown to be modestly decreasing (Wahlbeck *et al.* 2011).

Schizophrenia causes both direct and indirect costs, with total costs per person with the diagnosis estimated to be the highest among psychiatric disorders, although the direct costs of psychotic disorders have decreased between the estimates of 2004 and 2010 (Gustavsson *et al.* 2011). The total costs of psychotic disorders were estimated to be high in Europe (~94 billion) and in Finland (~1 billion) and close to total costs of mood disorders, despite the higher prevalence of the latter (Gustavsson *et al.* 2011).

2.1 The definition of schizophrenia

The definition of schizophrenia is based on the term dementia praecox, defined by Emil Kraepelin (1909). According to Kraepelin's definition, dementia praecox was a disorder that begins in early life and leads to chronicity. In Kraepelin's definition, hallucinations, delusions, stereotypes, thought disorder, negativism, and blunted affect were the main characteristics of the disorder. This definition simplified the diagnostics of psychosis in principle by combining the former heterogeneous group of three main categories (delusions, catatonia, and hallucinations) of non-affective psychosis as sub-types under the definition of "dementia praecox".

Eugen Bleuler (1911) was the first to use the term schizophrenia. The main difference compared to Kraepelin's definition was the thought that cognitive impairment shown as, for example, thought disorder and loosening of associations and attention was the primary symptom of schizophrenia. Bleuler also presented the thought of a continuum between schizophrenia and manic-depressive illness,

stating that affective symptoms could exist in schizophrenia as well. Bleuler proposed that schizophrenia was a disorder with a possibility of recovery, as has been later demonstrated (Bleuler 1978, Modestin *et al.* 2003).

2.2 Symptoms of schizophrenia

Current opinion of *the symptoms of schizophrenia* is that instead of three categories of positive, negative, and general symptoms, the symptoms are nowadays classified according to a five-factor model. These factors include factors of positive and negative symptoms, and factors of disorganization, excitement, and depression (van der Gaag *et al.* 2006, Wallwork *et al.* 2012).

Positive symptoms include hallucinations and delusions. Hallucinations in schizophrenia are usually hearing voices that are distractive and often commentary. More seldom, hallucinations are of other senses, such as seeing objects or beings that are not real or smelling things that others can't notice. Delusions are often thoughts of being followed or persecution, with other types of delusions also possible. Negative symptoms of schizophrenia include avolition, blunted affect, poverty of speech, asociality, and anhedonia.

The characteristic decline of cognitive functioning in schizophrenia, such as impairment of memory and speed of processing, are shown to correlate not only with disorganization but also with positive and depressive factors indicating challenges in measuring cognitive functioning using these models (Rodriquez-Jimenez *et al.* 2013).

2.3 Diagnosis of schizophrenia

Diagnosis of schizophrenia is currently based on diagnostic criteria that may vary regionally. The two most commonly used criteria are the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organization's (WHO) International Classification of Diseases and Causes of Death (ICD). These criteria are mainly similar, but a major difference is the difference in the requirement for the duration of symptoms. DSM-IV (American Psychiatric Association 1994) states that symptoms must exist for at least six months or longer, whereas ICD-10 (WHO 1992) considers symptoms definitive for schizophrenia after a duration of one month.

The previous version of DSM (DSM-III-R) required the existence of either bizarre delusions or prominent hallucinations, or at least two other positive or

negative symptoms of only 1 week or more, for diagnosis of schizophrenia, with a requirement of 6 months total duration of illness. DSM-III-R criteria did not separate as clearly into positive and negative symptoms as DSM-IV. Criteria of incoherence or loosening of associations were changed in DSM-IV under the descriptions of disorganized speech and behavior. Schizophrenia was categorized in DSM-III-R into five categories based on the duration of symptoms: subchronic (at least 6 months and less than 2 years), chronic (more than 2 years), subchronic with acute exacerbation, chronic with acute exacerbation, and in remission. These categories were left out of DSM-IV (American Psychiatric Association 1987).

In the near future, the diagnostic criteria of schizophrenia seem set to change, and proposals for forthcoming DSM-V also suggest that subtypes of schizophrenia are no longer used. The focus would be more on the severity of different symptoms such as delusions, hallucinations, depression, and cognition. The difference in duration criteria between DSM and ICD may also decrease in the forthcoming DSM-V and ICD-11 (WHO 2013). There will probably also be a new *attenuated psychosis syndrome* for research purposes, to make it possible to gather more systematic information on the mild psychotic symptoms that sometimes precede the onset of schizophrenia. The new definition of attenuated psychosis syndrome is one way to study the possibilities of shortening the delay of treatment in first-episode psychosis (Gaebel 2012, www.dsm5.org).

Table 1. Diagnostic criteria for schizophrenia according to DSM-IV (APA 1994).

Diagnostic criteria	Description
Characteristic symptoms	
At least one of the following:	Bizarre delusions Third-person auditory hallucinations Running commentary
OR two or more of the following:	Delusions Hallucinations Disorganized speech Grossly disorganized behavior Negative symptoms
Duration	1 month of characteristic symptoms With 6 months of social or occupational dysfunctioning
Exclusion criteria	Schizoaffective or mood disorders Direct consequence of substance use or general medical condition Pervasive developmental disorders

2.4 Epidemiology and risk factors of schizophrenia

2.4.1 Epidemiology

Estimates of the prevalence of schizophrenia have been relatively stable over the years (McGrath *et al.* 2004). The median incidence of schizophrenia has been estimated to be 15.2/100,000, the diagnosis being more common among males than females (1.4:1). The prevalence of schizophrenia has also been estimated to vary and some estimates have been made of a decrease in the incidence of schizophrenia (McGrath *et al.* 2004). Exposures related to urbanicity, economic status, and geographical location have also been associated with variations in prevalence and incidence of schizophrenia (McGrath *et al.* 2008).

One of the most interesting aspects in epidemiology of schizophrenia is the possibility to detect subgroups of the population with either higher or lower rates of schizophrenia, and therefore to study the risk factors and those factors that could decrease the risk of schizophrenia. A systematic review has indicated that the prevalence of schizophrenia is higher in migrants (1.8% with 95% confidence interval: 0.9-6.4), whereas the least developed countries had the lowest estimated prevalence of schizophrenia when compared to more developed countries (Saha *et al.* 2005). It has been presented that the incidence and prevalence of schizophrenia tends to be higher in the regions of high latitude, indicating the role of the environment or genetic pooling in the aetiology of schizophrenia (Saha *et al.* 2006, Kinney *et al.* 2009).

In Finland, there may be some differences in the prevalence of schizophrenia (Perälä *et al.* 2007, 2008). The life-time prevalence of schizophrenia in Finland was estimated as 0.87% when various sources (*e.g.* registers, case notes, and interviews) of information were used (Perälä *et al.* 2007). The highest prevalence of schizophrenia has been estimated to be in northern and eastern parts of Finland, and large geographical variation seems to be more important for the variation in the prevalence of schizophrenia than differences between urban and rural environments (Perälä *et al.* 2008). The explanations for the geographical variations in Finland remain inconclusive, but it is thought that area-related environmental factors together with socio-economical and biological (*e.g.* genetic isolates) factors may have led to an increase in prevalence (Perälä *et al.* 2008). The current estimate of the cumulative incidence of schizophrenia in the Northern Finland 1966 Birth Cohort (NFBC 1966) by the age of 44 years is 1.4% (Keskinen *et al.* 2013).

The variation in the prevalence of schizophrenia may have an effect on the length of DUP. In areas and societies where psychosis is rarer, DUP may become longer due to delayed diagnosis and treatment (Large *et al.* 2008, Chiliza *et al.* 2012). On the other hand, it is also possible that in the areas with a higher prevalence of psychosis and schizophrenia, the fear of stigma or prejudices in treatment may cause treatment delay. One could also hypothesize that in areas with a lower prevalence of psychosis, the DUP might be longer and some people with psychosis will never be diagnosed with schizophrenia, with either spontaneous recovery or death before the first contact with the psychiatric service.

2.4.2 Risk factors

Risk factors of schizophrenia have been studied widely and the risk factors could be divided into genetic and environmental factors. As the mapping of the human genome has been progressing, there have been hopes of finding definite disruption in the *genome for schizophrenia*. Studies of genetic schizophrenia have so far been inconclusive, partly because psychiatric diagnoses overlap in genetics (Lichtenstein *et al.* 2009). The mostly found risk-genes for schizophrenia include DISC1 (Tomppo *et al.* 2009) and DTNBP1 (Gill *et al.* 2009). Studies of some candidate genes of schizophrenia, such as COMT and its genotype, have shown inconsistent results (Okochi *et al.* 2009).

Genome-wide association studies (GWAS) have made it possible to analyze single nucleotide polymorphisms (SNP) and copy number variants (CNV) in schizophrenia. A recent meta-analysis found correlation with five SNPs (in BCL9 and C9orf5) and negative symptoms in schizophrenia (Xu *et al.* 2013).

One of the CNVs, deletion in 22q11.2, which is known to cause velo-cardio-facial syndrome, correlates with increased risk of schizophrenia (Kobrynski & Sullivan 2007, Gill *et al.* 2009). Some rare CNVs, such as deletions in chromosome 1q21.1 and 15q13.3, correlate with multiplied risk of schizophrenia (International Schizophrenia Consortium 2008, Stefansson *et al.* 2008, McGarthy *et al.* 2009).

Human leukocyte antigen (HLA) alleles, especially in the major histocompatibility complex (MHC), have been found to correlate with increased risk of schizophrenia in GWAS (International Schizophrenia Consortium 2009, Shi *et al.* 2009, Stefansson *et al.* 2009) with some alleles (DRB1*03:01 and B*08:01) also found to be protective (Irish Schizophrenia Genomics Consortium

& the Wellcome Trust Case Control Consortium 2 2012). Other genes that have been found to associate with schizophrenia in GWAS include ZNF804A (O'Donovan *et al.* 2008, International Schizophrenia Consortium 2009) and the neurogranin gene (NRGN) (Stefansson *et al.* 2009).

De novo mutations have also been associated to some extent with schizophrenia. This suggests that environmental factors have effects on the large scale of biological risk factors of schizophrenia (Rees *et al.* 2012). All in all, the gathered information on the genetics of schizophrenia has not yet provided clinical advances. The development of schizophrenia seems to be influenced by combinations of different areas of genetics (Doherty *et al.* 2012).

Environmental risk factors can be detected from pregnancy by noting the several possible confounders. Adverse events during pregnancy and delivery, infections in the central neural system during childhood, prenatal infections, and delays in development and abnormalities in early neuromotor functioning are some of the factors in very early life that have been associated with increased risk of schizophrenia in the NFBC 1966 and other studies (Jablensky *et al.* 2005, Isohanni *et al.* 2006, Brown 2008, Dalman *et al.* 2008, Clarke *et al.* 2009). There is also growing evidence of infections and autoimmune diseases in later life as risk factors of schizophrenia (Eaton *et al.* 2006, Potvin *et al.* 2008, Benros *et al.* 2011).

Childhood adversity is estimated to have a moderate effect on the development of schizophrenia when compared to healthy controls and anxiety disorders. A recent meta-analysis showed that schizophrenic subjects have fewer adverse events than subjects with dissociative disorder or post-traumatic stress disorder, and not more than people with other psychiatric disorders (Matheson *et al.* 2013).

Environmental stressors, such as social stressors and illicit drug use in adolescence or early adult life, increase the risk of psychosis for individuals with impaired neurodevelopment (Howes *et al.* 2004). Factors such as migration and ethnic minority status have been shown to correlate with increased prevalence of schizophrenia (Kirkbride *et al.* 2012), with probable mediation of chronic social adversity and discrimination (Morgan *et al.* 2010). It has also been stated that cannabis use may correlate with increased risk or earlier onset of schizophrenia (Di Forti *et al.* 2009).

Studies of the Northern Finland 1966 Birth Cohort have previously shown that unwanted pregnancy (Myhrman *et al.* 1996) and both low and high birth weight have been associated with increased risk of schizophrenia (Moilanen *et al.*

2010). Poor cognitive functioning may be associated with more probable or earlier onset of schizophrenia (Morgan *et al.* 2008), but in the NFBC 1966, excellent school marks were associated with later schizophrenia in male subjects (Isohanni *et al.* 2005).

A theoretical model of the genetic and environmental influence on the onset of schizophrenia has been described (van Os *et al.* 2010). The model is based on the idea of gene-environment interactions (GxE), for which the evidence in the field of psychiatry is still inconclusive. The model states that many risk factors, including genetics and pre- and perinatal factors, affect the neurodevelopment already before birth. Environmental risk factors, including use of cannabis, trauma, urban upbringing and minority group status, have different effects on the brain, neurocognition, and social cognition at different phases of development (van Os *et al.* 2010). The early biological risk factors were shown to be significant only for those subjects with a positive family history of psychosis in the NFBC 1966 (Keskinen *et al.* 2013).

In summary, several factors have been studied and associated with the development and onset of schizophrenia, but the exact causes and the entire aetiology of schizophrenia remain mainly unclear. What is known is that the onset of the disorder is often insidious and is difficult to distinguish from other changes in adolescence and early adulthood. It is not rare to think that social withdrawal and other prodromal symptoms are part of the development towards independent life. Further understanding of the etiology of schizophrenia could be achieved with longitudinal studies focusing both on biological and environmental factors in the general population (van Os *et al.* 2010). Ideally in the future, it could be possible to detect subjects with a high risk of psychosis during pregnancy or childhood, to realize accurate and rapid diagnosis after transition to acute psychosis, and to produce early intervention to minimize environmental risk factors.

2.5 Treatment of schizophrenia

Treatment of schizophrenia is nowadays recommended to include various elements based on individual characteristics of the disorder. Treatment is often offered over a long period of time due to the usual chronic course of the illness. Treatment of schizophrenia, as with treatment of other psychiatric disorders, is

primarily based on outpatient clinics with the option of treatment in psychiatric hospitals at acute phases of the illness.

The exact and early diagnosis for initiation of the correct treatment is essential in many ways for the treatment of schizophrenia, and is one way to shorten DUP and minimize its potential harmful effects.

2.5.1 Medication

The most used and recommended group of medicines are *antipsychotics*, also known as neuroleptics, which have been traditionally divided into two main groups, named typical and atypical antipsychotics. The main effect of these is based on their effect on the dopamine receptors in the brain, where by blocking the subtype D₂ dopamine receptors (D2), they have an effect on positive symptoms. There is no major difference in efficacy between typical and atypical antipsychotics (Crossley *et al.* 2010).

Antipsychotics have major side-effects, of which extrapyramidal effects such as dystonia and Parkinsonism are quite common (Crossley *et al.* 2010). Atypical antipsychotics less frequently cause extrapyramidal side-effects, but other harmful effects, such as weight gain, increased levels of blood glucose and cholesterol, and prolonged QT interval of the heart, are quite common (Manschreck & Boshes 2007, Chung & Chua 2011).

It has been shown that the main difference at dopamine levels in schizophrenia, compared to controls, is at a presynaptic level, and the effects of antipsychotics on dopamine levels are not long-lasting, requiring regular and long-term, sometimes even life-time, medication (Howes *et al.* 2012). Interestingly, one study found similar striatal dopamine synthesis in family degree relatives of individuals with schizophrenia subjects, as had been found in neuroleptic-naive first-episode psychosis when compared to healthy controls (Hietala *et al.* 1999, Huttunen *et al.* 2008). Higher D2 receptor binding in caudate has been found to be associated with poor cognitive functioning, with possible linkage to genetics of schizophrenia, providing support for early intervention with antipsychotics (Hirvonen *et al.* 2005).

The benefits of using antipsychotics in schizophrenia are acknowledged based on recent studies on their effect on reduce mortality (Tiihonen *et al.* 2011). On the other hand, regarding mortality, contradictory results have also been presented (Joukamaa *et al.* 2006, Weinmann *et al.* 2009). There is evidence of the greater degeneration of the brain among individuals with schizophrenia taking

antipsychotics (Ho *et al.* 2011). The low rate of long-term safety and effectiveness in patients over 40 years of age also questions the quite common life-time usage of antipsychotics in schizophrenia (Jin *et al.* 2013).

During the antipsychotic era the treatment of schizophrenia has moved towards treatment based on outpatient clinics instead of hospitals. However, the nature of this heterogeneous disorder has been shown in the NFBC 1966, in which not all subjects with schizophrenia need permanent antipsychotic medication to maintain remission (Moilanen *et al.* 2013). The detection of the reasons behind these different courses of illness would have great potential for providing various possibilities for early intervention and treatment.

Medication in prodromal phase and early phase of schizophrenia

Medication in the premorbid phase of the illness has been studied as one way of preventing psychosis. The evidence of the benefits of this predictive early intervention with antipsychotics versus their harmful side-effects, such as metabolic side-effects (Salimi *et al.* 2009), and comparison to other options such as psychosocial treatment is sparse (Marshall & Rathbone 2011, Bola *et al.* 2012).

There is no clear evidence of how long the antipsychotics should be used after the first-episode psychosis to prevent a relapse, but the current guideline in Finland (Finnish Psychiatric Association 2013) suggests the use of at least between two to five years, whereas the American Psychiatric Association (APA) recommends usage of at least 6 months and the National Institute of Clinical Excellence (NICE) at least 1 to 2 years.

2.5.2 Psychosocial treatments

Antipsychotics have had very limited efficacy on cognitive and negative symptoms of schizophrenia and functioning at social and occupational level is often not increased by current medications (Tandon 2011). Psychosocial treatments therefore may offer possibilities to find ways to improve social, negative, and cognitive dimensions and can also provide help in positive symptoms that are distractive even with medication. The dose of antipsychotic medication can also be significantly reduced by maximizing the use and benefits of other treatment options (Isohanni 1983).

Psychoeducation is a method of offering information on the illness and symptoms and treatments for subjects with psychosis and their families. This has been shown to increase the treatment adherence of subjects diagnosed with schizophrenia, resulting in a decrease in relapses and better social and global functioning (Lincoln *et al.* 2007a, Xia *et al.* 2011). Psychoeducation also has its limitations regarding efficacy, depending on, for example, the timing (Feldmann *et al.* 2002) and potential harmful effects such as increased insight, which may increase feelings of hopelessness (Carroll *et al.* 2004).

Cognitive remediation based either on computer programs or exercises done with the help of a therapist has recently been included as part of rehabilitation of schizophrenia, with the aim of increasing declined cognitive functioning (Wykes *et al.* 2011). Social Cognition and Interaction Training (SCIT), may have positive effects on aspects such as social and occupational functioning, and may even decrease the impairment caused by delusions (Combs *et al.* 2007).

Psychotherapies such as cognitive behavioral therapy (CBT) and psychoanalytic therapies have not been generally used in the treatment of schizophrenia, but lately there have been studies indicating the positive effects of CBT in the treatment of schizophrenia. In a multisite randomized controlled trial, CBT of six months, for subjects at high-risk of psychosis, did not prevent the onset of psychosis, but significantly reduced the severity of the symptoms (Morrison *et al.* 2012).

Psychosocial treatments have a lot of potential, especially in the treatment of the early phase of psychosis, due to the lack of side-effects that come with the use of medication. There is a need for methods with more precise detection of subjects with a high risk of psychosis, as well as for the development of more cost-effective psychosocial interventions directed especially at early intervention of psychosis.

2.5.3 Other treatments

In the past decade, the prospect of emerging treatment options and even preventive interventions for psychosis has been raised. The possible positive effects of *omega-3 fatty acid* have been discussed and one randomized controlled trial has found that long-chain omega-3 polyunsaturated fatty acids decreased the rate of transition to psychosis in subjects at risk, and reduced symptoms and improved functioning when compared to a placebo (Emsley *et al.* 2003, Amminger *et al.* 2010).

Physical activity and exercise including yoga have also had beneficial effects in schizophrenia (Gorczyński & Faulkner 2010, Vancampfort *et al.* 2012). There have been no studies of the effects of physical activity and exercise on prodromal phase or first-episode psychosis, but it is possible to assume that these methods could have beneficial effects of some scale in early intervention when combined with other methods of intervention.

Transcranial direct-current stimulation (tDCS) has shown some promise for treating positive and negative symptoms, with effects lasting up to 3 months (Brunelin *et al.* 2012). *Deep brain stimulation* of the ventral hippocampus has also been studied as a treatment option for schizophrenia in animal models with some positive effects (Ewing & Grace 2013).

2.6 Outcome and its predictors in schizophrenia

2.6.1 Definitions of outcome

Outcome studies in schizophrenia have shown the difficult course of the disorder for the majority of subjects, but the comparison of the results has not been easy due to methodological differences. For example, definitions used for outcomes have varied and there have also been variations in samples as especially studies of the early phase of the disorder often include subjects with different types of psychosis and therefore also the expected outcomes differ.

Outcome can be *measured* as the number of symptoms at a certain time point or at several points. Symptoms are usually measured using structured interviews such as the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS, Kay *et al.* 1987). BPRS and PANSS measure the severity of a wide range of psychotic and other psychiatric symptoms. The Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) are specified for the assessment of negative and positive symptoms respectively. PANSS also gives the possibility to analyze positive, negative, and general symptoms separately. By using the developed five-factor models, other symptomatic aspects in schizophrenia can also be assessed (van der Gaag *et al.* 2006, Wallwork *et al.* 2012).

One way to study the number of symptoms and the impact of them is the definition of *remission*, which is a phase of the illness that is relatively free of major symptoms of schizophrenia. Defined criteria state that a period of 6 months

with a simultaneous mild or less rating on positive and negative symptoms and disorganization can be considered as remission in schizophrenia (Andreasen *et al.* 2005). *Recovery* is a prolonged period of remission and was recently proposed to be defined rather strictly, such as by including both clinical and social recovery, and lasting at least two years without symptoms (Lieberman & Kopelowicz 2005, Faerden *et al.* 2008).

Factors such as quality of life, employment, utilization of psychiatric services or hospitalizations, and mortality can also be used when measuring the outcome of schizophrenia. These provide information on the real-life effects and costs of disorder, which are important especially when analyzing the costs and benefits of interventions such as early interventions. Quality of life has been estimated to correlate negatively with the severity of negative symptoms (Tomotake 2011) and this correlation has also been seen in subjects vulnerable to psychosis (Svirskis *et al.* 2007). Employment is thought to have a beneficial effect on other aspects of outcome (Schennach *et al.* 2012). The number and length of hospitalizations is often studied when assessing the effectiveness of treatment, and hospitalization can nowadays be seen as a marker of relapse.

In a meta-analysis, it was estimated that 40% of schizophrenia patients were considered as having a 'good outcome' without duration criteria for a good outcome (Hegarty *et al.* 1994). A systematic review of the outcome of first-episode psychosis concluded that 42% of patients had a 'good outcome' either on clinical or social/functional outcome without duration criteria for good outcome (Menezes *et al.* 2006). Warner (2004) examined the recovery from schizophrenia and estimated that 11-33% had achieved complete recovery and 22-53% achieved social recovery. In a more recent meta-analysis of 50 studies with at least 2 years of follow-up, 13.5% of subjects with schizophrenia had recovered with quite strict criteria for recovery (Jääskeläinen *et al.* in press). There has been no evidence in these studies that the outcome of schizophrenia would have improved over time (Hegarty *et al.* 1994, Warner 2004, Jääskeläinen *et al.* in press).

Previous studies of outcome in schizophrenia in the NFBC 1966 have shown that recovery (n=1 out of 59) and partial recovery (n=1 out of 59) were not common in this sample (Lauronen *et al.* 2005), and the majority of subjects, a total of 81% of those with schizophrenic psychoses, were re-hospitalized during the follow-up (Miettunen *et al.* 2006). Compared to the conclusion of the recent meta-analysis, the rate of recovery in schizophrenia may be lower in the NFBC 1966 (Jääskeläinen *et al.* in press).

2.6.2 Predictors of outcome of schizophrenia

The outcome of schizophrenia in its early phase is difficult to predict. Several factors may affect the prognosis of schizophrenia, although their predictive value is quite small (Jonsson & Nyman, 1991, Suvisaari *et al.* 1998, Harrison *et al.* 2001). One predictor of good outcome has been the early treatment response measured as improvement in PANSS in the first weeks of illness, although the improvement of negative symptoms has not been shown to be associated with better outcome (Jäger *et al.* 2009).

Better premorbid adjustment and older age of onset are two of the factors that predict remission in schizophrenia, whereas the subjects with relatively mild symptoms and psychopathology and better functioning at the onset of illness are thought to be more likely to achieve remission (Lauronen *et al.* 2007, Lambert *et al.* 2010, Haro *et al.* 2011, Kurihara *et al.* 2011, Schennach-Wolff *et al.* 2011). Female gender and better insight have been associated with better outcome (Leung & Chue 2000, Lincoln *et al.* 2007b), whereas family history of psychosis has been shown to correlate with more severe negative symptoms (Esterberg *et al.* 2010).

Recovery is less often achieved in schizophrenia than remission. The predictors of recovery include being married, having better cognitive functioning, and being employed, as well as not using antipsychotics in the follow-up (Qureshi *et al.* 1987, Schennach-Wolff *et al.* 2011). The predictive value of gender on the rate of recovery is unclear, with contradictory results (Auslander & Jeste 2004, Cougnard *et al.* 2006, Jääskeläinen *et al.* in press).

No correlation was found in the NFBC 1966 between delayed *early neuromotor development*, one of the risk factors for schizophrenia, and poor outcome (Jääskeläinen *et al.* 2008). In the study of predictors of short- and long-term clinical outcome, the insidious onset of illness predicted re-hospitalization in the first two years of illness, as well as poorer clinical outcome in the longer term, with factors such being single, early onset, and suicidal ideations during the first hospitalization (Juola *et al.* in press).

Marital status has been shown to correlate with occupational outcome, with being married or cohabiting associating with a decreased rate of disability pension, as well as a premorbid psychosocial stressor and later onset age (Miettunen *et al.* 2007). Not being married, smoking at the age of 14, and a definite psychosocial stressor before the onset of illness were correlated with increased severity of

negative symptoms in the follow-up. On the other hand, good school performance and using less alcohol at the age of 14 predicted lower levels of negative symptoms (Mäkinen *et al.* 2010). Female gender was associated with an increased probability of employment (Miettunen *et al.* 2007). A short first hospitalization and a family history of psychosis were linked to an increased risk of re-hospitalization (Miettunen *et al.* 2006).

Cognitive functioning may correlate with some of the predictors of outcome of schizophrenia. Especially the decrease in social cognition is likely to correlate with factors such as marital status (Green *et al.* 2008). Cognitive impairment of working memory, attention and perceptual processing, and verbal memory and processing have been shown to predict the return to work or school in the early phase of psychosis (Nuechterlein *et al.* 2011). A meta-analysis has shown that both impairment of neurocognition and social cognition have a small to medium effect on functional outcome in schizophrenia (Fett *et al.* 2011) and poor social cognition could also be associated with a decreased quality of life (Maat *et al.* 2012).

Short DUP has been associated with a higher rate of both remission and recovery (Marshall *et al.* 2005, Perkins *et al.* 2005). However, previous studies have not been able to prove the causality between long DUP and poor outcome, and this association may be confounded by potential mediating factors such as mode of onset or other markers of illness severity. The association between DUP and outcomes will be discussed in more detail later.

2.7 Brain morphology in schizophrenia

2.7.1 History and development of brain morphology studies in schizophrenia

Schizophrenia has always been mainly studied and treated as a disorder that is located in brain. A former method of treatment known as lobotomy is one example of this. Brain morphological changes in schizophrenia have been studied for more than a century, starting with post-mortem studies. The major technological development in the recent decades has provided new methods for schizophrenia research. After the finding of increased cerebral ventricular size in schizophrenia, which was related to cognitive impairment in a study using

computerized tomography (Johnstone *et al.* 1976), the interest in studying the brain morphology of schizophrenia has been increasing exponentially.

Since the development of imaging and mainly the introduction of *magnetic resonance imaging* (MRI), the possibilities to study and analyze exact volumes and functions of soft tissues such as the brain safely have vastly increased, and numerous studies and meta-analyses have been published of the altered brain morphology in schizophrenia (Shepherd *et al.* 2012, Haijma *et al.* in press).

As the causal relations are difficult to find in an often chronic disorder with unknown etiology, the conclusions of brain morphological changes in schizophrenia are still unclear. Various possible confounders may have an effect on brain morphology, and some of these are impossible to take completely into account. For example, the use of medication, such as antipsychotics or antidepressants, during the years of follow-up can only be roughly estimated, as medication is often taken or given irregularly without regular use of definitive measurements, such as blood samples, to define the exact amount of medication in the blood circulation.

Two different methodological techniques has been developed and established in analyzing the data from structural MRI. One perspective is to analyze the whole brain using *voxel-based morphometry* (VBM) for this analysis (Wright *et al.* 1995, Ashburner & Friston 2000), and the other approach is the *region of interest* (ROI), in which a certain region of the brain is chosen to be studied by manual tracing. In addition to these, many other technical methods and variations have been introduced, producing new information and also complicating the synthesis of results of the studies (Perlini *et al.* 2012).

2.7.2 Results of previous brain morphology studies

A *systematic meta-review* has concluded that high-quality evidence that would support grey or white matter changes in schizophrenia is very limited, and the large volume of lower-quality evidence has blurred the synthesis of the results of brain morphology studies in schizophrenia. This meta-review found evidence for gray matter reductions of the anterior cingulate, frontal and temporal lobes, hippocampus, amygdala, thalamus, and insula, without conclusive evidence of the effect of the duration of the illness on these changes. The only area of the brain where medication in schizophrenia was seen to have an impact on progressive

changes in brain morphology was an increase in the volume in basal ganglia (Shepherd *et al.* 2012).

Recently, a large synthesis of the previous studies was made as a *meta-analysis* of 317 studies focusing on differences in cross-sectional studies between medicated and non-medicated patient samples. 33 studies of 317 were done with antipsychotic-naïve subjects and the main finding was the significant decrease of intracranial and total brain volume in subjects with schizophrenia. For the subjects who had not used antipsychotics before the imaging, there were significant decreases in caudate nucleus and thalamus when compared to medicated subjects, and gray matter loss was in general less extensive in subjects without medication. The duration of the illness and a higher dose of antipsychotic medication at the time of scanning were also correlated with the reduction in grey matter (Haijma *et al.* in press).

Certain areas have been shown to relate to more *gray matter decrease* in subjects with schizophrenia. In first-episode psychosis, reduction in the whole brain volume and hippocampus was significant in a meta-analysis of 21 studies (Vita *et al.* 2006) and another meta-analysis has shown consistent gray matter reductions in the prefrontal and temporolimbic areas in subjects at enhanced clinical risk of psychosis (Fusar-Poli *et al.* 2012a). When it comes to studies with subjects in later phases of the illness, there has been a reported decrease in several regions of brain, of which the most common were deficits in the left superior temporal gyrus and the left medial temporal lobe (Honea *et al.* 2005).

In the NFBC 1966, previous studies of brain morphology have shown that brain volumes of subjects diagnosed with psychosis are smaller when compared to those of healthy controls, but volume reduction in the hippocampus and amygdala, and the shape of the hippocampus compared to controls, were not significant (Tanskanen *et al.* 2005). Total brain volumes of whole brain and gray and white matter have also been found to be smaller in subjects with schizophrenia than in controls (Tanskanen *et al.* 2009). Gray and white matter deficits and excess of CSF have been linked with longer duration of the illness in the NFBC 1966 (Tanskanen *et al.* 2010). Early motor development and adult executive functions, and their association to fronto-cerebellar systems, have been found to differ when comparing subjects with schizophrenia to healthy controls (Ridler *et al.* 2006).

When the effects of these brain morphological changes on cognitive functioning were studied, memory strategies were found to be poorer in schizophrenia than in controls, and poor memory and learning were associated

with a smaller anterior cingulate gyrus and a larger intracalcarine cortex in schizophrenia (Rannikko *et al.* 2012).

3 Duration of untreated psychosis

One of the main principles in medicine is the diagnostic validity and accuracy that determines the treatment. Early and accurate diagnosis makes correct treatment possible. It often also relieves worry, even in severe disorders, due to removal of uncertainty. Proper diagnostics with good timing often increase the quality and efficacy of treatment and decrease the excessive costs that may be caused by the treatment of misdiagnosed disorders and long disability leave while waiting for diagnosis.

The benefits of early diagnostics, intervention, and treatment in medicine are widely acknowledged, for example, in the treatment of cancers and infections, as well as in such an acute illness as myocardial infarction. However, even in treatment of acute coronary syndromes, there is a discussion of the right timing (Navarese *et al.* 2011, Jiang *et al.* 2012) and choice of treatment in early intervention (Kajimoto *et al.* 2012, Wallace *et al.* 2012).

The methods of screening and early detection of cancers such as breast cancer and prostate cancer have been discussed with partly unclear conclusions. This is due to the challenge in finding methods with good specificity and sensitivity that are available and effective and that cause little or no harm (Vernon *et al.* 2010, Magnus *et al.* 2011, Lumen *et al.* 2012). For example, valid diagnosis of prostate carcinoma may in some cases lead to excessive treatment and concern. Many somatic disorders such as hypertension and high levels of blood cholesterol can be cost-effectively treated by changing one's lifestyle, including habits of eating and exercise instead of medication.

In some neurological diseases such as dementia and Parkinson's disease, the assessment and diagnosis is made with a certain follow-up period before the onset of medication, considering the benefits and possible side-effects of treatment. There is active research trying to find effective treatments for these neurodegenerative disorders, but currently there is no effective treatment available, and therefore also the possibilities of primary prevention are being studied (Zheng *et al.* 2010, Moniz Cook *et al.* 2012, Murman 2012, Zhang *et al.* 2012).

Generally, it can be noted that regarding the illnesses where there is an immediate need of care and effective treatment exists without excessive risks of side-effects, treatment systems have been developed to detect these illnesses as early as possible, to prevent the negative effects that relate to delayed care. But

when the definite detection and safe treatment of a disorder is not possible, it is more common to monitor the illness so it is known what the causes are behind the symptoms and what might be the best available treatment. The basic principle for this is mentioned in the Hippocratic Oath: “never do harm to anyone”.

3.1 Untreated illness in psychiatry

Psychiatry in general is not known for its immediate diagnostics or treatment effects. One reason for this is the lack of biomarkers and specific endophenotypes of major psychiatric disorders. On the other hand, the poor public reputation of psychiatric services and fear of stigma may be one reason for the quite common delay of treatment in psychiatry. Psychiatric disorders are more related to psychological aspects of human health than somatic disorders. Many factors, such as various possible current or previous life-events, and/or characteristics of personality, or misuse of alcohol or drugs, may deter the psychiatric assessment at first contact and even for a prolonged time.

Definite diagnostics in psychiatry take time, partly based on diagnostic criteria that often include criteria for minimum duration of symptoms of the disorder. Heterogeneity and over-lapping of symptoms and characteristics between psychiatric disorders also challenge the accuracy of psychiatric diagnostics, especially in the early phases of disorders and cases with minimal or atypical symptomatology or treatment history (Isohanni *et al.* 1997, Moilanen *et al.* 2003). The current lack of definite diagnostic tools and biomarkers such as blood samples and imaging leaves the psychiatric treatment and descriptive diagnostics based on defined criteria dependent on the information gathered from the person and family, and a clinical assessment that takes time and effort, as well as diagnostic training and expertise.

When considering perhaps the most common psychiatric disorder, especially from the general health service point of view, the efficacy and outcomes of the treatment of depression have been discussed widely in public with some criticism towards the efficacy of antidepressants. Despite the relatively high incidence and prevalence of depression, the effects of the *duration of untreated illness* (DUI) in depressive disorders have not been widely studied. There is some evidence that long DUI might decrease the rate of remission in patients who need hospital treatment for their depression (Bukh *et al.* 2013).

Psychiatric treatment has been changing, especially since the 1980s, when the number of psychiatric hospital beds was significantly decreased and treatment

was focused on out-patient visits (Korkeila *et al.* 1998). This might have been one reason for modern and technological cultures to seek possibilities to speed up the treatment in psychiatry and to cut costs. The association between long-lasting symptoms before treatment initiation and poor outcome were increasingly published in 1986 (Crow *et al.* 1986, Johnstone *et al.* 1986, Rabiner *et al.* 1986). The general development and its effect on the length of DUP has been shown in a meta-analysis that studied DUP in countries with low incomes, stating that DUP tends to be longer in those countries (Chiliza *et al.* 2012).

3.2 Duration of untreated psychosis in schizophrenia

3.2.1 History of the concept

Duration of the illness before treatment as one potential factor in predicting outcome was studied already in the 1930s (Rupp & Fletcher 1940, Johanson 1958, Henisz 1966, Aché 1967, Helgason 1990). In the early 1990s, the definition of duration of untreated psychosis (DUP) was presented (Loebel *et al.* 1992). It was accompanied by the first speculations on its possible harmfulness, neuronal damage, and associated poor prognosis. Later on, DUP has become one of the most commonly studied predictors of outcome in schizophrenia (Perkins *et al.* 2005), but the studies are mainly based on clinical populations. General population-based studies are needed to use an epidemiologically principled study population and achieve long enough follow-up times. If the results of these studies indicate that early and correct timing of treatment is related to better prognosis of schizophrenia, this finding is significant for both the patient and society, since the primary prevention of schizophrenia is not yet possible (McGrath 2003).

Table 2 summarizes the previous meta-analyses and reviews regarding DUP and outcome. These meta-analyses reflect the challenges of measuring DUP and using DUP as a predictor of outcome, considering the inconsistency of the association between DUP and biological factors. However, there seems to be some consistency in studies of DUP and outcome, finding modest association between long DUP and poor outcome in the short term. The conclusions regarding the association between DUP and long-term outcome are unclear, and there is no conclusive evidence of the possible effect of DUP on brain morphology and cognition and the possible progression of changes in these.

When studying the effect of DUP on biological markers, it is critical that DUP is defined systematically in reliable methods (Compton *et al.* 2007, Singh 2007). To make this possible, and also to find new ways to shorten DUP, more information is needed from longitudinal follow-ups of the predictors of DUP.

Table 2. Meta-analyses and reviews of duration of untreated psychosis (DUP).

Authors, year	Number of studies	Main topic of the review	Conclusions	Comments
Reviews on association between DUP and outcomes				
Norman and Malla 2001	10	Association between DUP and recovery and remission	Evidence of association between short DUP and initial good treatment response. No evidence of the association between DUP and long-term outcome	Potential confounding variables were only discussed. Non-systematic review, done of relatively few studies.
Marshall et al. 2005	26	Association between DUP and total symptoms, depression/anxiety, negative symptoms, overall functioning, positive symptoms, and social functioning	Modest association between long DUP and poor outcome after treatment initiation in 2 years of follow-up	Systematic meta-analysis. Low possibility of reporting bias.
Norman et al. 2005	13	Association between DUP and clinical outcome Association between DUP and neurotoxic effects	DUP predicted remission of treatment outcome, especially remission of positive symptoms. Inconsistent findings	Review without meta-analysis and without presented systematic search strategy.
Perkins et al. 2005	43	Association between DUP and baseline symptoms, neurocognition, brain morphology, or functional measures or prospectively analyzed symptom change, response, or relapse; assessed psychopathology with clinician-rated instruments	Shorter DUP was associated with decreased severity of global psychopathology, positive and negative symptoms, and improved functional outcomes. At treatment initiation, DUP was associated with severity of negative symptoms but not with positive symptoms, general psychopathology, or neurocognition.	Systematic meta-analysis. Low possibility of reporting bias.

Authors, year	Number of studies	Main topic of the review	Conclusions	Comments
Macbeth and Gumley 2008	29	DUP's association with pre-morbid adjustment	No consistent correlation between DUP and premorbid adjustment.	Risk of bias not discussed.
		The associations between DUP and symptomatology and pre-morbid adjustment	Premorbid adjustment had more correlation to negative symptoms and quality of life, whereas DUP correlated to positive symptoms	Possibility of reporting bias estimated as medium.
Farooq et al. 2009	5	Association between DUP and outcome in low and middle income countries	Long DUP correlated with more severe symptoms and increased disability	Risk of bias not discussed and meta-regression not performed.
Boonstra et al. 2012	16	Association between DUP and negative symptoms in the long term	DUP shorter than 9 months associated with less severe negative symptoms in the short and long term.	Analyzed the original data of the samples
Challis et al. in press	5-18	Association between DUP and deliberate self-harm before and after treatment	Long DUP correlated with increased self-harm before treatment but not in follow-up.	
Other reviews on DUP				
Larsen et al. 2001	13	Early intervention and shortening DUP	Early intervention is challenging and reducing DUP is the best opportunity for this, instead of intervention in the prodromal phase.	Search protocol for literature review unclear.
Compton et al. 2007	48	Definition and measurement of DUP	The definition of DUP was quite consistent, but several limitations (e.g. lack of frequent inter-reliability rating and heterogeneous methods for defining DUP) were considered when measuring DUP.	Systematic review of studies included in Marshall <i>et al.</i> 2005 and Perkins <i>et al.</i> 2005

Authors, year	Number of studies	Main topic of the review	Conclusions	Comments
Singh 2007	13	Relevance and measurement of DUP	It is vital to measure DUP in standardized methods and DUP was seen as a relevant measure of the effect of early detection in early intervention services.	Non-systematic review
Lloyd-Evans et al. 2011	11	Shortening DUP	Reducing DUP may be possible using public awareness campaigns. Evidence was mixed.	Included studies from early intervention sites only.
Burns 2012	9	Cannabis use and length of DUP	No significant difference, trend of shorter DUP in users.	Systematic review and meta-analysis, but low number of studies with relatively high proportion of users (39%)
Cascio et al. 2012	27	Gender and DUP	Gender did not associate with the length of DUP.	Found heterogeneity in definitions of DUP
Chiliza et al. 2012	Not reported	DUP in developing countries	DUP longer in developing countries and outcome poorer, but remission more common than in industrialized countries.	Non-systematic review

3.2.2 Definition of duration of untreated psychosis

DUP is usually defined as the time between the first positive symptoms of psychosis and the onset of psychiatric treatment (e.g. medication or hospitalization) (Marshall *et al.* 2005). It may last several months, years, or even a period of more than 10 years (Scully *et al.* 1997).

The definition of DUP varies and there has been discussion on whether DUP can be measured with such consistent methods that it is possible to compare DUPs in different samples and the association between DUP and outcome (Singh 2007). The major difference may occur already in the definition of the onset of psychosis, and it is important to distinguish the concept of *duration of untreated illness* (DUI) starting from the very first symptom of the illness and DUP, which

is defined to begin from the onset of psychosis. A commonly used definition for the onset of psychosis refers to the severity of positive symptoms (at least 4) according to the Positive and Negative Syndrome Scale (PANSS) (Table 3).

The measurement of DUP is often methodologically challenging as well. DUP is usually defined retrospectively, even years after the onset of the illness, causing possible recall bias. This can be minimized by using as many sources as possible, such as interviews with relatives and information obtained from medical records (Table 3).

The end of DUP or the start of treatment of the first psychosis is generally simpler to define, but there is some variation in that as well. Some studies consider DUP to end when the subjects enter the study and psychosocial treatment and/or antipsychotic medication begins. In some inpatient samples, the end of DUP and the onset of treatment have been defined as the onset of first hospitalization. The beginning of antipsychotic medication has generally been thought to be most reliably defined as adequate treatment of antipsychotics and some have used the four-week period of antipsychotic use as an indicator of this. One problem for this definition has been the prodromal use of antipsychotics, which results in negative DUP when strictly defined (Singh 2007).

Instruments for estimating DUP and their reliability

Relatively many of the studies that have estimated DUP do not present the exact method for defining DUP, and even fewer of the studies have presented the inter-rater reliability rating for the definition of DUP (Compton *et al.* 2011). Many instruments have been developed or implemented for measurement of DUP. The Royal Park Multidiagnostic Instrument (RPMIP) has been used in some of the previous studies with adequate reliability (McGorry *et al.* 1996, Amminger *et al.* 2002, Harrigan *et al.* 2003). The Comprehensive Assessment of Symptoms and History (CASH) has been shown to have a slightly higher level of reliability, but it has been mainly used for diagnostic purposes with only a couple of studies defining DUP based on the CASH (Ho *et al.* 2000, Ho *et al.* 2003). The Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) has become one of the most commonly used instruments with acceptable reliability (Maurer & Häfner 1995). Other measurements of defining DUP include the Circumstances of Onset or Relapse Schedule (CORS), the Symptom Onset in

Schizophrenia inventory and the Nottingham Onset Schedule (NOS) (Compton *et al.* 2007).

The definition of DUP has been modified to measure the active period of psychosis, as psychosis is not a stable state but rather a fluctuating disorder (Norman *et al.* 2012). Lately, there has been suggestion of even defining the severity and frequency of psychotic symptoms before treatment. These "doses" of DUP, further divided into hallucinations and delusions, may be more challenging to measure, but on the other hand may be better predictors of some aspects of outcome at least regarding general psychopathology (Compton *et al.* 2011).

To sum up, the definitions of DUP have been heterogeneous between the studies, and the heterogeneity in the assessment of DUP has not always been properly excluded.

Table 3. Different definitions, assessment instruments, and lengths of duration of untreated psychosis (DUP) (modified from Singh 2007).

Authors, years	Start of DUP	End of DUP	Structured assessment	DUP, weeks mean	Comments
Addington et al. 2004	First positive symptom (PANSS 4 or higher)	First effective treatment	IRAOS	84.2	Commonly used and accepted definition.
Haas et al. 1998	The best estimate of onset of first psychosis from all available sources	First antipsychotic medication	No	74.4	The best estimate may correlate well with definition of IRAOS.
Lappin et al. 2006	The onset of psychotic phenomena (for 1 week or more)	First contact with mental health services	PPHS	11	May underestimate the length of DUP.
Malla et al. 2002	First psychotic symptoms contiguous with presenting episode	Antipsychotic therapy for 2 months or response earlier	No	44.6	The definition is slightly shorter due to use of continuous psychosis.
Rosen and Garety 2005	Appearance of psychotic symptoms	Initiation of medication	No	18.6	Recorded from medical notes. May underestimate the length of DUP.

Authors, years	Start of DUP	End of DUP	Structured assessment	DUP, weeks mean	Comments
Scully et al. 1997	Age at first admission to hospital	Age at first prescription of antipsychotics	No	722.8	Due to beginning sample collection in the pre-neuroleptic stage, the length of DUP is not comparable to other studies.
Szymanski et al. 1996	First noticed psychotic symptoms and decline in functioning	Entry into study	No	166.4	Study entrance included administration of antipsychotics (typicals and clozapine) on clinical judgment of treating physician.
Wiersma et al. 1998	Psychosis onset based on WHO instruments	Initiation of any form of treatment	Life Chart Schedule	Not reported	The comparison of measurements is not possible as the mean of DUP is not given.

IRAOS The Interview for the Retrospective Assessment of the Onset of Schizophrenia
 PANSS Positive and Negative Syndrome Sale
 PPHS Personal and Psychiatric History Schedule
 WHO World Health Organization

3.2.3 Determinants of duration of untreated psychosis

Determinants of DUP for an individual

When assessing the possibilities of shortening DUP and what the effects could be of this possible change in the length of DUP, it is critical to know what factors predict and relate to either short or long DUP. Previous studies have shown that subjects who are unemployed and living alone or homeless have longer DUP (Barnes *et al.* 2000, Chen *et al.* 2005, Morgan *et al.* 2006, Oliveira *et al.* 2010), whereas the effects of acute mode of onset and a family history of psychosis seem to shorten DUP (Chen *et al.* 2005, Compton *et al.* 2008). The effect of living with

family and the involvement of family in help-seeking on the length of DUP is unclear (Morgan *et al.* 2006 Compton *et al.* 2008). One study found that living in poverty and living with family members was associated with longer DUP (Compton *et al.* 2011). Factors such as higher insight, and decreased strength and coping capacities of informants or families have also been associated with longer DUP (Compton *et al.* 2009).

Chong *et al.* (2005) assessed the possible reasons and factors for not wanting to see a psychiatrist and found that besides the unnamed reasons, there were two categories of reasons: not realizing the existence of a problem, and the thought of problems being due to supernatural or mystical causes. The lack of knowing or finding other explanations for odd symptoms may not be that uncommon in Western societies either, although the finding was from an Eastern population. In two review articles on predictors of DUP, neither gender nor use of cannabis correlated with the length of DUP (Burns 2012, Cascio *et al.* 2012).

Determinants of DUP regarding the health-care system

Characteristics of DUP can also be divided into different categories in a wider perspective. One category of reasons for delayed treatment is related to a subject with psychotic symptoms such as avoiding the onset of treatment as long as possible, and on the other side there may be reasons in the health-care system that cause the delay in the onset of treatment. In most developed countries, psychosis is considered a disorder that it is recommended to treat rapidly and effectively. However, for various reasons such as financial restrictions, in developed countries not all needs for treatment of psychotic people may be met either, and this is even more common in developing countries (Chiliza *et al.* 2012).

The ability of health care to detect and diagnose psychosis may also vary, and it may be that nowadays the general knowledge of psychosis is wider in primary health care than it was earlier. But it is still possible that subjects with comorbidity such as substance use disorder may receive treatment only for the acute phase of psychosis, and after that phase they are not offered or they can not adhere to the follow-up and treatment for a longer period of time, when potentially psychotic symptoms causing the misuse of substances are not noticed (Wisdom *et al.* 2011).

There is also some variation in treatment practices in psychiatry, which adds to heterogeneity. Treatment of first-episode psychosis is generally quite straightforward in public health care, including usually mainly medication and

regular contact with the health service, with necessary support in other forms if needed. This may not, however, be the case for those subjects with more anxiety and depressive-like symptoms, whose psychotic symptoms may not be noticed in the early phases of the disorder and that are treated as anxiety or mood disorders. Therefore, some subjects with either forthcoming or already ongoing psychotic symptoms may receive treatment that has not yet been conclusively shown to be effective for treating psychotic symptoms (Fusar-Poli *et al.* 2007, Bowie *et al.* 2012, Ballon & Stroup 2013).

One feature of the heterogeneity of schizophrenia is *different modes of onset*. Mode of onset has been divided generally into four subtypes: acute, sub-acute, gradual, and insidious. The mode of onset may have some correlation with DUP and it has been suggested that it be taken into account as a covariate when studying DUP and outcomes in schizophrenia (Morgan *et al.* 2006, Moncrieff 2011).

3.2.4 Other concepts of untreated illness in schizophrenia

Duration of untreated illness (DUI) describes the period from the onset of the first, usually non-psychotic, symptoms in schizophrenia to the onset of treatment. The first symptoms are often negative symptoms, such as withdrawal and depression, and when they precede the onset of the first psychosis of schizophrenia, they are referred to as prodromal symptoms. *Delay in intensive psychosocial treatment* (DIPT) has been studied less than DUP, but some studies have shown that this period from the onset of the first psychotic symptoms to the start of intensive psychosocial treatment instead of medication might be more important when predicting the outcome of psychosis (Norman & Malla, 2001, de Haan *et al.* 2003).

Attenuated psychosis risk syndrome has been defined to describe the period between the onset of psychotic-like symptoms and decline in functioning and the onset of fulminant psychosis. This concept is one way to define the period referred to as an at-risk mental state or ultra-high risk of psychosis state.

3.2.5 Previous studies of duration of untreated psychosis and outcome in schizophrenia

DUP has been studied with various outcome measures in schizophrenia, with the main focus on clinical and social outcomes. Some of the studies have also analyzed the association with suicidality and mortality, which are relatively rare in the first years of illness. Possibly due to methodological challenges such as lack of statistical power, there has been no evidence of the association between longer DUP and increased suicidality (Shrivastava *et al.* 2010, Primavera *et al.* 2012). Some evidence has been found of an increased rate of suicide in areas with longer DUP (Large & Nielssen 2008), and a recent meta-analysis found a modest correlation between long DUP and an increased risk of deliberate self-harm (Challis *et al.* in press).

Some essential elements of outcome studies considering DUP are treatment adherence and insight, which have been studied on a limited scale (Dassa *et al.* 2010, Parellada *et al.* 2011). Long DUP seems to slightly increase (OR=1.12) the likelihood of non-adherence to treatment (Dassa *et al.* 2010). Insight was found to be significantly poorer at a two-year follow-up in subjects with longer DUP and schizophrenia spectrum disorder (Parellada *et al.* 2011). Studies of the possible correlation between DUP and somatic morbidity have not been published.

DUP and short-term outcome

Most of the studies in schizophrenia are cross-sectional studies a relatively short time after the onset of the disorder. Generally, two years has been used as a borderline between a short-term follow-up and a longer follow-up in schizophrenia studies (Faerden *et al.* 2008).

Since the first publication of the association between long DUP and poor clinical outcome (Loebel *et al.* 1992), numerous studies have been published on the subject. Before that, longer duration of the illness and symptoms before treatment, comparable usually more to DUI than DUP, as well as early help-seeking, had been associated with less likely recovery (Rupp & Fletcher 1940, Johanson 1958, Henisz 1966, Achte 1967, Helgason 1990).

Two previous meta-analyses of the association between DUP and outcome in schizophrenia mainly included studies with a relatively short follow-up in their meta-analysis. Perkins *et al.* (2005) included only studies from seven of 28 samples with a follow-up of longer than 2 years, whereas a meta-analysis by

Marshall *et al.* (2005) included only three of 26 studies with a follow-up longer than 2 years. Both meta-analyses found that the association between long DUP and poor outcome was not evident at the baseline. Only more severe negative symptoms and poorer quality of life had some significant correlation with long DUP at the baseline assessment. In the follow-up, the association between DUP and most categories of poor outcome was modest (Marshall *et al.* 2005, Perkins *et al.* 2005).

There have also been reports that suggest this association is somewhat similar in countries with lower income. Farooq *et al.* (2009) reported that long DUP correlated with more severe symptoms and increased disability in low and middle income countries.

DUP and poor *symptomatic outcome* has been quite consistently found in previous studies (Marshall *et al.* 2005, Perkins *et al.* 2005). The number or length of *hospitalizations* and their association with DUP have not been systematically studied previously in the first two years of the illness. Poorer *overall functioning* and *social functioning* have both been related to longer DUP in some of the previous short-term follow-ups (Marshall *et al.* 2005). The association between long DUP and poor *quality of life* has been found in a meta-analysis at the initial assessment and after 12- and 24-month follow-ups, but not at a 6-month follow-up (Marshall *et al.* 2005).

DUP and long-term outcome in schizophrenia

The longitudinal follow-up of subjects diagnosed with first-episode psychosis is demanding, and therefore the number of studies of DUP and outcome with a follow-up of 5-10 years or even longer is limited. In one sample, some association between longer DUP and poorer outcome was found at three time-points with a 4-, 8-, and 12-year follow-up (Whitty *et al.* 2008, Crumlish *et al.* 2009, Hill *et al.* 2012). Studies with more than 10 years of follow-up have shown inconclusive results (Waddington *et al.* 1995, Huber 1997, Scully *et al.* 1997, Wiersma *et al.* 1998, Bottlender *et al.* 2003, Röpecke & Eggers 2005, White *et al.* 2009).

The lack of association between DUP and *symptomatic outcome* measured using PANSS has been reported in three samples with long follow-up (Wiersma *et al.* 1998, Röpecke & Eggers 2005, Shrivastava *et al.* 2010), and in two samples an association between long DUP and poor long-term symptomatic outcome has been found (Scully *et al.* 1997, Bottlender *et al.* 2003).

Global functioning as an outcome has been studied in a few cross-sectional samples using the Global Assessment Scale (GAS, Endicott *et al.* 1976). Two of these samples have found an association between longer DUP and decreased functioning (Bottlender *et al.* 2003, Ichinose *et al.* 2010), while one study found no association (Röpeke & Eggers 2005). Functional outcome has only been analyzed longitudinally in three samples, and no association between DUP and poor outcome was found (Wiersma *et al.* 1998, White *et al.* 2009, Shrivastava *et al.* 2010). The same three studies are the only ones to analyze the association between DUP and hospitalization in the long term. Their results indicate that long DUP was not associated with an increased need for hospitalization after the first two years of illness (Wiersma *et al.* 1998, White *et al.* 2009, Shrivastava *et al.* 2010).

3.2.6 Previous studies of duration of untreated psychosis and brain morphology

The relationship between long DUP and unfavorable outcome could be explained by the development of the brain, which continues from the fetal period to early adulthood. Especially the time around the onset of schizophrenia has been observed to be active time in terms of changes in the brain (Pantelis *et al.* 2005). One hypothesis for the unfavorable consequences of untreated psychosis is that untreated psychosis is harmful, even toxic to the brain (Wyatt 1991, Olney & Farber 1995, Keshavan *et al.* 2005). Without treatment, this process could become chronic and cause irreversible damage. Correspondingly, the changes in brain tissue could be avoided with early intervention, including medication simultaneously with other treatment. This could explain why short DUP is related to better outcome in some studies.

However, the studies on this subject have been contrary in terms of results and conclusions (McGlashan 2005), and the toxicity of DUP is still under research (Keshavan *et al.* 2005). There have also been suggestions of the negative effects of antipsychotic medication to brain volume, and therefore the long-term effect of untreated first-episode psychosis needs to be assessed carefully (Ho *et al.* 2011).

A meta-analysis (Perkins *et al.* 2005) found five studies that had examined the correlation between DUP and brain morphology, but could not produce meta-analysis of these studies due to the heterogeneity of the methods used. Most of the

studies have found no association between DUP and brain morphology (Hoff *et al.* 2000, Ho *et al.* 2003, Ho *et al.* 2005).

The previously found associations between DUP and brain morphology in first-episode psychosis include gray matter decrements in the left temporal and left occipital cortices (Lappin *et al.* 2006), and smaller caudate volume (Crespo-Facorro *et al.* 2007a) among those with longer DUP. Takahashi *et al.* (2007) found the volumes of gray matter in the left planum temporale to be smaller when DUP was longer. However, negative findings in these studies included total white matter, gray matter, and CSF volumes, and other regions of the brain including each subregion of the prefrontal cortex and thalamus (Crespo-Facorro *et al.* 2007b). In another sample, long DUP correlated with reduction of gray matter total volume, with more specific deficits of the orbital–frontal and parietal regions (Malla *et al.* 2011) (Table 4).

In summary, despite some findings between DUP and altered brain morphology, there have been no replications of any of the previous findings that would indicate that DUP affects certain areas of the brain. The association between DUP and brain functions is unclear.

Table 4. Studies of duration of untreated psychosis (DUP) and brain morphology.

Authors, year	N	Regions of brain studied	Conclusions	Comments
Madsen et al. 1999	21	Frontal lobes	Long DUP predicted prefrontal sulcal enlargement	The only study using computerized tomography (all the other studies have used MRI). Five-year follow-up
Hoff et al. 2000	50	Lateral ventricular, temporal lobe, and cerebral hemispheric volumes	No association between DUP and brain structures	Studied also cognition, finding no differences
Ho et al. 2003	90-102	Frontal, temporal, parietal and occipital lobes of gray and white matter and surface anatomy measures	DUP did not correlate with any of the regions.	Did not assess smaller subcortical regions such as the hippocampus
Ho et al. 2005	105	Hippocampus	DUP did not correlate with volumes of hippocampus	73 subjects had schizophrenia, this group was not analyzed separately

Authors, year	N	Regions of brain studied	Conclusions	Comments
Lappin et al. 2006	81	Total volumes of gray and white matter and CSF and regions of gray matter	Long DUP associated with decrease of middle and inferior left temporal gyrus and middle occipital gyrus and left fusiform gyrus. Long DUP also associated with excess of left basal ganglia	DUP was defined as the period from the onset of psychosis to first contact with mental health services while other studies used medication as the end point
Crespo-Facorro et al. 2007a	76	Caudate nucleus	Long DUP correlated with smaller caudate nucleus	44 subjects with schizophrenia. Over half of the patients used alcohol, cannabis, or tobacco.
Crespo-Facorro et al. 2007b	61	Thalamus	DUP did not correlate with thalamus	Partly the same sample as above. Only right-handed subjects were included. 32 subjects had schizophrenia.
Takahashi et al. 2007	38	Superior temporal sub-regions, medial temporal lobe structures and frontal lobe regions	Long DUP correlated only with the volume reduction of left planum temporale	All subjects had schizophrenia with an average use of medication for ~1 year.
Malla et al. 2011	80	Gray matter	Long DUP correlated with deficits of orbital-frontal and parietal regions, as well as a significant reduction in whole gray matter volume	63 subjects had schizophrenia spectrum disorder and in this group, a difference was found only in the left rectal gyrus. The number of subjects with schizophrenia was not reported.

3.2.7 Duration of untreated psychosis in other psychotic disorders

Most of the studies regarding DUP are based on first-episode psychosis samples. This means that the majority of samples do not have a definite diagnosis at the baseline and diagnoses may change during the follow-up. This may have critical

effect on the results of the studies due to known variations between the outcome of different disorders, as well as variations in the length of DUP. Brief psychotic reaction and other acute psychotic disorders, as well as drug-induced psychoses, have short DUP if any treatment is required. This is partly due to the diagnostic criteria of these disorders, which set limits to the total length of symptoms at, for example, one month.

DUP has also been studied in schizoaffective disorder and bipolar disorder, type I, which may include long-lasting psychotic symptoms. In these disorders, and especially in subjects with bipolar disorders, DUP tends to be shorter than in schizophrenia, with a majority of subjects having DUP less than three months and very few subjects with DUP lasting more than a year (Conus *et al.* 2010, Schöttle *et al.* 2012). Interestingly, the outcome between these two disorders differed at the 12 month follow-up, as the subjects with schizoaffective disorder had more severe negative symptoms and poorer functioning than subjects with bipolar disorder (Conus *et al.* 2010). Non-adherence to treatment seems to be more common in schizoaffective disorder than in type I bipolar disorder, which may partly explain the higher rate of employment and the remission of positive symptoms in bipolar disorder (Schöttle *et al.* 2012).

Long DUP has been found to be the best predictor of diagnostic shift from bipolar disorder to schizoaffective disorder (Schöttle *et al.* 2012). As schizoaffective and bipolar disorder are generally known to have a better prognosis than schizophrenia, the importance of diagnostic assessment during the follow-up studies of DUP should not be underestimated.

3.3 Early intervention projects

Of all psychiatric disorders, it was psychosis that was the first to be studied in the possibilities and effects of early intervention. Its definite aim is to shorten DUP. The development of early intervention in the area of psychosis might be due to the fact that the psychosis is a severe disorder without a definite cure, usually affecting the life of the individual widely and on a long-term basis, also causing remarkable costs for society.

In the 1990s, several early intervention centers were established, most notably in Australia (the Early Psychosis Prevention and Intervention Centre (EPPIC), Edwards *et al.* 1994, McGorry *et al.* 1996) and also in Denmark (an early intervention randomized controlled trial called OPUS, Petersen *et al.* 2005),

Norway (Treatment and Intervention in Psychosis (TIPS), Melle *et al.* 2004), Sweden (Parachute, Cullberg *et al.* 2002), the USA (North American Prodrome Longitudinal Study (NAPLS), Addington *et al.* 2007), and Canada (the Prevention and Early Intervention Program for Psychoses (PEPP), Malla *et al.* 2003).

Early intervention focuses on detecting psychosis as early as possible and even before the onset of the illness, making it possible to study the possibilities of psychosis prevention in subjects at risk of psychosis. Early intervention requires widespread actions such as public awareness campaigns to increase the knowledge of psychosis, and offers mostly outpatient treatment with a psycho-educative approach to subjects and their families (Melle *et al.* 2006, Lloyd-Evans *et al.* 2011).

The first study of early intervention in psychiatry was commenced in the UK and showed that early intervention in psychiatric emergencies can decrease the use of hospitalization compared to standard treatment in psychiatric hospitals (Merson *et al.* 1992). Since that, especially early intervention in psychosis has been studied widely and also more recently with long-term follow-ups, and early intervention has become common practice in many places. The main aim of these projects was to shorten DUP and they led to the definition of attenuated psychosis syndrome. The shortening of DUP turned out to be relatively challenging and intervention in the prodromal phase before the onset of psychosis even more challenging (Larsen *et al.* 2001). Some of the projects managed to achieve this, while others have not shown immediate effects of shortening DUP (Johannessen *et al.* 2001, Petersen *et al.* 2005, Chen *et al.* 2011).

The follow-ups of at least 5 years have shown that the effects of early intervention may not last in the long term (Bertelsen *et al.* 2008, Gafoor *et al.* 2010). In one study with a follow-up of 10 years, early detection of psychosis was associated with higher recovery rates and employment, but also higher levels of excitative symptoms (Hegelstad *et al.* 2012). Very recently, there has been discussion of whether early intervention is cost-effective. This was done in a review of eleven articles raising questions about whether the investments in the treatment in the early phase of an often long-term disorder are as good as hoped (Amos 2012).

3.4 Prevention of psychosis

The ultimate goal of *early intervention* is the idea of prevention of schizophrenic psychosis. The idea is based on the thought that psychosis could be prevented by using interventions such as medication or psychosocial treatments for subjects who are at high risk of being psychotic in the future. The risk assessment is based on the prodromal symptoms of psychosis and other information such as decline in functions. Different definitions have been given, such as at risk mental state (ARMS) (McGorry & Singh 1995) and ultra-high risk (UHR) state for psychosis (Yung *et al.* 2004). The remarkable effort in early intervention of schizophrenia has promoted the ideas of the possibility to prevent schizophrenia, or at least delay the onset of psychosis and improve the prognosis (Yung *et al.* 2007, Salokangas & McGlashan 2008).

The problem in this assessment is the relatively low number of subjects who eventually would be psychotic, as the proportion of subjects estimated to be at risk of psychosis who actually transition to psychosis varies in studies between 10-45% in a two-year follow-up (Fusar-Poli *et al.* 2012b). This leads to the situation where the majority of subjects estimated to be in an at-risk mental state would be exposed to potentially harmful effects of antipsychotic medication.

Psychosocial intervention such as psychotherapy also comes with the possibility of adverse effects such as stigma, and also costs. These risks should not be taken when the actual risk of psychosis may be lower than the probability of not having psychosis in the future, noting also the lack of conclusive evidence of the efficacy of one type of intervention (McGorry *et al.* 2009, Fusar-Poli *et al.* 2012b). This is one reason for the upcoming definition of attenuated psychosis, to be included only in the research version of DSM-V (www.dsm5.org), to gather more information to increase the chances of developing more beneficial and less harmful ways to intervene early in psychosis.

The concept of *prodromal phase*, which precedes psychosis, is also problematic due to its retrospective character (Häfner *et al.* 2005) and possible long-lasting symptoms (such as negative symptoms, cognitive decline, obsessive behavior, depression, and mild positive symptoms) (Harrigan *et al.* 2003). For that reason, especially in prospective studies, it has been suggested to use the term “at high risk of psychosis”, or ultra-high-risk of psychosis (UHR), or at risk mental state (ARMS) (Svirskis *et al.* 2005, Svirskis *et al.* 2007). A recent comprehensive review of studies of high-risk states for psychosis has presented

the definitions and instruments of definitions for high-risk criteria for psychosis (Fusar-Poli *et al.* 2012b).

Despite some promising results of early interventions, such as integrated psychological intervention (Bechdolf *et al.* 2012), at the moment it seems that there are no possibilities to effectively prevent psychosis or schizophrenia (Kirkbride & Jones 2011). The possible additional benefits could be gained with very early intervention during or even before pregnancy and during early development and childhood (Bird *et al.* 2010, Brown & McGrath 2011, Kirkbride & Jones 2011).

3.5 Summarizing earlier research

There is some evidence of a correlation between long DUP and a poor clinical and social outcome in the first years of illness. However, it is unclear whether and how DUP relates to outcomes and brain morphology in schizophrenia in the long term. Earlier studies also lack unbiased population-based samples. The results of studies on DUP and brain morphology are heterogeneous and practically no clear and consistent evidence is found of the association between long DUP and more drastic changes in brain morphology.

When concluding the information still required to be studied on DUP, it can be noted that the concept of DUP and sample setting has been shown to vary between studies. Therefore, the conclusions of the generalized effects of DUP remain unclear. The importance of studying DUP and various factors describing the outcome of the disorder in different phases of the illness is emphasized as the current trend of early intervention, although the long-term effects of untreated psychosis and various interventions are not completely known.

The current thesis focuses on the longitudinal correlations of DUP with outcomes in schizophrenia systematically in the literature and within a unique and epidemiologically principled sample, to provide new information. Previous studies have not studied the long-term association between DUP and brain morphology.

4 Aims of the study

4.1 Aims of the study

The Northern Finland 1966 Birth Cohort (NFBC 1966) study aims to produce new information on the etiology of psychotic disorders, early risk factors, and epidemiology. This helps to improve the understanding of psychotic disorders and may be one step towards primary prevention of schizophrenia. One aim is to clarify the etiology and outcomes of schizophrenia and attempt to obtain new information for use in the development of treatments for schizophrenia by analyzing current treatment practices. The aims of this doctoral thesis were:

- I To determine what is currently known about the association between DUP and long-term outcomes in schizophrenia.
- II To study the possible association between the duration of untreated psychosis and outcomes in schizophrenia in the NFBC 1966.
- III To study the relationship between the duration of untreated psychosis and brain morphology in schizophrenia in the NFBC 1966.

4.2 Hypotheses

The hypotheses of this study were:

- I There is an association between longer DUP and poor long-term outcome in previous studies.
- II There is an association between longer DUP and poor outcome in schizophrenia in the NFBC 1966.
- III Longer DUP relates to smaller gray-matter density in schizophrenia in the NFBC 1966.

5 Material and methods

5.1 Meta-analysis (I)

5.1.1 Data collection

Collection of the data, including the literature search and analyses of abstracts and full-text, was performed applying the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (Moher *et al.* 2009). The literature was searched from different databases using the following search terms: (“duration of untreated psychosis” OR “delay in treatment” OR “treatment delay” OR “initiation of treatment” OR “duration of untreated illness”) AND (psychosis OR “psychotic disorders” OR schizophrenia OR schizoaffective OR schizopreniform).

5.1.2 Study selection

Study selection was done based on five pre-defined selection criteria, which required that the sample of original studies consisted mostly of subjects with schizophrenia, diagnosis was done using structured diagnostic system criteria, the sample size was at least 20 subjects, the definition of DUP was comparable to other studies, and the study had studied the association between DUP and one or more clinical or social outcomes with a minimum length of follow-up of 2 years. Randomized controlled trials were excluded from the meta-analysis.

The outcome was categorized in nine groups: symptoms measured as positive symptoms, negative symptoms, global clinical outcome, clinical remission, social functioning, employment, global outcome, quality of life, and hospital treatments. The detailed definitions of these categories are presented in original publication I.

5.1.3 Statistical analysis

Random-effects models were used in order to pool overall estimates of effect sizes. In the random-effects analysis, each study was weighted by the inverse of its variance and the between-studies variance. Results from unadjusted analysis were included when possible. Correlation coefficients can be interpreted as small

0.10, moderate 0.30, and large 0.50 effects (Cohen 1992). In the current study, negative correlation indicates that long DUP is associated with poorer outcome.

Detailed information on *meta-regression* (Sterne 2009), which was used to estimate the effect of possible covariates and of tests of *heterogeneity*, is described in original publication I. Possible publication bias was studied using the Begg's test for small-study effects (Sterne 2009). An alpha level of 0.05 was used for all statistical tests. Stata version 11 (Stata Corporation 2009) was used in all analyses.

5.2 The Northern Finland 1966 Birth Cohort (II, III)

5.2.1 Study population

The NFBC 1966 is an unselected, general population birth cohort ascertained during mid-pregnancy. It is based on 12,068 women who lived in the area of Oulu and Lapland and their 12,058 born children (Rantakallio 1969). The cohort currently includes 10,934 people who were alive and lived in Finland at 16 years old.

In the NFBC 1966, there are 111 individuals with a validated diagnosis of schizophrenia and 55 with other psychosis diagnoses with the onset of illness occurring before the end of 1997 (Isohanni *et al.* 1997, Moilanen *et al.* 2003).

5.2.2 Ascertainment and sampling of people with psychosis (II, III)

Register-based information on outcome was used for all individuals who, at any time, fulfilled the DSM-III-R criteria for schizophrenia (n=111) (Isohanni *et al.* 1997, Moilanen *et al.* 2003, Haapea *et al.* 2007). 89 individuals with a diagnosis of schizophrenia were included. 22 subjects were excluded, as information regarding the onset of psychosis was not available in the medical records for 17 subjects, and DUP had ended after 1995 for 5 subjects (follow-up time less than 5 years).

All subjects with a diagnosis of schizophrenia or other psychosis were invited for a field survey in 1999-2001 to the University Hospital of Oulu. Data on outcomes from assessments based on clinical interviews (SCID (Structural Clinical Interview for DSM-III-R, Spitzer *et al.* 1989)) was available for subjects who participated in the field survey. This data included PANSS, CGI (Clinical

Global Impression), and SOFAS (Social and Occupational Functioning Assessment Scale). During the interview, subjects were asked about their current and past psychiatric medication and information on the use of medication was also available from medical records.

54 of 61 subjects with schizophrenia had a successful MRI scan of the brain in 1999-2001 (Haapea *et al.* 2007, Tanskanen *et al.* 2005, 2009, 2010). It was possible to define DUP for 47 of these individuals, of which one subject was excluded as an outlier.

5.2.3 Assessment of the duration of untreated psychosis (II, III)

The duration of untreated psychosis (DUP) was defined retrospectively based on information in the medical records from hospitals and health centers. Ratings were made independently of the outcome of subjects. The information gathered included the onset of first psychotic symptoms, the onset of first psychiatric hospitalization, and the onset of antipsychotic medication.

The onset of psychotic symptoms was defined as the onset of positive symptoms that were considered to be at least moderate symptoms corresponding to 4 points or more on PANSS. DUP was defined as the period between the onset of first psychotic symptoms and the time of the beginning of treatment. The DUP assessment is reported in detail in original publications II and III.

5.2.4 Assessment of outcomes (II)

Outcome variables were divided into three categories in the NFBC 1966: short- and long-term outcome and course of illness. The outcome variables of the first two years of the follow-up were defined as the short-term outcome. Variables with at least five years of follow-up, on average 11-20 years, were used to describe the long-term outcome.

The short-term outcome regarding hospital treatments was studied as the *length of the first psychiatric hospitalization, re-hospitalization, and cumulative number of hospital treatment days due to psychosis within two years. Occupational recovery and decreases and increases in employment* were measured after the first two years of illness. The data regarding the *symptoms* at first psychiatric hospitalization was available based on the OPCRIT version 3.3

(Operational Criteria Checklist for Psychotic Illness) checklist (McGuffin *et al.* 1991).

The long-term outcome was measured using the *cumulative number of treatment days* at hospital due to psychosis in two time periods (1999-2000 and 2007-2008), *disability pension* until the end of the year 2000, *employment* in 1999-2000, *remission* according to Andreasen *et al.* (2005), symptoms from PANSS according to factors defined by van der Gaag *et al.* (2006), and SOFAS.

The course of illness was analyzed as *the time to disability pension*, *proportional time spent at work and in psychiatric hospital* weekly during the first 10 years of follow-up, *the cumulative number of any psychiatric treatment days* until the end of 2008, and as *revolving door syndrome* (Miettunen *et al.* 2006). Variables are described in detail in original publication II. In addition to these variables, quality of life was measured using a questionnaire (15D) and the global outcome was combined from variables describing employment, hospitalizations, and symptoms.

5.2.5 Brain morphology (III)

Data of brain morphology was collected in the field survey in 1999-2001 using MRI scanning of the brain at the University Hospital of Oulu, Department of Radiology. Detailed information on technical parameters of scanning and analysis of the MRI data are described in original publication III.

The analysis of MRI data for each subject was done by first segmenting the image into maps of gray matter, white matter, and CSF using Brain Activation and Morphological Mapping (BAMM) software (Brammer *et al.* 1997, Suckling *et al.* 1999a, Suckling *et al.* 1999b). The gray matter maps were analyzed in 116 anatomical regions. For this purpose, a brain template was used to transform the gray matter maps of all subjects onto the same axial orientation in the FSL software (Jenkinson & Smith 2001). After this, it was possible to estimate the mean densities of 116 cortical and subcortical anatomical gray-matter areas using Automated Anatomical Labeling (AAL) (Schmahmann *et al.* 1999). 116 areas were combined into 17 larger regions for the first stage of analysis (Tzourio-Mazoyer *et al.* 2002).

5.2.6 Statistical methods

Statistical analysis in original publication II

The logarithmic transformation ($\ln+1$) of DUP was used in statistical analyses because the distribution of DUP was skewed, with most subjects having a relatively short DUP. Associations between outcome variables and DUP were analyzed using a univariate analysis of variance for categorical and a linear regression analysis for continuous variables.

To analyze the possible effect of selection bias, those who were excluded ($n=22$) and the final sample ($n=89$) were compared using cross-tabulation and a Mann-Whitney U-test for various variables. It was also analyzed whether the length of DUP differed between those who participated in the survey in 1999-2001 ($n=47$) and those who did not ($n=42$). Statistical analyses were made using PASW Statistics v. 18.

Statistical analysis in original publication III

The effect of logarithmic DUP on the regions of brain areas were modeled using linear regression analysis. For only those areas that passed a threshold ($\alpha = 0.05$) in stage one of the analysis, the association was examined between DUP and the gray-matter density of component sub-regions. SPSS versions 15.0 to 18.0 were used to conduct the analyses. Details of the statistical analyses are described in original publication III.

6 Ethical considerations and personal involvement

The study design of the Northern Finland 1966 Birth Cohort is under constant review by the Ethics Committee of the Oulu University Hospital (formerly the Ethical Committee of Oulu University, Faculty of Medicine). The research plans for the 31-year follow-up of the NFBC 1966 study were accepted by the Ethical Committee of Oulu University, Faculty of Medicine, on June 7th 1996; the 34-year psychiatric follow-up on March 30th 1998; and the 43-year follow-up on February 18th 2008. Data protection has been scrutinized by the Privacy Protection Agency, as well as by the principles from the Ministry of Health and Social Affairs in 1994, when the permission to have information on the study sample was obtained. Informed consent was inquired from all the participants, and those subjects who declined use of their data have been excluded from the study.

The author of this thesis has participated in the Northern Finland 1966 Birth Cohort study as a researcher since 2006. Due to the longitudinal nature of the NFBC 1966 study, the author has not participated in collection of all of the data used in the original studies II and III. The author has participated in the design of all the original studies, as well as in defining and measuring the duration of untreated psychosis for the subjects diagnosed with schizophrenic psychosis in the NFBC 1966. The author was a correspondent in interviews in the NFBC 43-year psychiatric follow-up study. Statistical analyses of all original articles (I-III) have been made by the author, together with Adjunct Professor Jouko Miettunen, PhD Marianne Haapea, and PhStud Merja Kyllönen. A systematic literature search for meta-analysis was done by MA Noora Hirvonen. The author participated in the planning of the literature search and read the abstracts and articles, and collected the data from the articles. The transformation of MRI images into estimates of gray-matter density was done by MSc Xavier Chitnis. The author was involved as one author in the writing of the review articles of the NFBC 1966 (Isohanni *et al.* 2009, 2010, 2011). The author has written the first and final versions of all the original articles (I-III). The author has also been the corresponding author in all the original studies and coordinated the correction and resubmission process for all the original studies.

7 Results

7.1 Meta-analysis of duration of untreated psychosis and long-term outcomes (I)

The search produced 4495 results and, after the removal of duplicates, 2835 publications were identified. Based on the information on abstracts, 167 articles were selected for comprehensive evaluation. 56 studies were found from other sources, leading to a total of 223 studies that were evaluated. 36 articles analyzing 31 different samples were included in the meta-analyses.

The mean age of onset in the studies was 29 years, the mean length of follow-up was 8.3 years, and the mean length of DUP was 61.4 weeks. The number of studies in different outcome categories varied from 6 to 17.

7.1.1 The association between duration of untreated psychosis and outcome categories

Long DUP was associated with more severe symptoms in all categories (positive symptoms: $r=-0.16$; negative symptoms: $r=-0.15$; global clinical outcome: $r=-0.16$; remission: $r=-0.18$). The estimated correlation between DUP and the *hospital treatments* from 10 samples was small and not statistically significant ($r=-0.10$) (Figure 1).

Long DUP also correlated with poor *social functioning* ($r=-0.19$) and global outcome ($r=-0.19$). *Employment* and *quality of life* did not correlate with DUP significantly (Figure 1).

7.1.2 Heterogeneity and covariates

Significant heterogeneity was found in all but two outcome categories. Heterogeneity between studies of DUP and global clinical outcome was close to being statistically significant and no sign of heterogeneity between studies of DUP and remission was found.

When the effects of different covariates on correlation of DUP and outcomes were analyzed, only a few significant effects of covariates were found. *The quality score of the study* had an effect on the correlation between DUP and hospital treatments ($p=0.006$), with DUP having more significant correlation with

hospital treatments in studies with lower quality scores. The *length of follow-up* affected the correlation between DUP and negative symptoms ($p=0.048$). A *lower income level of the country* resulted in lower correlation between DUP and positive symptoms ($p=0.013$) and global clinical outcome ($p=0.007$).

Correlations were not affected statistically significantly when one study was excluded at a time in the influence study. There was no statistically significant publication bias.

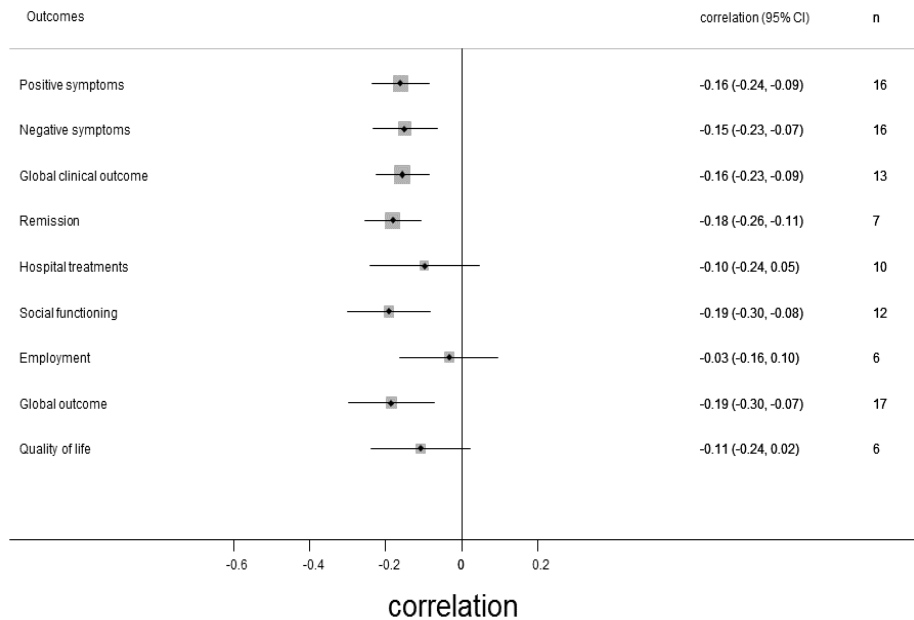


Fig. 1. The correlations between DUP and clinical outcomes, hospital treatments, and social functioning (original publication I, Figure 2).

7.2 The association between duration of untreated psychosis and outcome in the Northern Finland 1966 Birth Cohort (II)

7.2.1 Characteristics of the sample

The mean DUP was 225 days (SD = 329) and the median DUP was 121 days. Sex, educational level, alcohol abuse, and socioeconomic status were not statistically

significantly associated with DUP. The mean duration of illness at the end of 2008 was 20.6 years (SD 3.9). These variables were not associated with DUP.

In attrition analysis, the only difference between the sample (n=89) and the 22 excluded cases was the onset age of the illness, which was significantly higher (mean 21.8 vs. 26.1 years, p=0.001) in the group of excluded subjects. DUP did not differ (p=0.901) between those who participated (n=47) and those who did not participate (n=42) in 1999-2001.

7.2.2 Duration of untreated psychosis and short-term outcome

Longer DUP was associated with a longer *duration of the first psychiatric hospital treatment* and an increased *risk of re-hospitalization within two years following discharge*, even when adjusted for covariates (Table 5). DUP was not associated with a cumulative number of hospital treatment days during the first two years, occupational recovery, or symptoms in the short-term.

Table 5. Associations between duration of untreated psychosis (DUP) and statistically significant outcome variables, adjusted with covariates (original publication II, Table 4).

Outcome variables	N	Adjusted ¹		Adjusted	
		Wald	Sig.	Wald	Sig.
Longer length of first psychiatric hospitalization	86	8.2	0.004	NA	NA
Re-hospitalization in 2 years after the end of DUP	87	4.5	0.034	5.9	0.015 ²
Decreased risk of disability pension due to psychosis	86	5.3	0.021	7.4	0.006 ³

¹ Adjusted with sex and onset age of schizophrenia.

² Adjusted with sex, onset age of schizophrenia, and length of first psychiatric hospitalization.

³ Adjusted with sex, onset age of schizophrenia, length of first psychiatric hospitalization, and re-hospitalization in 2 years after the end of DUP.

NA= Not applicable

7.2.3 Duration of untreated psychosis and long-term outcome and course of illness

The only statistically significant association between DUP and long-term outcome was the association between longer DUP and decreased *rate of disability pension*. This association remained significant when adjusted for covariates (Table 5).

Among the whole sample, in survival analyses, there was no significant association between the length of DUP and the time to disability pension (Figure 2) (mean 3.4 years (SD 4.3), median 1.9 years) or the time to re-hospitalization after the discharge from the first hospital treatment (Figure 3). DUP was not associated with remission, PANSS, SOFAS, total number of hospital days before 2008, or revolving door syndrome.

When the whole course of hospitalizations and occupational capacity was compared between groups of short DUP (\leq median) and long DUP ($>$ median), *the proportion of time spent in hospital* was smaller ($p=0.027$) and *the proportional time spent at work* was higher in the long DUP group ($p=0.042$). These associations remained significant when adjusted for onset age of illness and sex.

In the NFBC 1966, the length of DUP did not significantly correlate with quality of life when measured using a 15D questionnaire ($r=0.02$) or global outcome ($r=0.10$).

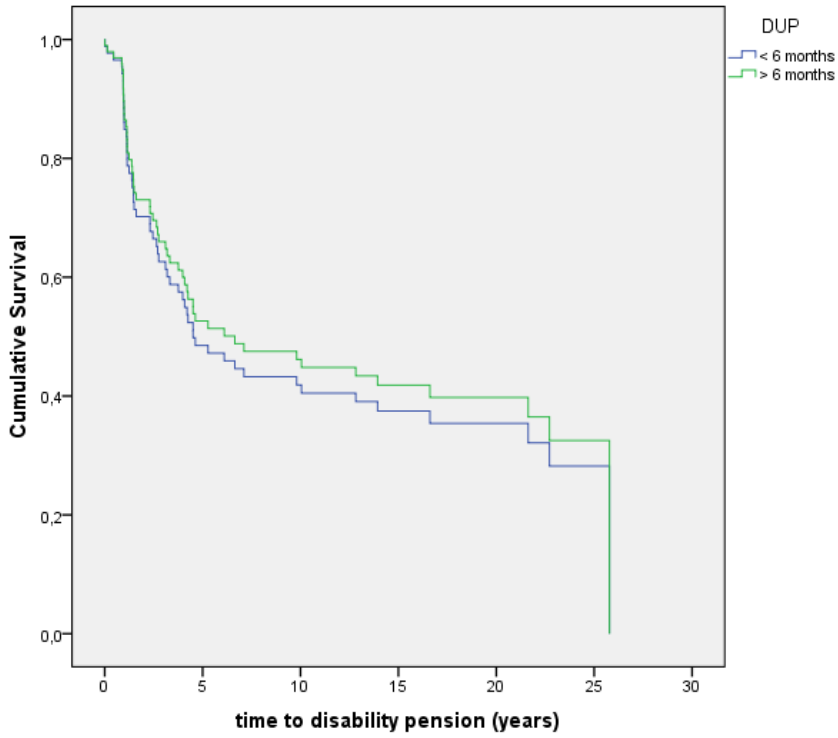


Fig. 2. Survival curve of the association between duration of untreated psychosis (DUP) and time to disability pension (p=0.689, n=54).

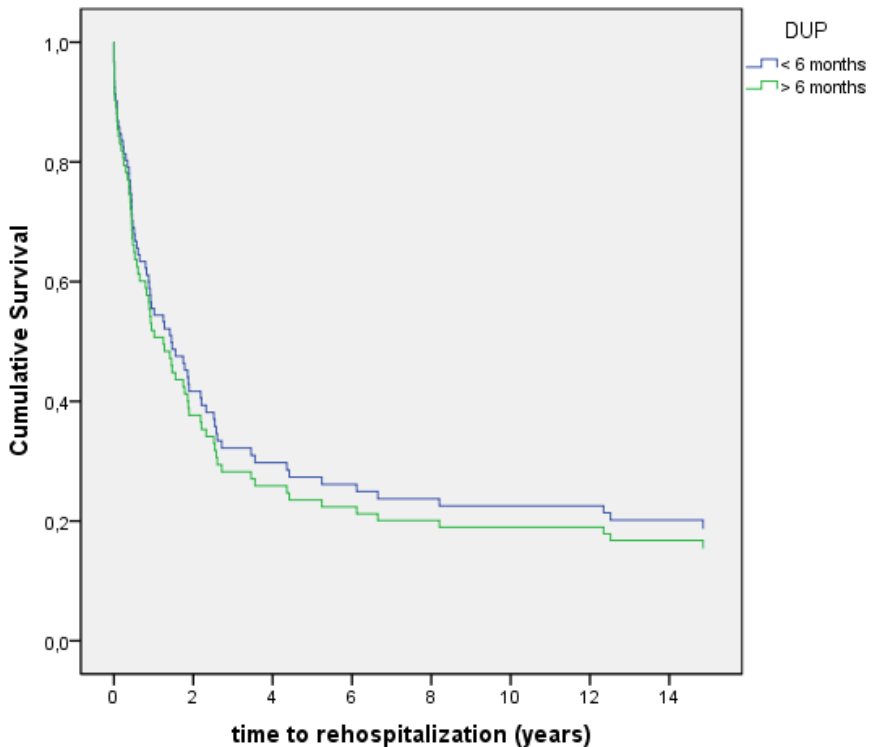


Fig. 3. Survival curve of the association between duration of untreated psychosis (DUP) and time to re-hospitalization ($p=0.669$, $n=71$).

7.3 Duration of untreated psychosis and brain morphology in the Northern Finland 1966 Birth Cohort (III)

7.3.1 Characteristics of the sample

The mean of DUP was 228 days and the median 143 days (range 0-955 days). DUP was not significantly associated with sex, education, antipsychotic medication, time from onset of illness, number of days in psychiatric hospitalization, alcohol abuse, and socioeconomic status.

7.3.2 Association between duration of untreated psychosis and brain morphology

DUP did not correlate with total gray or white matter or CSF volume. There was an association with longer DUP and smaller gray-matter density of right subcortical gray nuclei ($p=0.047$) when analyzed using sex, ICV, and time after illness onset as covariates. When long-term use of antipsychotic medication, number of days in psychiatric hospital, and alcohol abuse were added as covariates, an association was found only between longer DUP and smaller gray-matter density of the right limbic area ($p=0.026$) (Figure 4).

Using the same covariates in a secondary analyses of the right limbic area, smaller gray-matter densities of the hippocampus were statistically significantly associated with longer DUP ($p=0.013$) (Figure 5). Lower gray-matter density in the superior temporal gyrus was also linked with longer DUP ($p=0.038$).

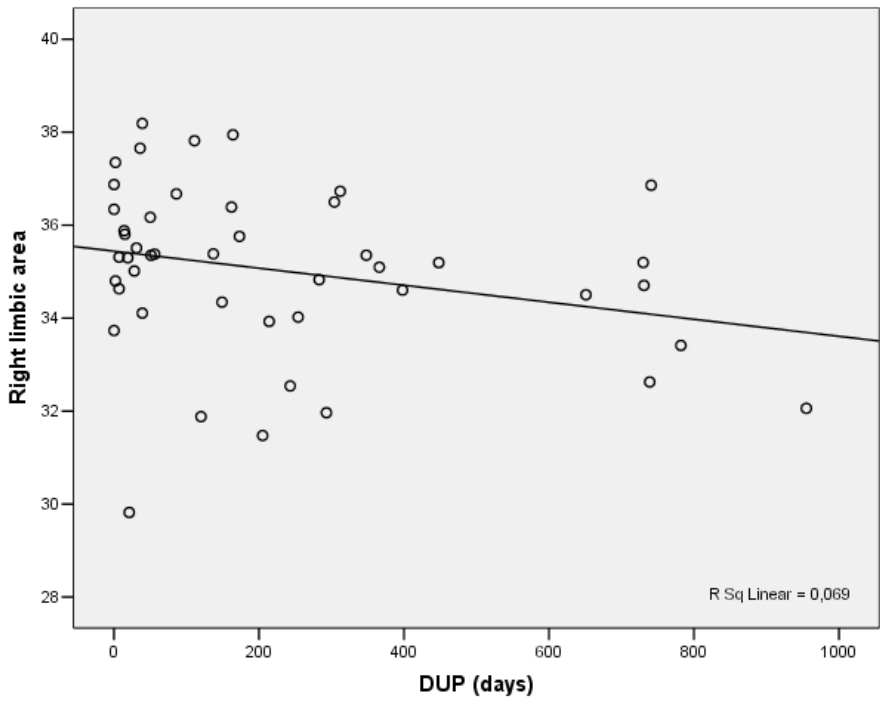


Fig. 4. The association between duration of untreated psychosis (DUP) and gray-matter density of the right limbic area ($p=0.026$, $n=46$).

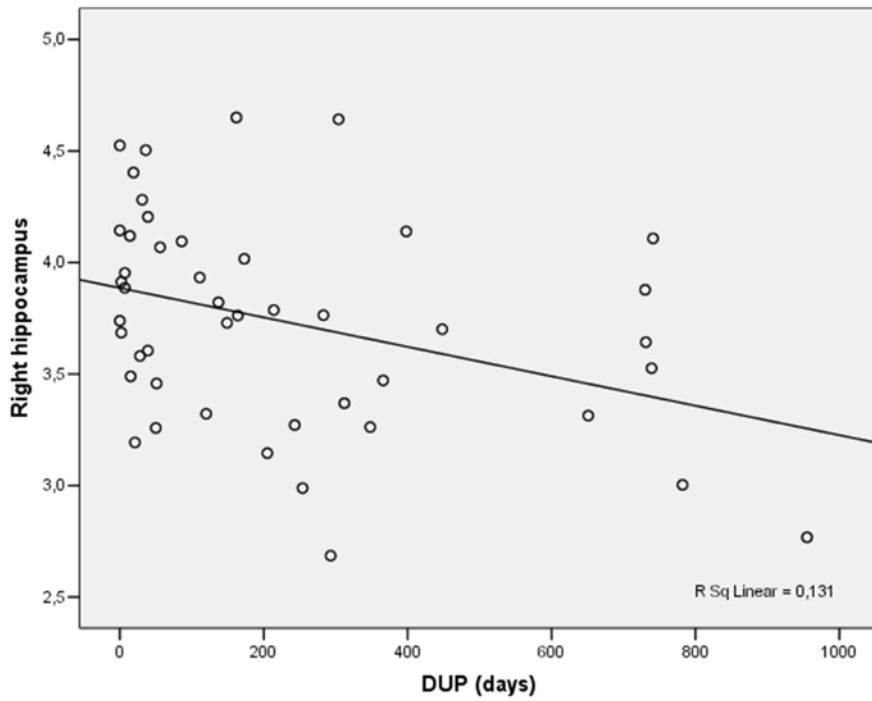


Fig. 5. The association between duration of untreated psychosis (DUP) and the gray-matter density of the right hippocampus ($p=0.013$, $n=46$) (original publication III, Figure 1).

8 Discussion

8.1 Main findings

In the *meta-analysis* (I), there were small correlations between long DUP and more severe positive and negative symptoms and poor clinical outcome, social functioning, and global outcome. Employment, quality of life, and hospital treatments were not associated with DUP and these factors have not been studied separately with DUP in a meta-analysis before. Covariates had little or no effect on the correlation between DUP and outcomes.

In the *NFBC 1966*, longer duration of untreated psychosis in schizophrenia was found to be associated with an increased length of first hospitalization and more frequent re-hospitalization in the first 2 years of follow-up (II). In the long-term follow-up, long DUP was associated only with a decreased probability of disability pension, decreased hospital treatments, and an increased rate of employment. The finding of long DUP's association with a relatively better outcome in the long-term follow-up was unexpected, considering especially the previous studies of DUP with short follow-ups.

There was only some association between DUP and *brain morphology* in the *NFBC 1966* (III). Long DUP correlated with decreased gray-matter density in the right limbic area and especially the hippocampus after more than 10 years from the onset of the first psychosis. The association was also statistically significant when possible confounders were added to the analysis (III). The association between DUP and decreased gray-matter density in the hippocampus has not been reported previously.

8.2 Discussion of results

8.2.1 *Meta-analysis of association between duration of untreated psychosis and long-term outcomes (I)*

DUP and clinical outcome

Long DUP had a small correlation with poor long-term clinical outcome measured with *symptoms, global clinical outcome, and remission*. The estimated

effect sizes of DUP on long-term clinical outcomes were at about the same level in all four categories. The results are similar to earlier meta-analyses, although correlations were marginally smaller compared to those presented in previous meta-analyses (Marshall *et al.* 2005, Perkins *et al.* 2005, Boonstra *et al.* 2012). The correlation between DUP and *remission* as defined by Andreasen *et al.* (2005) has not been studied in a meta-analysis before.

Long DUP correlated modestly with a decline in *social functioning* and poor *global outcome* but not with *hospital treatments*, *quality of life*, or *employment*. These correlations between DUP and social functioning and global outcome have not been widely studied previously in a meta-analysis.

The relatively modest effect of DUP on long-term outcome in schizophrenia is not that surprising, considering the various factors that may impact the course of the illness. Therefore, the lack of long-term correlation between DUP and some outcomes is somewhat comforting for the treatment expectations of subjects with long DUP.

In addition, the lack of association between DUP and hospital treatments, employment, and quality of life indicates that some of the subjects with longer DUP do not necessarily need treatment as much and as early as others. These subjects may have characteristics that protect them from the negative effects of DUP.

Of the covariates, only the *length of follow-up*, estimated *quality score*, and *income level* had a significant effect on some of the correlation between DUP and outcome. It seems that during the course of the illness, the relatively small correlation between DUP and poor clinical outcome, and in some aspects poor social functioning, remains rather stable. However, this does not prove that long DUP causes poor outcome (McGlashan 2008).

The mode of onset is a possible confounder (Moncrieff 2011) and it was taken into account in some of the original studies, without a significant effect on the correlation between DUP and outcome (Bottlender *et al.* 2003, Ichinose *et al.* 2010, Chang *et al.* 2012). It seems that the mode of onset is not that strongly correlated with the length of DUP, and DUP can be studied as an independent predictor of outcome.

8.2.2 Duration of untreated psychosis and short-term outcome in the Northern Finland 1966 Birth Cohort (II)

The association between long DUP and increased *length of first hospitalization* and *risk of re-hospitalization* in the first two years of illness was an expected finding. It may well be that subjects with long DUP had more symptoms and a more severe type of illness when they were hospitalized for the first time due to psychosis, although there was no difference in the available data. This could explain the need for longer hospital treatment and the need for further hospital treatment. Reliable information on symptoms was available for fewer than half of the subjects, and therefore there is no certainty of the reason for the increased hospitalizations. One explanation might be the poor insight that leads to longer hospital treatment and to the discontinuation of antipsychotic medication and higher risk of relapse after the first hospitalization (Hill *et al.* 2010).

The finding of increased hospitalizations at the beginning of the illness might also reflect the way the health care system compensates for the potential harmful effects of prolonged untreated psychosis. The DUP in Finland is relatively short compared to that reported in other studies (Kalla *et al.* 2002). Well organized public health care may well have been one of the pioneers in early intervention (Isohanni & Nieminen 1992), with educated psychiatric nurses and psychologists in health centers around Finland (Salokangas 1994, Joukamaa *et al.* 1995).

Earlier studies of the association between DUP and employment in the short term are few, as studies have focused on the estimates of global and social functioning during interviews (Marshall *et al.* 2005, Perkins *et al.* 2005). Based on the long-term findings of this study, one could assume that at least for some individuals diagnosed with schizophrenia, the possibilities and abilities for occupational recovery should be considered by various methods in earlier phases of the illness, to support their rehabilitation considering their own aims and strengths.

8.2.3 Duration of untreated psychosis and long-term outcome in the Northern Finland 1966 Birth Cohort (II)

In the general population-based sample, there was no evidence of harmful effects of long DUP on long-term outcomes in schizophrenia. Over half of the subjects with information on DUP were interviewed in 1999-2001, and there was no

evidence of more severe symptomatology or psychopathology for subjects with long DUP. However, the association between long DUP and *decreased rate of disability pension and hospitalizations and increased employment* in the long term might describe some beneficial factors behind the concept of DUP that are very much worth noting and that are not possible to study in clinical patient samples with only cross-sectional follow-up data available. To my knowledge, the association between DUP and outcome with a long (10 years or more) follow-up has not previously been studied in an unselected population-based sample.

The lack of association between DUP and *symptomatic outcome* measured with PANSS in the NFBC 1966 corresponds with the findings of three other samples with a long follow-up (Wiersma *et al.* 1998, Röpcke & Eggers 2005, Shrivastava *et al.* 2010). Only a few samples have displayed an association between DUP and a very long-term symptomatic outcome using PANSS (Scully *et al.* 1997, Bottlender *et al.* 2003).

Better *occupational functioning* may be explained by better cognitive performance, which has been associated with longer DUP (Norman *et al.* 2001, Dassa *et al.* 2010). Post-hoc analyses for comparisons between the four groups defined by the length of DUP and disability pension did not provide conclusive evidence of a reason why subjects with long DUP had better occupational functioning. This may be due to a lack of power, as subgroups were small in these analyses. It would be possible to make similar comparisons between groups defined by the length of DUP and employment, but the groups would be even smaller, as employment was not as common as not being on a disability pension.

A small subgroup with long DUP may exist where non-treatment may reflect an effort to adapt to the insidious illness. It is possible and sort of logical to think that some subjects with long DUP have more abilities and the will to fight against the serious disorder. They might have had experiences of psychosis and treatment of psychosis in their relatives or close ones, and might also have psychosocial and other coping mechanisms that maintain their psychiatric wellness and functioning in the course of the severe illness.

One might speculate as well that treatment, especially at hospitals and in the very early phases of psychosis, is something that does not necessarily promote the abilities and strengths of patients if work rehabilitation is not included (Honkonen *et al.* 2007, Tsang *et al.* 2010). It is possible that some subjects with long DUP do not co-operate as well as those who seek help in the very early phases of the disease. This will to fight against the disorder and the authorities may have been one factor that has actually worked for the benefit of subjects with long DUP.

They have remained part of working society and perhaps learnt the ways to cope with their psychotic symptoms. This is something that might also have been affected by the family, friends, and working environment of the subjects (Tsang *et al.* 2010).

It is also possible that some subjects with long DUP have a higher tolerance of positive symptoms and do not need as much treatment in the very early phases of the illness as subjects who seek help at the very beginning of positive symptoms. There might be differences in positive symptoms and how they affect one's life, whether the symptoms are more paranoia or more commenting hallucinations. The possible variations in the disturbance of positive symptoms, as well as the different styles of coping with psychotic illness, have been studied in a limited way (Modestin *et al.* 2009).

The true clinical significance of the association between long DUP and better occupational outcome in the long-term remains unclear, given that it has been shown that granted disability pension is associated with decreased mortality and other beneficial factors in schizophrenia (Kiviniemi *et al.* 2011). The outcome measures, especially relating to employment and disability pension, are also affected by society and the current economic situation. This possibly remarkable effect is difficult to take into account in analyses.

8.2.4 Duration of untreated psychosis and brain morphology in the Northern Finland 1966 Birth Cohort (III)

Previous studies of DUP and brain morphology are few. This was the first study of DUP and brain morphology with an unselected, population-based sample with subjects with several years of illness. Previous studies have been first-episode studies focusing on the early phase of the illness. The longest duration of illness in previous studies has been up to 5 years (Takahashi *et al.* 2007).

Some previous studies have mostly analyzed large anatomical areas (Hoff *et al.* 2000, Ho *et al.* 2003), while others have focused on smaller areas, such as the hippocampus (Ho *et al.* 2005) or caudate nucleus (Crespo-Facorro *et al.* 2007a). A combination of these methods was used in the NFBC 1966 by first studying large anatomical areas and then performing secondary analyses only inside those areas that passed an initial threshold for association.

When comparing the results of this study to previous studies, it can be suggested that as a whole, the results for gray and white matter and CSF are

similar, with no association (Hoff *et al.* 2000, Ho *et al.* 2003, Lappin *et al.* 2006). Decreased gray-matter density in the right hippocampus has not previously been linked with DUP (Ho *et al.* 2005). Not all previous studies have analyzed the same brain regions, which makes it difficult to compare results.

Abnormalities in anatomy and function of the hippocampus are thought to have a major role in the pathophysiology of schizophrenia. The hippocampus is essential for normal physiological functions, such as information processing, learning, and memory. Impairments in cognition and memory commonly found in schizophrenia are thought to be linked with gray-matter deficits of the hippocampus. There have been a few meta-analyses that have indicated that the volume of the hippocampus is reduced in schizophrenia (Nelson *et al.* 1998, Wright *et al.* 2000). However, some studies have failed to find a similar association (Csernansky *et al.* 2002, Meda *et al.* 2008). All in all, considering the cognitive decline in schizophrenia, it is interesting that long DUP was correlated with decreased gray-matter density of the hippocampus in the NFBC 1966.

Table 6. Summary of the main results of associations between duration of untreated psychosis (DUP) and outcomes in the Northern Finland 1966 Birth Cohort (NFBC 1966) and other studies.

Outcomes	NFBC 1966 short-term	Other studies short-term	NFBC 1966, long-term	Other studies, long-term
Positive symptoms	Not significant	Long DUP → more symptoms	Not significant	Long DUP → more symptoms
Negative symptoms	Not significant	Long DUP → more symptoms	Not significant	Long DUP → more symptoms
Global clinical outcome	Not significant	Long DUP → poor outcome	Not significant	Long DUP → poor outcome
Remission	Not studied	Long DUP → poor outcome	Not significant	Long DUP → poor outcome
Hospital treatments	Long DUP → poorer outcome	Not systematically studied	Long DUP → better outcome	Not significant
Social functioning	Not studied	Not significant	Not significant	Long DUP → poor outcome
Employment	Not significant	Not systematically studied	Long DUP → better outcome	Not significant
Global outcome	Not studied	Long DUP → poor outcome	Not significant	Long DUP → poor outcome

Outcomes	NFBC 1966 short-term	Other studies short-term	NFBC 1966, long-term	Other studies, long-term
Quality of life	Not studied	Long DUP → poor outcome	Not significant	Not significant
Brain morphology	Not studied	Various inconclusive findings	Long DUP → lower gray-matter density in right hippocampus	Not studied

8.3 Strengths and limitations of the study

8.3.1 Strengths of the study

Meta-analysis of the association between DUP and long-term outcome (I)

The literature search for meta-analysis was done in several databases, and articles published in languages other than English were included. The estimation of the general quality of publications is a strength of the study. Criteria requiring the majority of subjects to have been diagnosed with schizophrenia and at least three of four with schizophrenia spectrum disorder are somewhat stricter than used by previous meta-analyses (Perkins *et al.* 2005).

The meta-analysis was the first to systematically analyze the association between DUP and clinical remission (Andreasen *et al.* 2005), and hospital treatments and the effect of various possible covariates on the correlation between DUP and outcome.

DUP and outcomes in the NFBC 1966 (II, III)

The main strength of the study is a large and epidemiologically sound population-based sample. The information on the birth cohort is reliable and it has been collected longitudinally, from the second trimester of gestation to this day. Due to the vast amount of information and the long follow-up, it is possible to search for the causalities between variables. The longitudinal and highly reliable information available from national registers provides an extremely rare opportunity to study longitudinal effects on occupational outcome and hospitalizations, for example.

The sample is not selected, and this makes it possible to find reliable epidemiologic information, which can be utilized in clinical work. The significance of the results in this sample is also emphasized because of the fact that the duration of untreated psychosis has not been previously studied in birth cohorts. The unique study set might explain why the presented results differ somewhat, compared to earlier, mainly clinical studies (Marshall *et al.* 2005, Perkins *et al.* 2005). The current study design might lead to more naturalistic and conservative results regarding the association between DUP and outcome. Another strength is the possibility to analyze short- and long-term outcomes in the same sample, as well as the possibility to use mode of onset as a covariate.

For analyses of brain morphology, the reliability of the results was increased due to the non-existence of illicit drug users in the study. The study complements existing studies of DUP and brain structure in first-episode psychosis and provides information on how DUP affects brain structure after 10 years of illness.

8.3.2 Limitations of the study

Meta-analysis of the association between DUP and long-term outcome (I)

The challenges of studying DUP in the long term in one sample reflect in a meta-analysis as well. There were not too many studies analyzing the longitudinal effects of DUP that met our inclusion criteria. This indicates that definitive conclusions should not be made of the longitudinal effects of DUP on, for example, employment and quality of life.

Measurements of outcome used for clinical and scientific purposes in psychiatry and schizophrenia are not as exact as they are in some other fields of medicine. This and the heterogeneous phenotypes of schizophrenia may explain some of the perceived heterogeneity between the included studies.

Definitions of DUP and the estimated lengths of DUP vary between the included studies and some studies with remarkably different definitions of DUP or untreated illness before treatment were not included in the meta-analysis (Compton *et al.* 2011). The proposed definition of doses of DUP, which takes into account not only the duration of symptoms but also the severity, may be a better way to measure the possible harmful effects of DUP and decrease the heterogeneity found in this study, after the number of studies using this method of defining DUP has increased (Compton *et al.* 2011).

Some of the earliest studies in delayed treatment and long-term outcome in schizophrenia (Rupp & Fletcher 1940, Achte 1967, Scully *et al.* 1997) were not included in the meta-analysis due to variation between definitions of diagnosis and length of DUP. The exclusion of randomized controlled trials, most notably the OPUS trial, should not cause an under-estimation of the correlation between DUP and outcome. Most of the outcome variables in OPUS did not correlate with DUP at a 2-year follow-up, and those variables that did correlate had similar correlations to those found in original publication I (Jeppesen *et al.* 2008, Petersen *et al.* 2008). In the long term, the correlation between DUP and outcome in the OPUS trial is likely to be smaller, based on the decrease in the positive effect on outcome of early intervention between 2 and 5 years (Bertelsen *et al.* 2008).

The differences in the original samples and the methods used in them may affect the results and conclusions of the meta-analysis. The transformation of effect sizes in the original studies was done by using equations based on normal distribution (Rosenthal 1994, Borenstein *et al.* 2009). This may cause inaccuracy, which was reduced by the use of random weights.

DUP and outcomes in the NFBC 1966 (II, III)

Limitations of studying DUP in the NFBC 1966 include the relatively small number of subjects diagnosed with schizophrenia (n=89 out of 111). This might cause statistical weakness in the statistical analyses, but when compared to other studies, it is possible to get statistically significant results in sample sizes like this.

One limitation is the method of the definition of the duration of untreated psychosis, which was based mostly on medical records. High quality and continuous recording of the information guaranteed that the duration of untreated psychosis was possible to define in most cases. Measurement of DUP from medical records is challenging and there is no ideal way to define the onset of illness. Onset of treatment can be defined robustly from medical records. In Finland, medical records both in primary (GPs) and specialist level care have high quality; for example, 83% were adequate for diagnostic validation purposes (Isohanni *et al.* 1997) and include information written by doctors and nurses, and also in some cases from other sources, mainly family members. Information on medical records has been and is being collected prospectively and depends mostly on people who treat patients: therefore, the questions and interviews vary as

subjects have been treated in different parts of Finland, mostly between the years 1980 and 1997.

In the extensive birth cohort data, it was not possible to perform interviews concerning the beginning of psychotic symptoms on subjects who were all diagnosed with schizophrenia several years before the study began. When considering the possibility of interviews, it is worth noting the cognitive deficits and its effect on subjects' ability to remember the onset of an illness that happened several years ago. It is also worth noting that this sample was not originally designed to study DUP, and in principle and practice this kind of prospective study is difficult in a large birth cohort setting (Welham *et al.* 2009).

In this study, DUPs were started to define in 2006, which is on average 15 years after the onset of illness. DUP was defined from medical records based on the information that was recorded of onset of psychotic symptoms. Negative symptoms and social isolation or inability to go to school or to work were not considered as markers of psychotic illness, although it did in some cases correlate with the onset of psychosis.

A technical limitation of the study relates to the used scanning parameters. Although an advantage is that all participants were scanned in the same magnet using the same software, a limitation is that the slices collected were 3mm thick, which is less than optimal, potentially limiting the sensitivity to detect small differences between groups (Tanskanen *et al.* 2009). There are many confounding and intervening factors during follow-up that may affect the results, such as medication, length of illness, and progression of the disease itself. However, these were taken into account in statistical analyses, although the paucity of the information concerning the lifetime usage of antipsychotic medication is a limitation.

The method employed in this study to produce segmented brain tissue maps does not conserve the volume of the voxel occupied by a specific tissue, and therefore the voxel intensities represent gray-matter density, or concentration. In recognition of this, comparisons with other studies that have used different techniques that account for volume changes in gray matter after processing should be interpreted with these methodological differences in mind.

There is a possibility of false positive finding as gray-matter densities of various different brain regions were analyzed with DUP. However, as brain regional densities correlate to a degree with each other, Bonferroni correction was considered to be over-conservative and was not performed for that reason.

Previous studies have had high a non-participation rate, and it is not known whether this has affected their results (Ho *et al.* 2003, Lappin *et al.* 2006, Crespo-Facorro *et al.* 2007a, 2007b). It is possible that subjects with more severe illness and progressive changes of brain morphology have been excluded – or vice versa. In the NFBC 1966, there were some severely ill non-participants, which could cause a moderate bias (Haapea *et al.* 2007).

The results of this study describe relatively well the effects of DUP in the population-based sample in Finland. The birth cohort provides an opportunity to study the effects of DUP in a wider perspective and without the need to limit the follow-up of the sample to one or a few study centers. Due to well-organized publicly funded health care, the reasons and consequences of DUP may, however, differ from those in other parts of the world.

Long DUP and the negative prognosis with which it is sometimes correlated may not be shown in Finland that strongly. This may also be due to the cultural characteristics of Finland and the relatively small cities and societies, which are more capable of detecting and supporting people in the early phases of psychosis. Therefore, Finland and other Scandinavian countries may not be ideal locations for studying the effects of DUP on this longitudinal disorder when comparing the results to other sites. However, within well-organized public health care, the real effects of DUP on individuals may be possible to detect with less confounding of the different paths to treatment.

8.4 Theoretical discussion

8.4.1 Duration of untreated psychosis as an indicator and marker of difficult disease with poor prognosis

Long DUP has generally been viewed as a negative phenomenon, associated with poor outcome, particularly in the short term. The questioned theory of the toxicity of psychosis is one of the common reasons for aiming to shorten DUP. It is possible that long DUP adapts individuals with it more to a role of having psychosis, possibly also causing an increase in stigma.

However, the situation seems to be more complex. DUP seems to be a variable containing multiple and mixed individual and clinical characteristics. This is not surprising, because this variable is defined using mainly time. The complex and stochastic quality of DUP might explain why limited evidence was

found of an association between long DUP and poor short-term outcome in schizophrenia in the NFBC 1966.

The relation between DUP and long-term outcome in the NFBC 1966 partly conflicted with the original hypothesis and with results of earlier studies. The results of the meta-analysis, however, supported the hypothesis of association between long DUP and poor outcome. Long DUP may be a sign of a different pheno- and endophenotype of illness with insidious onset that leads to a long period of untreated psychosis and that is related to poor outcome in the short term (Morgan *et al.* 2006, Owens *et al.* 2010, Moncrieff 2011).

The heterogeneity of schizophrenia and common psychotic-like symptoms in the population without a decline in functioning suggest that a continuum in psychosis makes it possible for some subjects with long DUP to adapt to psychosis during DUP. These subjects could be unlikely to participate in long follow-up studies or intense intervention programs if they are employed, for example.

On the other hand, DUP is very harmful for some subjects who definitely benefit from early intervention. Although it is unlikely that psychosis itself would cause any biological effects, such as in brain morphology, immediately during the first-episode, the stressful period might have some interaction with the biology of the brain and even genetics. On the basis of results regarding the long-term outcome in schizophrenia in the NFBC 1966, the possible harmful social effects of DUP should be considered more, along with the protective factors of these.

8.4.2 Duration of untreated psychosis as a marker of different brain morphology

The finding of the association between long DUP and increased employment and decreased disability pension is somewhat contradictory compared to the finding of long DUP and decreased gray-matter density of the right side of the hippocampus. The hippocampus plays a critical role in a variety of cognitive functions, and a decreased density of gray matter in this area could thus relate to loss of memory, for example. However, there is little evidence of a correlation between longer DUP and cognitive deficits (Perkins *et al.* 2005, Lappin *et al.* 2007, Galderisi *et al.* 2009).

It has been suggested that hippocampal shape is more sensitive to pathological changes in schizophrenia than volumetric changes (Csernansky *et al.* 1998, Csernansky *et al.* 2002). The results of studies analyzing the shape of the

hippocampus in schizophrenia have been inconclusive (Csernansky *et al.* 1998, Lieberman *et al.* 2001, Narr *et al.* 2001, Pegues *et al.* 2003, Weiss *et al.* 2005). There may also be disturbances in the normal right–left asymmetry of the hippocampus in schizophrenia (Fukuzako *et al.* 1997).

A longer duration of untreated psychosis may enhance the loss of gray-matter density in the hippocampus, but this does not seem to affect the real life of subjects, unless these subjects are working in less demanding environments in terms of cognition. The effect of the length of DUP on cognition has previously been studied mainly on first-episode subjects or with one to two years of follow-up. There has not been any convincing evidence that longer DUP would be correlated with a decline in cognition at that stage of the illness (Rund *et al.* 2007, González-Blanch *et al.* 2008, Galderisi *et al.* 2009, Goldberg *et al.* 2009, Liu *et al.* 2011, Malla *et al.* 2011). It is to be noted that cognitive decline could be occurring already in the prodromal phase (Fusar-Poli *et al.* 2011, 2012c), and therefore the long-term effects of DUP should not differ much from the ones observed at first-episode psychosis, unless the effect of psychosis differs from the effects of the prodromal phase (Wood *et al.* 2010).

8.4.3 Descriptive lifespan model

The aetiology of schizophrenia includes a complex network of different, interacting pathogenic influences (Isohanni *et al.* 2009, 2010). The complex nature of the development of schizophrenia also has an effect on the diagnosis of schizophrenia. In a comprehensive theory, genetic and environmental influences in neuronal development cause functional alterations and pathophysiological changes of different neurotransmitter systems in the brain, leading to various versions of phenotypes (Isohanni *et al.* 2009, 2010).

The NFBC 1966 study has been identifying some of these developmental trajectories throughout the lifespan. Systems theory may help to integrate different types of evidence collected across many different categories and thus provide a coherent framework to guide future research (Isohanni *et al.* 2009). A model system view integrates the findings of DUP in schizophrenia in the NFBC 1966 with other findings of developmental trajectories (Figures 6 and 7). It is a descriptive, multi-level lifespan model on the developmental pathway to schizophrenia and on the course of illness. The descriptive model is focused on time-dependent (longitudinal), measurable, epidemiologically identified

properties. It includes vulnerability and risk factors before illness onset and reflects their effect on the course of the illness (Isohanni *et al.* 2009).

Birth cohort and register studies have provided important insights into how the developmental trajectory of individuals who develop disorders differs from their peers (Isohanni *et al.* 2009, 2010). The developmental pathways seem to be inflexible and most of the factors are currently non-modifiable, especially in the early phases of development. The shortening of DUP and early intervention therefore provide rare opportunities and possibilities to change the developmental pathway of psychosis.

This is however only a small window to target during the longitudinal course of the development of schizophrenia. Biological and environmental factors have been shown to be associated via interactions to alterations in the risk of schizophrenia from the time before pregnancy and during early development. Although direct interventions are not currently realistic at those stages, it is still possible to provide additional support for subjects who could have an increased risk of developing schizophrenia. It is also possible to aim to decrease some risk factors, such as perinatal infections and complications of delivery, as much as possible (Kirkbride & Jones 2011).

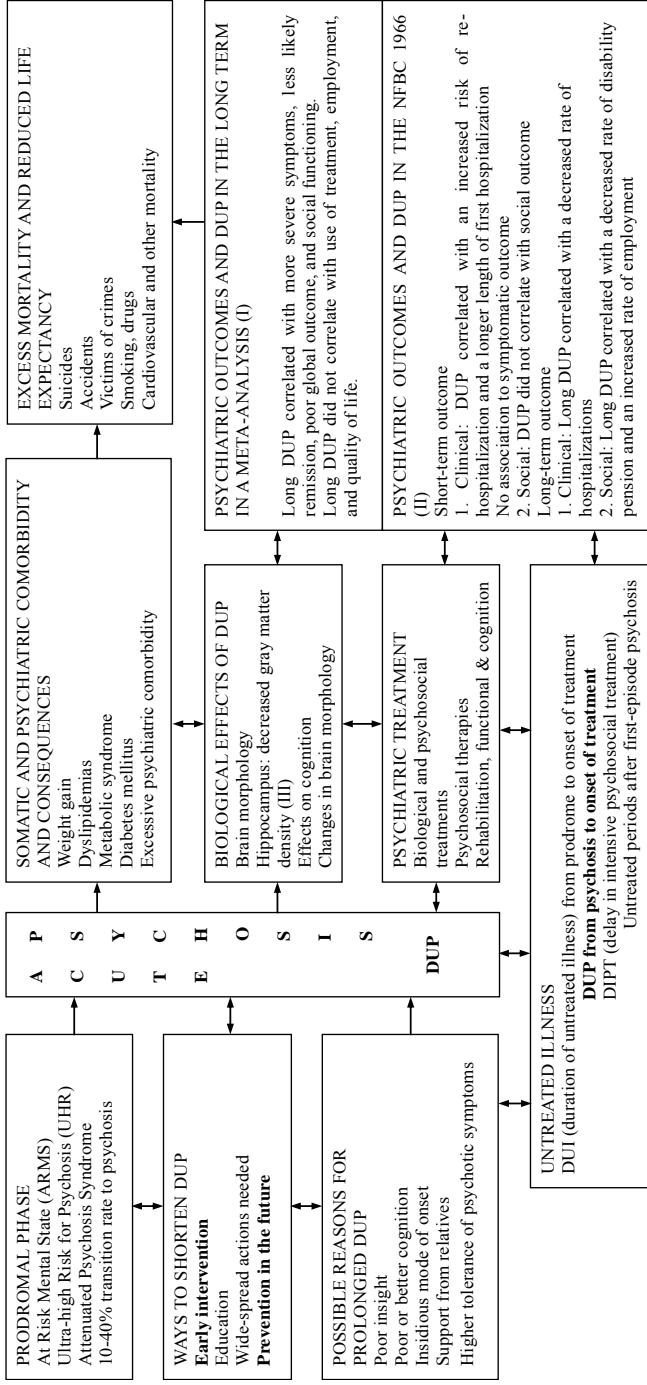


Fig. 7. Descriptive life span and multilevel model of schizophrenic psychoses, focusing on acute psychosis, duration of untreated psychosis (DUP), and outcomes. Modified from Isohanni et al. 2009.

8.4.4 Theoretical discussion of the value of studying duration of untreated psychosis

DUP is generally a relatively short period of time for people with schizophrenia and many factors before the onset may affect the length of DUP. This period of time is not an independent factor in the early course of schizophrenia and the possible premorbid factors behind short or long DUP, such as personality, temperament, and early development, are still widely unknown. It is interesting that DUP has some correlation with the long-term outcome and also with brain morphology (Figures 6, 7). The rather complex course of the illness could be affected by shortening the DUP or by making an impact on the factors that cause prolonged DUP, as long as primary prevention of schizophrenia is not a reality.

The definition of DUP is challenging and the mechanisms that lead to prolonged untreated psychosis are unclear. The heterogeneity of disorder and the concept in and between studies limits the possibilities to find correlations, especially when studying biological factors where associations can be confounded. It seems possible to analyze the clinical outcome using structured definitions of outcome, such as clinical remission (Andreasen *et al.* 2005), without major heterogeneity. The heterogeneity could be decreased with measurable biological markers to conclusively define the onset of psychosis.

Although *studying DUP* and its causes and consequences is challenging, the studies in this field have given some needed attention to the importance of the early phases in the treatment of psychosis, as well as the aim of improving the outcomes in schizophrenia. There has been some criticism of the concept and whether it is too closely related to mode of onset, for which insidious onset has been previously known to be associated with poor outcome (Morgan *et al.* 2006, Moncrieff 2011). The results of this thesis indicate that long DUP should not be studied only as harmful phase in the disorder, but also from the perspective of studying the mechanisms that make it possible for some subjects to live with psychosis for long periods without treatment.

DUP and other untreated periods of schizophrenia need to be carefully defined for future studies to find out what leads to a delay or cut-off of treatment. It is still to be found out what the factors are that make it possible for some subjects with schizophrenia to cope with their illness and symptoms with less support than other subjects. It is also possible that subjects with long DUP might

receive or choose to get different treatment for schizophrenia during the course of the illness. This might reflect on the treatment of somatic illnesses as well.

So far, DUP has helped to raise the discussion of importance of early intervention and treatment in psychosis and psychiatry. In the future the concept of DUP should be developed to describe the untreated period in a more comparable way between studies, with only a few different and closely related ways to measure the length of DUP while assessing the reliability of the ratings done in the studies. DUP is one of the possible concepts that can describe the very early phases of the illness in an accurate way with precise assessment on proper scales, when all things are taken into account.

9 Conclusion

9.1 Main conclusions

The *meta-analysis* of DUP and long-term outcomes in schizophrenia indicates that some aspects of poor outcome are associated with long DUP during the later phases of the illness as well. However, the effects were relatively small. The small but mostly consistent correlation between long DUP and poor clinical outcome indicates that early intervention in psychosis may have positive effects on the long-term clinical course.

In the *NFBC 1966*, however, no evidence was found of an association between long DUP and poor long-term *outcome*. DUP seems to be a variable containing multiple and mixed individual and clinical characteristics. This is not surprising, because this variable is defined using mainly time. The complex and stochastic quality of DUP might be one reason for limited evidence to support the hypothesis of the association between long DUP and poor short-term outcome and for partly conflicting correlation between DUP and long-term outcome regarding original hypothesis.

DUP was found to be associated with *brain morphology* in a population-based sample including subjects after an average of 11 years from the onset of the illness. According to results in the *NFBC 1966*, the regional gray-matter densities in the limbic areas tend to be smaller with a longer DUP. The same areas have previously been found to differ between individuals with schizophrenia and controls. At the moment, there is no strong evidence of toxic effects of DUP on brain morphology.

9.2 Clinical implications of the study

There has been discussion as to whether current evidence of the positive effects of early interventions in psychoses continues in the long term (Bosanac *et al.* 2010, Moncrieff 2011). An alternative view is that long DUP may be a sign, proxy, and marker of a different pheno- and endophenotype of illness, with insidious onset, that leads to a long period of untreated psychosis and that is related to poor outcome in the short term (Morgan *et al.* 2006, Owens *et al.* 2010, Moncrieff 2011). The importance of early intervention and the effects of DUP should not be

assessed only by measuring symptoms and information gathered from interviews, but other possible sources of information should also be utilized.

The results in the NFBC 1966 indicate that longer DUP may be associated with an increased need for hospitalization at the beginning of the illness but, after several years of illness, a longer DUP may predict less hospitalizations and better occupational functioning. Early detection of psychosis might help to decrease the need for hospital treatment in the first years of illness, but the long-term outcome may depend more on other factors than the length of initially untreated psychosis. Although the long-term effects of early interventions are unclear, it is worth noting that good prognosis in the first years of illness is a predictor of a good long-term outcome (Jäger *et al.* 2009). Therefore, by developing early intervention in psychosis, it may also be possible to improve the long-term outcome for some individuals with schizophrenia.

The professionals working in psychiatry and general medicine, as well as other fields of society, should be more aware of detecting psychosis and how first-episode psychosis is treated. The treatment should not, however, be focused on the aims and terms defined by the view of society or health care, but rather from the aspects of the people who have psychosis. Psychiatric treatment should be planned and managed together with the patient and their relatives, with aims that are realistic and shared. One limitation of this study is the lack of information on the burden of psychosis on relatives and family of individuals with psychosis during and after DUP. The perceived and experienced feelings of stigma could also have remarkable effects on well-being that it was not possible to study in this data set.

9.3 Future research

Although some aspects of DUP and its association with outcome in schizophrenia have been clarified by studies included and discussed in this thesis, there are still many aspects that have not yet been concluded.

9.3.1 Duration of untreated psychosis and outcome in schizophrenia

The association between DUP and short-term outcome has been widely known, with evidence supporting the association between long DUP and poor outcome. The correlation between long-term outcome and DUP has now been systematically estimated and it was shown that DUP correlates with poor clinical

outcome in the long term. However, there was no evidence to support the idea that long DUP might cause increased costs due to increased hospitalizations, an increased rate of disability pension, or decreased employment during the course of the illness. Neither there was evidence that DUP correlates with quality of life. These are the aspects with other longitudinal measurements of outcome that could be more focused on in the future.

In particular, the correlation between long DUP and better long-term occupational functioning in the NFBC 1966 is something that could be studied more in the future. The subjects with better occupational recovery may have either individual characteristics, environmental factors such as family, or a certain type of work environment to support their occupational recovery and protect them from the detrimental effects of the disorder. The detection of these factors could provide additional tools to be used in the rehabilitation of subjects with first-episode psychosis who could achieve recovery.

The definition of DUP for the subjects (n=39) within the NFBC 1966 with first-episode psychosis after 1997, as well as inclusion of schizophrenia spectrum psychoses in the analyses and continuing the follow-up of the sample, could provide more information for more detailed group comparisons. The possibility to define DUP in the Northern Finland 1986 Birth Cohort (NFBC 1986) and to analyze and compare those results to ones in the NFBC 1966 is also a unique way to study the effects of DUP in two comparable samples.

In summary, the following themes are to be studied in the future of DUP and outcome in schizophrenia:

- I The difference between subjects who manage to have a good outcome despite long DUP in the long term, when compared to subjects with long DUP and poor outcome and short DUP and good outcome.
- II The predictive value of premorbid factors such as early development, perinatal factors, familial risk or background, temperament, or school performance on the length of DUP and in that way the different paths of outcome and the treatment pathways during the course of the illness.
- III The correlation between DUP and somatic illnesses and their treatment and morbidity in the longitudinal follow-up.
- IV The association between DUP and the use of antipsychotic medication during the course of the illness.

9.3.2 Duration of untreated psychosis and brain morphology in schizophrenia

The evidence of the possible correlation between DUP and brain structure in schizophrenia is still sparse. The findings of mainly decreased gray-matter volumes or densities in different areas of the brain are not yet possible to assess systematically and conclusively in a meta-analysis, due to the heterogeneity of methods used in the studies. The possible progressive degenerating effect of DUP on changes in brain morphology is still unclear and could be studied more in the future.

In the NFBC 1966, it is possible to study the effect of DUP and other factors on progressive brain morphological changes since 1999-2001, assessed in repeated structural MRI rescans between 2008 and 2011. This will help to identify the determinants for different biological and clinical phenotypes of disorder, providing an increased likelihood of developing more targeted and effective interventions and treatments for subjects currently diagnosed with schizophrenia. The possible confounding effect of psychiatric medication on the association between DUP and brain morphology could be analyzed with more detailed information on the longitudinal use of medication.

The hypotheses of future studies in DUP and brain morphology include the following:

- I Duration of untreated psychosis may associate with increased progressive change in brain morphology in the 9-year follow-up.
- II DUP may be correlated with different functioning of the brain, especially in the hippocampus.

9.3.3 Predictors of duration of untreated psychosis

DUP is affected by many things, such as the person having psychosis and the person's relatives, as well as society and the culture of psychiatric health care as part of it. Many possible factors during the early life and later development of a person's life may cause a prolonged untreated period during first-episode psychosis, and these have not yet been studied in birth-cohort samples. With the available data in the NFBC 1966, it is possible to study what the relations are between early predictors and DUP: for example, whether or not DUP is related to early developmental factors previously correlated with schizophrenia, such as

wantedness of pregnancy, perinatal complications, early motor development, and scholastic performance.

Several factors describing individual characteristics, such as temperament and cognitive capacity, may correlate with DUP and prognosis either independently or via interactions. In the NFBC 1966, it is possible to study how the use of psychiatric medication, mainly antipsychotics, modifies the association between DUP and outcomes. The studying of the factors preceding the onset of psychosis is one way to gather more information on the clinically important prodromal phase, with the aim of more specific detection of and interventions for subjects in an at-risk mental state for psychosis. There are many possibilities for detecting differences in neurodevelopment and motor functioning, with sensitive motoric measurement identified as a possible method for detecting subjects at risk of psychosis (Wilquin & Delevoye-Turrell 2012). The NFBC 1966 provides a unique opportunity for studying neurodevelopment and premorbid factors from pregnancy.

The hypotheses for the forthcoming studies of DUP and premorbid factors are:

- I Long DUP may be correlated with poor and good functioning in adolescence and before the onset of illness.
- II Factors such as temperament and development in childhood relate to the length of DUP. Some subjects with long DUP may be less social and others may be able to cope with changes in the environment.
- III The early neural development may be correlated with the length of DUP and the factors of these may help to detect the several possible subtypes of schizophrenia and also to give information for early intervention at different stages.
- IV The role of public health care and other services in the length of DUP may be important and this is possible to study by measuring, for example, the number of contacts to health services during DUP.
- V Several sociodemographic factors, such as background of the family, social and economic states, and geographical variations, may have an impact on DUP.

9.3.4 Duration of untreated psychosis and cognition in schizophrenia

The possible effects of DUP on cognition in the long term have not yet been studied, but based on the finding of the decreased gray-matter density of the right side of the hippocampus in subjects with long DUP, this should be one of the aims of future research. Previous studies have not been able to study the possible progressive change in cognition in mid-life with 10 years of follow-up, for which data is available in the NFBC 1966.

The aim of the forthcoming studies on DUP and cognition in the NFBC 1966 is to study the correlation between DUP and cognitive functioning in field studies conducted in 1999-2001 and 2008-2010, and the possible change between these. It is also possible to assess the possible association between DUP and cognitive decline during childhood and adolescence to some extent, to find out at which point the intervention of this neurodevelopmental disorder should occur to have best effect.

9.4 Concluding remarks

This thesis confirms the previous findings of the small association between long DUP and poor outcome, even in long-term follow-up. However, it was shown that not all aspects of outcome were inversely correlated with the length of DUP, and this is a new and interesting finding. The found association between long DUP and decreased gray-matter density of the right hippocampus is also novel. It is to be concluded that DUP is a concept with clinical and biological meaning, and although there are some methodological challenges, the concept should continue to be studied in the future.

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Original publications

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

- I Penttilä M, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. The association between duration of untreated psychosis (DUP) and long-term outcome in schizophrenia. A systematic review and meta-analysis. Manuscript.
- II Penttilä M, Miettunen J, Koponen H, Kyllönen M, Veijola J, Isohanni M, Jääskeläinen E (2013) Association between duration of untreated psychosis and short- and long-term outcome in schizophrenia within the Northern Finland 1966 Birth Cohort. *Schizophrenia Research* 143: 3–10.
- III Penttilä M, Jääskeläinen E, Haapea M, Tanskanen P, Veijola J, Ridler K, Murray GK, Barnes A, Jones PB, Isohanni M, Koponen H, Miettunen J (2010) Association between duration of untreated psychosis and brain morphology in schizophrenia within the Northern Finland 1966 Birth Cohort. *Schizophrenia Research* 123: 145–152.

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Original publications are not included in the electronic version of the dissertation.

1190. Murugan, Subramanian (2012) Control of nephrogenesis by Wnt4 signaling : mechanisms of gene regulation and targeting of specific lineage cells by tissue engineering tools
1191. Nikkilä, Jenni (2013) *PALB2* and *RAP80* genes in hereditary breast cancer predisposition
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