Juha Käkelä

FAMILY HISTORY OF MENTAL DISORDERS AND LONG-TERM OUTCOME IN SCHIZOPHRENIA
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Abstract

The aim of this dissertation was to investigate the association between family history of mental disorders, especially psychosis, and long-term social, occupational and clinical outcome in schizophrenia. In addition, the association of pregnancy, birth and early development related factors with occupational and clinical outcome in schizophrenia were analysed. Two meta-analyses and the Northern Finland Birth Cohorts 1966 and 1986 (NFBC1966 and NFBC1986) were used to gather the data.

In the meta-analyses family history of psychosis was associated with poorer long-term clinical, occupational and global (i.e. combined occupational, social and clinical) outcome in schizophrenia. NFBC1966 is an unselected, population-based sample of 12,058 live-born children and includes 161 individuals with schizophrenia spectrum disorder. NFBC1986 is also an unselected, population-based cohort and consists of 9,432 live-born children and includes 189 individuals with psychosis.

In the NFBC1966 study family history of any mental disorder was associated with more severe positive and emotional symptoms, but was not associated with other clinical symptoms or social, occupational or global outcome in schizophrenia. The family history of psychosis was not associated with outcomes. Regarding pregnancy, birth and early development related factors, it was found that young maternal age was associated with higher probability of being hospitalised with schizophrenia. In the NFBC1986 study a family history of any mental disorder was associated with higher number of days spent at hospital and higher number of hospitalisations, but it was not associated with occupational outcome or disability pension in psychotic disorders. A family history of psychosis was not associated with outcomes.

This study suggests that family history of psychosis has a small association with clinical, occupational and global outcome in schizophrenia. There is less research regarding the association between family history of any mental disorder and outcome in schizophrenia, but based on the cohort studies family history of any mental disorder could be even stronger outcome predictor than family history of psychosis. Family history of mental disorders and especially psychosis is a strong risk factor for schizophrenia, and based on this study it seems to also associate with poorer outcome.

Keywords: family history, long-term outcome, mental disorder, psychosis, schizophrenia

Meta-analyysien mukaan psykoosin sukurasitus oli yhteydessä huonompaan pitkän ajan kliiniseen, työkykyyn liittyvään ja kokonaisennusteeeseen (yhdistetty sosiaalinen, kliininen ja työnteon ennuste) skitsofreniassa.


Mikä tahansa suvussa esiintyvä mielenterveyshäiriön esiintyminen suvussa on yhteydessä pitkän ajan ennusteeeseen, mutta kohorttitutkimusten perusteella millä tahansa suvussa esiintyvällä mielenterveyshäiriöllä voi olla jopa suurempi yhteys ennusteeeseen kuin psykoosin sukurasituksella. Mielenterveyshäiriöiden ja etenkin psykoosin esiintymisen suvussa on voimakas skitsofrenian riskitekijä, ja tämän tutkimuksen mukaan se on myös yhteydessä huonompaan ennusteeeseen.

Asiasanat: mielenterveyshäiriö, pitkän ajan ennuste, psykoosi, skitsofrenia, sukurasitus
To my family
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Oulu, April 2018

Juha Käkelä
Main definitions

Long-term follow-up

In this study, long-term follow-up is defined as a time period of at least two years from the onset of the illness.

Mental disorder

In this study (any) mental disorder refers to all psychiatric diagnoses, with the exception of organic mental disorders, mental retardation, disorders of psychological development, behavioural and emotional disorders with onset usually occurring in childhood and adolescence, and unspecified mental disorders.

Negative symptoms

Symptoms of psychosis, which refer to reduction of normal functions and include e.g. emotional withdrawal, blunted affect, stereotyped thinking and lack of spontaneity.

Outcome

The patient’s psychiatric and/or functional status after illness onset at the end-point of follow-up. In this study the outcome is assessed based on clinical (symptoms, hospitalisations), occupational (work history, disability pension), social (frequency and quality of social contacts) and/or global (combined occupational, social and clinical course) outcomes.

Positive symptoms

Symptoms of psychosis, which refer to reality distortion and include e.g. hallucinations, delusions, grandiosity and suspiciousness.
Psychiatric disorder

In this study the terms psychiatric disorder and mental disorder are used as synonyms.

Psychosis

In this study psychosis refers to all non-organic psychosis diagnoses.

Schizophrenia

In this study schizophrenia generally refers to schizophrenia spectrum disorders, i.e. schizophrenia, schizotypal, schizoaffective and delusional disorder.
Abbreviations

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<tr>
<td>95% CI</td>
<td>95% confidence interval</td>
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<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
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<tr>
<td>CGI-S</td>
<td>Clinical Global Impression – Severity scale</td>
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<td>CRHC</td>
<td>Care Register for Health Care</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>FCP</td>
<td>Finnish Centre for Pensions</td>
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<tr>
<td>SII</td>
<td>Social Insurance Institution of Finland</td>
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<tr>
<td>GAF</td>
<td>Global Assessment of Functioning</td>
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<td>GAS</td>
<td>Global Assessment Scale</td>
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<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
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<td>NFBC1966</td>
<td>Northern Finland Birth Cohort 1966</td>
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<tr>
<td>NFBC1986</td>
<td>Northern Finland Birth Cohort 1986</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
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<td>SANS</td>
<td>Scale for the Assessment of Negative Symptoms</td>
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<td>SAPS</td>
<td>Scale for the Assessment of Positive Symptoms</td>
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<tr>
<td>SCID-I</td>
<td>Structured Clinical Interview for DSM-IV Axis I Disorders</td>
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<tr>
<td>SCOS</td>
<td>Strauss-Carpenter Outcome Scale</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SMD</td>
<td>Standardised mean difference</td>
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<td>SOFAS</td>
<td>Social and Occupational Functioning Assessment Scale</td>
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List of original publications

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


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

The worldwide prevalence of schizophrenia is approximately 0.4% (Saha et al., 2005). In Northern Finland the lifetime prevalence of schizophrenia is estimated at as high as 1.8% (Suvisaari et al., 2012). Schizophrenia is often chronic, severe and causes significant deficit in functioning, and is therefore a very burdensome disease in terms of personal suffering, health care expenses and cost to society (WHO, 2008; Phanthunane et al., 2010; Gustavsson et al., 2011; Garcia-Ruiz et al., 2012; Millier et al., 2014). Deficits in social and occupational functioning are common (Marwaha & Johnson, 2004; Warner, 2004) and, for example, in Finland as much as 80% of patients with schizophrenia are on disability pension and only 7% are working (Perälä et al., 2008). Only 13% of individuals with schizophrenia attain clinical and social recovery (Jääskeläinen et al., 2013). Individuals with schizophrenia have a 2.4 times higher risk of death due to natural causes and a 12 times higher risk of death due to suicide compared to the general population (Saha et al., 2007).

Genetic factors have a considerable role in the aetiology of schizophrenia, as suggested by adoption, twin and family studies (Tsuang et al., 1991). Family history of schizophrenia is a strong risk factor for schizophrenia with a 6.6-9.9 relative risk among first-degree relatives (Lichtenstein et al., 2009; Mortensen et al., 2010). A recent meta-analysis (MacBeth et al., 2015) showed an overall odds ratio (OR) of 5.8 for the association between parental and offspring schizophrenia spectrum disorder. Genetic and environmental risk factors combined increase the risk of schizophrenia even further (van Os et al., 2004; Wahlberg et al., 2004). To date studies have not been able to recognise a single gene that has a large effect on the risk of schizophrenia, and a genome-wide association study reported 108 schizophrenia-associated genetic loci (Ripke et al., 2014).

Several studies suggest that the course and severity of schizophrenia is associated with a family history of schizophrenia or other psychosis (Doeherty et al., 1996; Kendler et al., 1997; Malaspina et al., 1998). Esterberg et al. (2010) have reviewed the impact of family history of psychosis on positive and negative symptoms of schizophrenia, suggesting that the presence of psychosis in the family is associated with more severe negative symptoms. Family history of psychiatric disorders (presence of any psychiatric disorder) has been associated e.g. with higher rate of rehospitalisation and higher risk of relapse (Feldmann et al., 2001; Ciudad et al., 2012).

Family-related environmental factors may have a substantial effect on outcome in schizophrenia (Ezeme et al., 2016; Ran et al., 2017) and family interventions
may improve the outcome (Mayoral et al., 2015; Claxton et al., 2017). Adverse events in childhood increase the risk of mental disorders (Varese et al., 2012; Kajeepeta, 2015; Heslin et al., 2016; Dahl et al., 2017). In families with schizophrenia adverse issues such as prenatal health problems, deficits in mother-infant interaction and environmental disruptions are elevated (Wan et al., 2007; Walder et al., 2014). Studying the effect of family environment on outcome is challenging since the family environment is always an individual experience, and measuring a single characteristic, such as presence or absence of a specific disorder in the family, provides a rather limited view on the variables that may explain the outcome.

This doctoral thesis investigates how family history of psychiatric disorders, especially psychosis, affect long-term clinical, social, occupational and global outcome in schizophrenia. Since a family history of psychiatric disorders can be considered to affect schizophrenia outcome through biological (i.e. genetic) and environmental factors, it was also studied whether pregnancy, birth and early development related factors predict employment and hospitalisation in schizophrenia. Two meta-analyses and the Northern Finland Birth Cohorts 1966 and 1986 (NFBC1966 and NFBC1986) were used to gather the information.
2 Schizophrenia and other psychoses

2.1 Symptoms of schizophrenia and other psychoses

In schizophrenia the common symptoms are e.g. hallucinations, delusions, impairments in emotions and behaviour, and decline in cognitive and social functioning, but the total symptom spectrum is wide-ranging including also e.g. thought echo, neologism and mutism. Nevertheless, there is not a single common symptom for all patients with schizophrenia. Psychotic symptoms (e.g. hallucinations and delusions) are present in all psychoses, but in schizophrenia there is also a substantial decline in cognitive and social functioning and the duration of the symptoms is typically longer (WHO, 1992; APA, 2013).

2.2 Psychiatric diagnostic systems

The psychiatric diagnoses in this thesis are based on the International Classification of Diseases (ICD; WHO, 1992) and Diagnostic and Statistical Manual of Mental Disorders (DSM; APA, 2013). The tenth revision of the ICD (ICD-10) was released in 1992, ICD-9 in 1978 and ICD-8 in 1967. The fifth edition of the DSM (DSM-5) was released in 2013, DSM-IV in 1994, DSM-III-R (revised version of third edition) in 1987, and DSM-III in 1980. The diagnostic criteria of schizophrenia according to ICD-10 and DSM-5 are presented in Table 1.

Table 1. Diagnostic criteria of schizophrenia according ICD-10 and DSM-5.

<table>
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<tr>
<td>Either at least one of the following symptoms</td>
<td>Criterion A: at least two of the following symptoms (at least one must be 1, 2, or 3)</td>
</tr>
<tr>
<td>a) Thought echo, thought insertion/withdrawal, thought broadcasting</td>
<td>1. Delusions</td>
</tr>
<tr>
<td>b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception</td>
<td>2. Hallucinations</td>
</tr>
<tr>
<td>c) Hallucinatory voices commenting or voices conversing or voices coming from some part of the body</td>
<td>3. Disorganised speech</td>
</tr>
<tr>
<td>d) Persistent bizarre delusions</td>
<td>4. Grossly disorganised or catatonic behaviour</td>
</tr>
<tr>
<td>Or at least two of the following symptoms</td>
<td>5. Negative symptoms</td>
</tr>
<tr>
<td>a) Persistent hallucinations in any modality</td>
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</table>
b) Neologisms, thought disorder, incoherence or irrelevant speech

c) Catatonic behaviour (e.g. excitement, posturing or waxy flexibility, negativism, mutism and stupor)

d) "Negative" symptoms (e.g. marked apathy, paucity of speech, and blunting or incongruity of emotional responses)

Disturbances for a significant proportion of the time in at least one major area of social or occupational functioning, such as work or interpersonal relations

Duration criteria

The symptoms should have been clearly present for most of the time during a period of 1 month or more

Criterion C

Continuous signs of the disturbance persist for at least six months, including active phase of criterion A symptoms for at least one month

Exclusion criteria

Organic brain disease; Alcohol or drug intoxication, dependence or withdrawal;
Manic or depressive episode before the occurrence of the above symptom criteria

Depressive or bipolar disorder with psychotic symptoms and schizoaffective disorder must be ruled out

Criterion E

The symptoms are not a result of substance use or another medical condition

Criterion F

Relationship to Global Developmental Delay or Autism Spectrum Disorder; the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are present for at least one month

2.3 Incidence and prevalence of schizophrenia and other psychoses

The incidence of schizophrenia has been reported to be 15.2 per 100,000 person-years (McGrath et al., 2004; Kirkbride et al., 2012), and the incidence of all psychoses is 31.7 per 100,000 person-years (Kirkbride et al., 2012). The lifetime prevalence for schizophrenia is 0.4% worldwide (Saha et al., 2005). In Finland, life-time prevalence of schizophrenia is 0.9% and all psychotic disorders 3.1% (Perälä et al., 2007). Prevalence of schizophrenia is highest in Eastern and Northern Finland (Perälä et al., 2008).

Although the prevalence of schizophrenia is the same for men and women (Saha et al., 2005), the incidence is higher for men (1.15-fold) than for women (van
der Werf et al., 2014). At age 20-29 the incidence rate is 4.15/10,000 person-years for men and 1.71/10,000 person-years for women, but after the age of 50 the incidence rate is higher for women than for men (van der Werf et al., 2014). There is no gender difference in the risk of affective psychoses by the age of 45, but thereafter the rates are higher for women (Kirkbride et al., 2012). Changes in the diagnostic system may have an effect when studying the changes in prevalence over time (Filatova et al., 2017b).

2.4 Aetiology of schizophrenia and other psychoses

2.4.1 Genetics

Genetic factors have a considerable role in the aetiology of schizophrenia, as suggested by adoption, twin and family studies (Tsuang et al., 1991). To date, studies have not been able to recognise a single gene that has a large effect on the risk of schizophrenia, and a large genome-wide association study (36,989 cases and 113,075 controls in a meta-analysis of 52 studies) reported 108 schizophrenia-associated genetic loci (Ripke et al., 2014). Further research on the genome-wide association study has revealed that individuals with a family history of schizophrenia have a greater polygenic loading for schizophrenia (Bigdeli et al., 2016). In addition, several microRNAs regulate schizophrenia risk genes and therefore have a role in the aetiology of schizophrenia (Hauberg et al., 2016), and excessive complement activity has a role in the development of schizophrenia and may help explain the reduced number of synapses in the brains of individuals with schizophrenia (Sekar et al., 2016). Whole-exome sequencing studies of smaller samples frequently report new risk genes (Salvoro et al., 2018; John et al., 2018) and other genetic risk factors (Liu et al., 2018; de Vrij et al., 2018) for schizophrenia.

2.4.2 Family history as a risk factor

There is a large amount of research regarding risk factors for psychoses. Family history of schizophrenia is the strongest known risk factor for schizophrenia (Lichtenstein et al., 2009; Mortensen et al., 2010; Rasic et al., 2014; MacBeth et al., 2015), and the heritability estimate of schizophrenia is 81-85% based on twin studies (Cardno et al., 1999; Sullivan et al., 2003) and 67% based on a general
population cohort (Wray & Gottesman, 2012). Other mental disorders in the family also increase the risk of psychosis (Sørensen et al., 2009). In fact, there is an ‘overlap’ between family history of psychiatric disorders and risk of psychiatric disorders, i.e. the presence of one psychiatric disorder in the family increases the risk of several other psychiatric disorders (Steinhausen et al., 2009; Dean et al., 2010). For example, with parental schizophrenia the lifetime rate of any offspring mental disorder is 47%, the lifetime rate of depression is 13%, and the lifetime rate of schizophrenia is 12%, and with parental bipolar disorder or depression the lifetime rate of offspring schizophrenia is 4% (Rasic et al., 2014). Having a first-degree relative with schizophrenia increases the risk of many non-psychotic psychiatric disorders, such as affective disorder, anxiety disorder, substance use disorder, bulimia and disorders of childhood onset (DeVylder & Lukens, 2013). A genetic connection has been proposed for autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia in a genome-wide analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

There is detailed information in the literature regarding familial mental disorders as risk factors for schizophrenia. With parental personality disorder the OR for offspring schizophrenia is 1.61-3.83, and with parental alcohol dependence the OR for offspring schizophrenia is 2.14-3.06 (Sørensen et al., 2009). Having one parent with a non-affective psychosis increases the incidence rate of schizophrenia 4.07-fold, and having one parent with any other psychiatric disorder than psychosis increases the incidence rate of schizophrenia 2.37-fold compared to having no parental psychiatric history (Dean et al., 2010). With a family history of psychosis the OR for schizophrenia is 2.60, with a family history of bipolar disorder the OR for schizophrenia is 2.46, and with any other psychiatric disorder the OR for schizophrenia is 2.31 (Agerbo et al., 2015). According to the Helsinki high-risk study, the cumulative incidences of schizophrenia are 6.7%, 5.0%, 6.7%, 0% and 0.6% among offspring of mothers with schizophrenia, schizoaffective disorder, other schizophrenia-spectrum disorders, affective disorders and controls, respectively (Niemi et al., 2004).

Regarding psychoses other than schizophrenia, based on a review by Jääskeläinen et al. (2017), a family history of psychosis and bipolar I disorder increase the risk of psychotic depression. In three of the studies reviewed, a family history of any mental disorder increased the risk of psychotic depression and in two studies it did not increase the risk of psychotic depression (Jääskeläinen et al., 2017). In one of the original studies (Heslin et al., 2016) a family history of
psychosis had an OR of 12.85 for psychotic depression and a family history of any mental disorder had an OR of 10.68 for psychotic depression. Consequently, when studying family history, it is sensible to investigate the family history of as many psychiatric illnesses as possible.

2.4.3 Other risk factors

Risk factors of schizophrenia

Genetics alone does not explain the total risk of psychosis (Kirkbride & Jones, 2011) and a substantial number of identified biological and environmental risk factors are also involved. High paternal age, obstetric complications and use of cannabis were identified as risk factors for schizophrenia in a meta-review (Matheson et al., 2011), and there was also some indication of motor dysfunction and low IQ being risk factors. More recent reviews have identified the following risk factors for schizophrenia: deficits in IQ and motor function in youth aged 16 years or younger (Dickson et al., 2012), delayed early motor development (Filatova et al., 2017a), social withdrawal in childhood (Matheson et al., 2013), parental communication deviance (de Sousa et al., 2014; Roisko et al., 2014), urban environment (Vassos et al., 2012) and Chlamydia pneumoniae infection (Gutiérrez-Fernández et al., 2015). Also low social class (Corcoran et al., 2009), maternal stress during pregnancy (Khashan et al., 2008), maternal smoking (Stathopoulou et al., 2013), parent-child separation during development (Paksarian et al., 2015), mother’s anaemia during pregnancy (Sørensen et al., 2011) and unwanted pregnancy (McNeil et al., 2009) have been identified as risk factors for schizophrenia in original studies.

Risk factors for schizophrenia in the NFBC1966 have been reviewed by Jääskeläinen et al. (2015): male gender, birth complications, high birth weight and length, unwanted pregnancy, viral central nervous system infections in childhood, later achievement of early motor milestones such as standing up and walking without support and low IQ at age 14. In addition, factors that protect against schizophrenia have been identified: wanted pregnancy, no multiparity, mother working outside home, having a two-parent family, higher BMI, good grades in school, upper school level, and having a sport hobby in childhood (Keskinen et al., 2016).
Risk factors of psychosis

Previous reviews of the field have identified the following general risk factors for psychosis: central nervous system viral infection during childhood as a risk factor for non-affective psychosis (Khandaker et al., 2012), adverse life events in childhood as a risk factor for psychosis (Varese et al., 2012) and autoimmune disease as a risk factor for psychosis (Benros et al., 2014). An original study identified the following risk factors for psychotic depression: living alone (OR 2.26), being unemployed (OR 2.12), having contact with friends less than monthly (OR 4.24), having no close confidants (OR 4.71), having experienced childhood adversity (OR 2.57) and having more neurological soft signs (OR 1.15) (Heslin et al., 2016). In one study negative family environment increased the risk of psychosis independently of family history of psychosis, and positive family environment was protective against psychosis for those with a family history of psychosis (González-Pinto et al., 2011). Coeliac disease has been associated with increased risk of non-affective psychosis (hazard ratio 1.55) and especially with non-schizophrenic non-affective psychosis (hazard ratio 1.61) (Ludvigsson et al., 2007). Also poor functioning, long duration of subthreshold psychotic symptoms, high levels of depression and reduced attention have been found as predictors of having psychosis (Yung et al., 2004).

In summary, although there were a lot of similarities, less than half of the risk factors of psychosis were also mentioned as a risk factor for schizophrenia. Many of the studies on psychosis also included individuals with schizophrenia, and therefore a clear separation between schizophrenia and other psychoses cannot be made. Of the studies related to psychoses other than schizophrenia, less than half of the mentioned risk factors were the same as for schizophrenia, as similarly found when comparing all psychoses to schizophrenia.

Aetiological models

As no single risk factor have gained an essential role in the aetiology of schizophrenia, aetiological models consisting of multiple factors have been proposed over time: the vulnerability-stress model (Zubin & Spring, 1977), the gene-environment interaction model (van Os et al., 2008), the two-hit hypothesis (Maynard et al., 2001), the hybrid model (Salokangas et al., 2001), the developmental psychopathology model (Wan et al., 2008) and the progressive neurodevelopmental model (Fatemí & Folsom, 2009; Andreasen, 2010; Nour &
Howes, 2015). With the exception of the progressive neurodevelopmental model, these models propose that both genetic and environmental exposure have an essential role in the pathogenesis of schizophrenia, which is supported by epidemiological studies (MacDonald & Schulz, 2009), and therefore they support the investigation of family history of psychosis.

2.5 Family history of psychosis

2.5.1 Environmental effect of family history of psychosis

The presence of a mentally ill parent in the family may expose children to an adverse environment. In families with a first-degree relative with schizophrenia issues such as prenatal health problems, smoking during pregnancy, preterm births, deficits in mother-infant interaction, substance abuse, living with single parent and environmental disruptions are elevated (Wan et al., 2007; Lin et al., 2009; Matevosyan, 2011; Walder et al., 2014; Ranning et al., 2016).

It seems that environmental risk factors may be more critical for those with a family history of psychosis. For example urbanity, communication deviance in the family, and social adversities in childhood increase the risk of schizophrenia more with individuals with a family history of psychosis (van Os et al., 2004; Wahlberg et al., 2004; Wicks et al., 2010).

Based on this, it is not surprising that family environment may also affect schizophrenia outcome, and family interventions may improve the outcome. This issue is discussed further in section 3.2.2.

Among (unaffected) individuals with a family history of psychosis, cognitive performance is lower (Korver et al., 2012; Bora et al., 2014) and formal thought disorder, neuropsychological performance deficits and dysfunctional metacognitive beliefs are more common (Cotter et al., 2017; Demjaha et al., 2017; Hauser et al., 2017). Approximately 50-70% of children of parents with schizophrenia manifest a variety of difficulties including socioemotional, cognitive, neuromotor, speech-language problems and psychopathology, and around 10% will develop psychosis (Liu et al., 2015).

Consequently, a family history of psychosis or other psychiatric illness may affect family members through both genetic and environmental influences, and it is often difficult to separate these two issues. It should be noted that in reality a family cannot be simply categorised as being either sick or healthy or having a
presence or absence of a given set of problems, rather it is a dynamic entity with a fluctuating environment resulting in subjective experience (Wu, 2011). The timing of illnesses of family members, changing roles of family members at different phases of life, and the protecting factors in the family all contribute to the outcome (Schlosser et al., 2012). Therefore, studying only the presence or absence of mental disorder in the family provides a limited understanding when trying to explain the predictors of outcome.

2.5.2 Definition of family history

The presence of a family history of psychiatric disorder depends largely on how ‘family history’ is defined. Definitions vary. One approach is based on the degree of relationship. A first-degree relative refers to a parent, sibling or offspring. A second-degree relative refers to a grandparent, grandchild, uncle, aunt, nephew, niece or half-sibling. A third-degree relative refers to a great-grandparent, great-grandchild or first cousin. In practice, the common approach is to take only the parents into account.

2.6 Schizophrenia research in Finland

Schizophrenia research has been active in Finland for over fifty years. Novel research has been carried out on genetics (Singh et al., 2016; Liuhanen et al., 2017; SUPER 2018), risk factors (Suvisaari et al., 2013; Keskinen et al., 2015), register-based antipsychotics studies (Taipale et al., 2017; Tiihonen et al., 2017) and adverse effects of antipsychotic medication (Husa et al., 2017). Also, there is unique birth cohort research (Jääskeläinen et al., 2015), outcome studies (Achte et al., 1986), register studies (Salokangas et al., 2002; Kiviniemi et al., 2013; Simoila et al., 2017), a national deinstitutionalisation study (Salokangas & Saarinen, 1998) and, e.g., the fascinating Helsinki High-Risk Study (Niemi et al., 2004), the Finnish Twin Cohort (Koskenvuo et al., 1984) and the Finnish Adoption Study of Schizophrenia (Wahlberg et al., 2004).
3 Outcome in schizophrenia and other psychoses

The illness course in schizophrenia significantly varies between individuals (Zipursky et al., 2013). The course of the illness is often lifelong and involves at least some level of impairment (Giusti-Rodriguez & Sullivan, 2013). Roughly 40% of individuals with schizophrenia are considered to have a ‘good outcome’ based on systematic reviews (Hegarty et al., 1994; Menezes et al., 2006), noting that the definition of ‘good outcome’ is not straightforward. Outcome can be measured in different ways and divided into different dimensions, as presented below.

3.1 Different outcomes and outcome measures

3.1.1 Clinical outcome

Description and measures

Clinical outcome in schizophrenia typically refers to the symptomatology of the patient, and the symptoms are often divided into positive symptoms, which refer to reality distortion (e.g. hallucinations and delusion), negative symptoms, which represent a reduction of normal functions (e.g. blunted affect and emotional withdrawal) and some other aspects of illness, such as general psychopathology (Kay et al., 1987).

The scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1984a), Scale for the Assessment of Positive Symptoms (SAPS, Andreasen, 1984b), Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) and Brief Psychiatric Rating Scale (BPRS, Overall & Gorham, 1962) are widely used measures of clinical symptomatology in schizophrenia. SAPS measures positive symptoms, SANS negative symptoms, and PANSS both positive and negative symptoms as well as general psychopathology. BPRS is similar to PANSS in including positive and negative symptoms as well as general psychopathology, but it includes only 24 measured items compared to 30 in PANSS. The Clinical Global Impression – Severity scale (CGI-S, Guy, 1976) is a 7-point scale that requires the clinician to rate the severity of the patient's illness using the clinician's past experience with patients who have the same diagnosis. Hence, the CGI-S is not specific to a certain disorder, and when used to rate schizophrenia it does not
specify which symptom dimension is being rated but, in practice, is most likely to be a more specific measure of clinical outcome than any other outcome category. There is also a Clinical Global Impression – Schizophrenia scale (CGI-SCH, Haro et al., 2003), which is designed specifically to assess positive, negative, depressive and cognitive symptoms of schizophrenia. Many of the above mentioned measures are also used in measuring remission, which is presented in section 3.1.5. Also hospitalisation (i.e. number of days spent at hospital or frequency of admissions to hospital) can be used as a measure of clinical outcome (Gmür, 1991).

Findings in the literature

Reduction in PANSS or BPRS score during the first 2-6 weeks of treatment is often used as a measure of treatment response to antipsychotics in the literature. According to a review by Samara et al. (2015), the definition of this ‘early response’ to treatment varies, being for example as low as ≥ 20% and as high as ≥ 50% reduction in the PANSS score. Larsen et al. (2000) define the onset of psychotic symptoms as a score of 4 or higher on one of the positive items in PANSS. The hospitalisation rate in schizophrenia varies substantially according to the literature. In a two-year follow-up 18-25% of individuals with schizophrenia were rehospitalised (Ganev et al., 2007; Zhang & Dai, 2012), and as much as 71% were readmitted to hospital in a 10-year follow-up (Chi et al., 2016), and 50-80% were rehospitalised during a follow-up period of two decades (Eaton et al., 1992). According to one study, 20% of the cohort members were hospitalised on any given day throughout the length of the 13-year follow-up period (Munk-Jørgensen et al., 1991).

3.1.2 Social outcome

Description and measures

Social outcome measures social activity, such as frequency of social contacts and quality of relationships. The five most commonly used social functioning scales in the assessment of schizophrenia are the Social Functioning Scale (SFS), the Social and Occupational Functioning Assessment Scale (SOFAS), the Disability Assessment Scale (DAS II), the Global Assessment of Functioning (GAF) scale and the Global Assessment Scale (GAS) (Burns & Patrick, 2007). The SFS
(Birchwood et al., 1990) is a 79-item scale measuring issues such as social engagement, interpersonal communication, pro-social activities, recreation, independence and employment. The SOFAS (Spitzer et al., 2000) is a single-item scale with a numeric value from 0 to 100 measuring ability to function in key aspects of life: free-time activities, personal and social relationships, working or studying and self-care. The DAS II (WHO, 1985) has 12 or 36 items and measures understanding and communicating, getting around, self-care, getting along with others, household and work activities and participation in society. The GAF and GAS are presented in section 3.1.4.

Findings in the literature

Social functioning in individuals with schizophrenia is poorer compared to healthy controls of the same age (Meesters et al., 2010). Individuals with schizophrenia exhibit difficulties in identifying emotions, feeling connected to others, inferring people's thoughts and reacting emotionally to others (Green et al., 2015). Based on a worldwide study (Haro et al., 2011) 42-73% of patients with schizophrenia are socially active (i.e. having more than one social contact during the past 4 weeks or having a spouse or partner), and 18-35% achieve functional remission, which was defined as having good social functioning for a period of 6 months. According to a 10-year follow-up study, 68% of individuals with psychosis were single (Morgan et al., 2014). Seventy two percent of individuals with schizophrenia perceive having poor social support, and greater social support from friends and family improves quality of life in schizophrenia (Munikanan et al., 2017). Also, more frequent social interaction predicts remission in first-episode psychosis (Bjornestad et al., 2016).

3.1.3 Occupational outcome

Description and measures

Occupational outcome is a measure of working ability or work history, which can be measured, e.g., as an amount of workdays per time period or percentage of time in work. Disability pension can also be used as a measure of occupational outcome, being a strong indicator of inability to work. An example of an occupational
measure is SOFAS, although the measure does not provide separate results regarding occupational outcome.

Findings in the literature

The employment rate of individuals with schizophrenia in Europe is roughly 10-22%, while in the USA it ranges from 3% to 42.8% (Marwaha & Johnson, 2004, Marwaha et al., 2007). In Finland, as much as 80% of patients with schizophrenia are on disability pension and only 7% are employed (Perälä et al., 2008). In the UK, the employment rate of individuals with schizophrenia decreased markedly during the 1980s and 90s (Marwaha & Johnson, 2004). The low employment rate in schizophrenia may be partly due to reasons other than working skills. For example low self-esteem, stigmatisation, fear of losing financial benefits, side-effects of medication, poor work history caused by breaks in education and employment due to the illness, discrimination and employer’s belief that individuals with schizophrenia can only perform low-skilled jobs may also affect the employment rate of individuals with schizophrenia (Bevan et al., 2018).

3.1.4 Global outcome

Description and measures

Global outcome refers to a combination of different outcomes, and is considered as a ‘sum of outcomes’. It may include clinical, occupational and social aspects of outcome, or a specific combination of them (Harrison et al., 1996).

Global outcome can be measured using a combination of different outcome measures (e.g. PANSS and SOFAS), or a single global outcome measure. Examples of global outcome measures are the Strauss-Carpenter Outcome Scale (SCOS, Strauss & Carpenter, 1977; Nieman et al., 2012), Global Assessment Scale (GAS, Endicott et al., 1976) and Global Assessment of Functioning (GAF, APA, 1987; Startup et al., 2002). The SCOS has nine questions regarding social and occupation functioning, clinical symptoms and general functioning in life. The GAF measures social, occupational, and psychological functioning on a numerical scale from 0 to 100. The GAF is similar to SOFAS but also considers symptom severity. GAS is an older version of GAF and uses a similar numerical scale from 0 to 100.
Findings in the literature

According to a systematic review by Menezes et al. (2006), 42% of individuals with first-episode psychosis were reported to have a good outcome and 27% a poor outcome after an average of 35 months follow-up. Most of the original studies used several definitions of outcome (such as relapse, remission, recovery, good/intermediate/poor outcome, course, rehospitalisation, employment, symptoms, social functioning, social relationships, mortality and suicide), and several outcome measures (such as CGI, SANS, SANS, PANSS, GAS, GAF, BPRS and SCOS). Based on a meta-analysis by Hegarty et al. (1994) the proportion of patients with schizophrenia who had improvement in outcome was 49% during 1956-1985 and only 35% during 1895-1955 after an average of 5.6 years follow-up, where clinical, social and occupational outcome criteria were considered.

3.1.5 Remission

Description and measures

The remission criteria of Andreasen et al. (2005) have been widely used in schizophrenia. According to these criteria, remission is defined as mild symptoms in all core aspects of psychopathology, with specific numerical scores on the commonly used SAPS, SANS, PANSS and BPRS scales, and maintenance of these scores over a period of six months. Previous to this, remission criteria focused more on positive symptoms (Lieberman et al., 1993).

Findings in the literature

Based on a review with long-term follow up (range 5-59 years) remission rate varies from 7% to 52% (Lang et al., 2012), while another review reported a 17-78% remission rate (AlAqeel & Margolese, 2012). Interestingly, the patient, the relatives of the patient and the psychiatrist tend not to share the same opinion regarding the patient’s remission status (Karow et al., 2012). Good subjective well-being was most important for remission estimated by patients, good subjective well-being and symptom reduction by family members, and better symptom scores, well-being and functioning by psychiatrists. Outcome is often assessed only in terms of clinical symptoms and/or functioning (work ability, social skills). Therefore, integrating the patients’ subjective
opinion with assessment tools could help to better understand the associations between outcome and outcome predictors.

3.1.6 Recovery

Description and findings in the literature

There are many different definitions of recovery, and Liberman et al. (2002) suggest that symptomatology, vocational functioning, independent living, and social relationships should be assessed in order to evaluate recovery. For example, Whitehorn et al. (2002) define symptomatic recovery as a PANSS items score of < 3 and functional recovery as a SOFAS score of > 60 and a GAF score of > 50. Based on a review by Faerden et al. (2008), there are 18 different definitions of recovery in schizophrenia, 17 of which require minimal or no symptoms, and all 18 of which differ in their definition of functional recovery. The defined criteria of recovery are also essential, as according to one study (Shrivastava et al., 2010) 61% of patients with first-episode schizophrenia achieve recovery based on clinical criteria, 26% based on social criteria, and 23% based on both clinical and social criteria. Approximately 11-33% attain complete recovery according to Warner (2004), where the recovery is defined as loss of psychotic symptoms and a return to a pre-illness level of functioning. According to an extensive meta-analysis by Jääskeläinen et al. (2013), the recovery rate of individuals with schizophrenia is 13.5% where the recovery is defined as ‘improvements in both clinical and social domains, and evidence that improvements in at least one of these two domains had persisted for at least two years’. According to the meta-analysis, the recovery rate varied significantly per country based on average per capita income (13.0% in high income, 12.1% in upper-middle income and 36.4% in low or lower-middle income countries).

3.2 Predictors of outcomes in schizophrenia and other psychoses

3.2.1 Family history of mental disorders

Several studies suggest that a family history of psychosis predicts the illness course in schizophrenia (Docherty et al., 1996; Kendler et al., 1997; Malaspina et al., 1998). Esterberg et al. (2010) have studied the impact of family history of psychosis
on onset age and positive and negative symptoms of schizophrenia in a meta-
analisis, suggesting that the presence of psychosis in the family is associated with
younger age-at-onset and more severe negative symptoms. Family history of
schizophrenia has been associated with lower cognition in schizophrenia (Walker
& Shaye, 1982; Wolitzky et al., 2006; Goldberg et al., 2011). Having a first-degree
relative with a schizophrenia or bipolar disorder is a significant risk factor for
suicide in first-episode psychosis (Björkenstam et al., 2014). Family history of
psychiatric disorders (presence of any psychiatric disorder) has been associated e.g.
with a higher rate of rehospitalisations, more severe negative symptoms and higher
risk of relapse (Feldmann et al., 2001; Borkowska & Rybakowski, 2002; Ciudad et
al., 2012). Both family history of psychosis and family history of any mental
disorder are predictors of homelessness (Ran et al., 2006). Having a first-degree
relative with depression disturbs psychiatric service utilisation after discharge from
hospital due to first-episode psychosis (Gearing et al., 2016).

3.2.2 Family environment

Family environment may affect outcome in schizophrenia. Good family
relationships increase the likelihood of a good response to antipsychotic treatment
(Ezeme et al., 2016), whereas social isolation and living apart from relatives
(Harvey et al., 2007) and low economic status of the family results in poorer
clinical outcome (lower rate of remission, higher PANSS scores, lower GAF scores)
and poorer employment status (Ran et al., 2011; Ran et al., 2017). Relatives’ higher
expressed emotion of warmth protects against relapse in first-episode psychosis
(Lee et al., 2014) whereas relatives’ critical comments increase the risk of relapse
in schizophrenia (Roseliza-Murni et al., 2014). The family environment may play
a larger role for patients with chronic schizophrenia than in first-episode psychosis
(Butzlaff & Hooley, 1998; Koutra et al., 2014). Family interventions improve
family relationships and increase relatives’ empathy (Riley et al., 2011; Girón et
al., 2015) and, based on reviews, reduce the risk of relapse and rehospitalisation
(Rodrigues et al., 2008; Bird et al., 2010; Pharoah et al., 2010; Glynn, 2012;
McFarlane, 2016; Claxton et al., 2017) and improve medication adherence and
social impairment (Pharoah et al., 2010) and also, based on original studies, reduce
psychotic symptoms (Girón et al., 2010; Koolaee & Etemadi, 2010; Devarmane
et al., 2011; Calvo et al., 2014; Mayoral et al., 2015) and increase quality of life
(Tas et al., 2012; Mayoral et al., 2015) and work ability (Ran et al., 2015) in
schizophrenia.
3.2.3 Early development related predictors

Few studies have been carried out on the early developmental and environmental predictors of outcomes in schizophrenia. Pre-natal exposure to environmental adversities increases the risk of rehospitalisation (Levine et al., 2014) and patients born in winter have shorter periods of psychiatric hospitalisation during first admission (Rodrigo et al., 1991). Since family history of psychiatric disorders can be hypothesised to affect outcome through genetic and environmental effects, it would also be worthwhile to investigate how pregnancy, birth and early development related factors predict outcome in schizophrenia, because these early predictors can also be hypothesised to have genetic and environmental effects.

3.2.4 Other predictors

Outcome predictors of schizophrenia

According to reviews, predictors of poor outcome in schizophrenia include more severe negative symptoms (Bromet et al., 2005; Lang et al., 2013), male gender (Hor & Taylor, 2010; Lang et al., 2013), low level of education (Lang et al., 2013), high level of education (Hor & Taylor, 2010) and longer duration of untreated psychosis (DUP) (Bromet et al., 2005; Lang et al., 2013; Penttilä et al., 2014). In addition, cognitive impairment, recurrent hospitalisations, poor premorbid functioning, prior suicide attempts, comorbid substance misuse and living in a developed rather than a developing country have been described as predictors of poor outcome in schizophrenia (Bromet et al., 2005; Hor & Taylor, 2010; Lang et al., 2013). According to one review (Zipursky et al., 2014), treatment adherence may have a dramatic influence on the illness course, as patients who stop taking antipsychotic medication have a relapse rate of 77% during one year follow-up, in contrast to 3% in patients who continue medication. Long-acting injectable antipsychotics reduce hospitalisations as opposed to oral antipsychotics among patients with schizophrenia based on a review (Lafeuille et al., 2014). Based on a large register study the risk of rehospitalisation is about 20% to 30% lower during long-acting injectable treatments compared with equivalent oral formulations, and among oral antipsychotics clozapine is associated with the lowest risk of rehospitalisation and lowest rate of treatment failure (defined as psychiatric rehospitalisation, suicide attempt, discontinuation or switch to other medication, or death) (Tiihonen et al., 2017). Based on reviews, cognitive behavioural therapy
improves clinical symptoms in schizophrenia (Sarin et al., 2011) and is beneficial in medication-resistant schizophrenia (Rathod et al., 2008), cognitive remediation therapy improves cognition and functioning (Wykes et al., 2011) and supported employment improves employment outcomes (Campbell et al., 2011) in schizophrenia. The effect of family interventions is presented in section 3.2.2. Electroconvulsive therapy may be effective in treatment-resistant schizophrenia (Lally et al., 2016).

Regarding genetics research, a high polygenic risk was associated with more severe symptoms and greater need for hospitalisation (Meier et al., 2016), the MDR1 gene rs2032582 G/G genotype increased delusional symptoms in men (Tovilla-Zarate et al., 2014), DRD2 gene 141C insertion increased positive symptoms (Xiao et al., 2013), single nucleotide polymorphisms (SNPs) in the GABRB2 gene were associated with more severe positive symptoms (Tsang et al., 2013), SNPs in the GRM3 gene were associated with more severe psychotic symptoms (Bishop et al., 2011), SNPs in the TCF4 gene were associated with more severe negative symptoms (Wirgenes et al., 2012), rs6584400 minor alleles in the NRG3 gene increased positive symptoms (Meier et al., 2013), polymorphisms in the COMT gene were associated with negative symptoms among women (Li et al., 2012), BDNF G196A gene rs6265 polymorphism was associated with positive symptoms (Zhai et al., 2013) and the UBE2K and SIAH2 genes increased positive symptoms (Bousman et al., 2010) in schizophrenia.

**Outcome predictors of psychosis**

Being male, having an acute illness onset, having personality assets (presence of a trustworthy relationship and/or an activity to improve skills) and being married predicted improvement in social functioning in a 15-17 year follow-up study in schizophrenia or other non-organic psychosis (Ganev, 2000). In a review by Coentre et al. (2017), suicidal behaviour was associated with previous suicide attempt, sexual abuse, comorbid polysubstance use, lower baseline functioning, longer time in treatment, recent negative events, older age, longer DUP, higher positive and negative symptoms and depressive symptoms in first-episode psychosis. Other predictors of poor outcome in psychosis are, based on reviews, use of typical neuroleptics (Menezes et al., 2006), lower intelligence and lower levels of antioxidants (Díaz-Caneja et al., 2015). Predictors of good outcome in psychosis are, based on reviews, combination of pharmacotherapy and psychosocial therapy (Menezes et al., 2006), greater cortical thickness and greater
gray matter volume (Díaz-Caneja et al., 2015). In addition, poor premorbid social adjustment predicts poorer functional outcome in first-episode psychosis (Ayesa-Arriola et al., 2013).

In summary, roughly half of the mentioned outcome predictors of psychosis were also described as an outcome predictor for schizophrenia.

### 3.2.5 Summary of literature

The literature findings are summarised in Table 2.
Table 2. Summary of literature.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia</th>
<th>Psychotic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>15.2 per 100,000 person-years worldwide</td>
<td>31.7 per 100,000 person-years worldwide</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.4% worldwide, 0.9% in Finland</td>
<td>3.1% in Finland</td>
</tr>
<tr>
<td>Family history as a risk factor</td>
<td>Disorders in the family that increase the risk of schizophrenia: parental schizophrenia (OR 5.8), non-affective psychosis (4.1-fold), any other mental disorder than psychosis (OR 2.4) and alcohol dependence (OR 2.1-3.1); family history of psychosis (OR 2.6), bipolar disorder (OR 2.5) and any other mental disorder (OR 2.3).</td>
<td>Disorders in the family that increase the risk of psychotic disorders: family history of psychosis (OR of 12.9 for psychotic depression), family history of any mental disorder (OR of 10.7 for psychotic depression).</td>
</tr>
<tr>
<td>Other risk factors</td>
<td>Risk factors for schizophrenia: high paternal age, obstetric complications, use of cannabis, motor dysfunction, low IQ, delayed early motor development, social withdrawal in childhood, parental communication deviance, urban environment, Chlamydia pneumoniae infection, low social class, maternal stress during pregnancy, maternal smoking, parent-child separation during development, mother’s anaemia during pregnancy, unwanted pregnancy, male gender, high birth weight and length.</td>
<td>Central nervous system viral infection during childhood and coeliac disease as a risk factor for non-affective psychosis; adverse life events in childhood, negative family environment, long duration of symptoms and high levels of depression as a risk factor for psychosis; living alone, being unemployed, having contact with friends less than monthly, having no close confidants, having experienced childhood adversity and having more neurological soft signs as a risk factor for psychotic depression.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Clinical: 18-25% are rehospitalised in a two-year follow-up and as much as 71% are rehospitalised in a 10-year follow-up</td>
<td>Social: Social functioning is poorer compared to healthy controls of the same age; 42-73% are socially active; 18-35% achieve functional remission; 68% are single in a 10-year follow-up</td>
</tr>
<tr>
<td></td>
<td>Occupational: Employment rate 10-22% in Europe, 3-43% in USA, 7% in Finland</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Schizophrenia</td>
<td>Psychotic disorders</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Global</td>
<td>42% of individuals with first-episode psychosis have a good outcome and 27% a poor outcome after 35 months follow-up.</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>Remission rate varies from 7% to 78% in long-term follow-up</td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td>18 definitions of recovery; recovery rate varies from 11% to 33%</td>
<td></td>
</tr>
<tr>
<td>Predictors of outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>Family history of schizophrenia predicts lower cognition; family history of any mental disorders predicts higher rehospitalisation rate, relapse, homelessness, and more severe negative symptoms.</td>
<td>First-degree relative with schizophrenia or bipolar disorder predicts suicide in first-episode psychosis.</td>
</tr>
<tr>
<td>Family environment</td>
<td>Satisfactory family relationship increases the likelihood of good response to antipsychotics treatment; social isolation and living apart from relatives results in poorer clinical outcome; low economic status of family results in poorer clinical outcome and employment status; relatives' critical comments increase risk of relapse.</td>
<td>Relatives' higher expressed emotion of warmth protects against relapse in first-episode psychosis.</td>
</tr>
<tr>
<td>Early development related predictors</td>
<td>Pre-natal exposure to environmental adversities increases risk of rehospitalisation; patients born in winter have shorter periods of psychiatric hospitalisation.</td>
<td>Being male, having an acute illness onset, having personality assets and being married predict improvement in social functioning in schizophrenia or other non-organic psychosis; use of typical neuroleptics, lower intelligence and lower levels of antioxidants predict poor outcome in psychosis.</td>
</tr>
<tr>
<td>Other predictors</td>
<td>Predictors of poor outcome in schizophrenia: more severe negative symptoms, male gender, longer DUP, cognitive impairment, recurrent hospitalisation, poor premorbid functioning, prior suicide attempts, comorbid substance misuse, and poor treatment adherence. Also several findings regarding genetics and poor outcome.</td>
<td></td>
</tr>
</tbody>
</table>
4 Aims of the study

The aim of this thesis was to investigate in three original publications and one additional meta-analysis how family history of psychosis and other mental disorders affect long-term clinical, social, occupational and global outcome in schizophrenia and other psychoses, and in one original publication how pregnancy, birth and early development related factors associate with employment and hospitalisation in schizophrenia. All the selected predictors of outcome (i.e. family history of psychosis, family history of any mental disorder and the selected early factors) are known risk factors for schizophrenia. The Northern Finland Birth Cohorts 1966 and 1986 and two meta-analyses were used to gather the information for the thesis.

4.1 Aims of the study

The specific aims were:

I To systematically review how family history of psychosis affects long-term (at least two-year) clinical, occupational, social and global outcome in schizophrenia (Study I and additional meta-analysis).

II To investigate how family history of mental disorders, especially psychosis, affect long-term social, occupational, clinical and global outcome in schizophrenia in the Northern Finland Birth Cohort 1966 (Study II).

III To investigate how family history of mental disorders, especially psychosis, affect long-term occupational and clinical outcome in psychotic disorders in the Northern Finland Birth Cohort 1986 (Study III).

IV To investigate how pregnancy, birth and early development related factors predict employment and hospitalisation in schizophrenia in the Northern Finland Birth Cohort 1966 (Study IV).

4.2 Hypotheses of the study

The hypotheses tested were:

I Family history of psychosis is associated with poorer long-term clinical, occupational, social and global outcome in schizophrenia.
II Family history of mental disorders, especially psychosis, is associated with poorer long-term social, occupational, clinical and global outcome in schizophrenia.

III Family history of mental disorders, especially psychosis, is associated with poorer long-term occupational and clinical outcome in psychotic disorders.

IV Pregnancy, birth and early development related risk factors are associated with a lower level of employment and a higher level of hospitalisation in schizophrenia.
5 Materials and methods

5.1 Meta-analyses of family history of psychosis and outcome in schizophrenia (Study I and additional meta-analysis)

5.1.1 Study I

Data collection

In the literature search the guidelines of Meta-analysis of Observational Studies in Epidemiology (MOOSE, Stroup et al., 2000) were applied. A computerised literature search of articles was conducted using seven electronic databases: Scopus, Science Direct, PubMed, ISI Web of Knowledge, PsycINFO (Ovid), CINAHL (EBSCO) and Academic Search Premier (EBSCO). The following keywords were used: {schizo* or psychotic or psychoses or psychosis} and {recovery or remission or outcome or outcomes or course or prognosis or longitudinal or follow-up} and {"family history" or familial or "parental risk" or "parental history" or heritability}; the search was limited to title and abstract. There was no time or language limit. In addition, an extensive manual search of literature was conducted utilising an earlier literature review of the study group (Jääskeläinen et al., 2013).

Study selection

The studies to be included in the analysis were required to meet the following criteria: the study evaluated the association between family history of psychosis and occupational (e.g. employment history or disability pension), social (frequency of social contacts and quality of relationships) or global (combined occupational, social and clinical course) outcome in schizophrenia; at least 80% of individuals had a schizophrenia-spectrum diagnosis (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder); follow-up time was at least 2 years since onset of illness; the majority (> 50%) of individuals were older than 16 years at the onset of psychotic symptoms; the study sample included more than 20 participants to minimise inclusion of studies with insufficient power and reliability; non-English articles were included where possible; and the study was not a clinical trial or intervention study.
Studied outcomes

The studied outcomes were social, occupational and global outcome.

Statistical methods

Since heterogeneity was expected in the associations between family history of psychosis and outcomes, random effects models were used in order to pool estimates of effect sizes. In the random effects analysis, each study was weighted by the inverse of its variance and the between-studies variance. If the selected studies presented other effect measures than correlation coefficients, they were transformed to correlations using the formulas presented by Rosenthal (1994) and Rosenthal et al. (2000). Possible publication bias was studied using the Egger's test for small-study effects (StataCorp, 2009) and funnel plots. The heterogeneity of the studies was assessed using $I^2$ statistics, and the statistical significance of the heterogeneity was tested using chi-square test. The metan command of Stata version 11 (StataCorp, 2009; Sterne, 2009) was used in the analysis.

5.1.2 Additional meta-analysis

Preface

The association between family history of psychosis and clinical outcome (symptoms) in schizophrenia has been previously studied in a meta-analysis including literature up until 2008 (Esterberg et al., 2010), and therefore the current literature search included literature from 2008 onwards, and a meta-analysis was made combining studies from the current literature search and the meta-analysis by Esterberg et al. (2010).

Data collection

A computerised literature search of articles was conducted using the electronic database PubMed. The following keywords were used: {schizopr* or schizoaffective or psychotic or psychosis or psychoses} and {course or prognosis or longitudinal or follow-up} and {symptoms or PANSS or BPRS or SANS or SAPS} and {"family history" or familial or "parental risk" or "parental history" or
heritability\}. Only articles published since 1.1.2008 were included in the systematic
literature search. There was no language limit.

In addition, all of the studies from the meta-analysis by Esterberg \textit{et al.} (2010)
that studied the association between family history of psychosis and symptoms in
schizophrenia were reviewed.

\textit{Study selection}

The studies from the systematic literature search to be included in the analysis were
required to meet the following criteria: the study evaluated the association between
family history of psychosis and symptoms in patients with schizophrenia or other
psychosis; at least 80\% of the individuals had a schizophrenia-spectrum diagnosis
(schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional
disorder); the majority (> 50\%) of individuals were older than 16 years at the onset
of psychotic symptoms; the study sample included more than 20 participants to
minimise inclusion of studies with insufficient power and reliability; and the study
was not a clinical trial or intervention study. The same criteria were applied to the
studies of the meta-analysis by Esterberg \textit{et al.} (2010).

\textit{Studied outcomes}

The clinical symptoms (PANSS, BPRS, SANS and SAPS scores) were studied as
outcome.

\textit{Statistical methods}

Due to the expected heterogeneity of the associations between family history of
psychosis and outcomes, random effects models were used. The effect size of the
standardised mean difference (SMD) between groups was described with Hedges’
g. The Hedges’ g value is comparable with Cohen’s d but preferable for small
sample sizes. The Hedges’ g effect size can be interpreted as small 0.20, moderate
0.50 or large 0.80 (Cohen, 1992). Publication bias was studied using the Egger's
test for small-study effects (StataCorp, 2013). The heterogeneity of the studies was
assessed using $I^2$ statistics, and the statistical significance of the heterogeneity was
tested using chi-square test. The metan command of Stata version 13 (StataCorp,
2013; Sterne, 2009) was used in the analysis.
5.2 Northern Finland Birth Cohorts 1966 and 1986

5.2.1 Study population

The association between family history of psychiatric disorders and outcome of schizophrenia in the NFBC1966 (II)

The study population is based on the Northern Finland Birth Cohort 1966, which is a general population birth cohort of 12,068 expecting women and their 12,058 live-born children with an expected delivery date in 1966 in the provinces of Lapland and Oulu, Finland (Jääskeläinen et al., 2015). In total 10,934 of these individuals, who were living in Finland at the age of 16, gave permission for their data to be used.

To identify members with psychosis, the nationwide Care Register for Health Care (CRHC) was used to detect individuals with psychosis diagnosed by the end of 2008, and the registers from the Social Insurance Institution of Finland (SII) were used to find subjects treated only as outpatients (psychosis diagnosed by the end of 2008) including subjects with sick leave or disability pension due to psychosis or entitled to reimbursable medication due to a psychotic disorder. Based on these criteria 266 individuals with psychosis and known address were selected and invited to participate in a psychiatric study conducted during 2008-2011 at approximately 43 years of age. The psychiatric study included an interview, and the Structured Clinical Interview for DSM-IV (SCID I–interview, First et al., 2002) resulting in DSM-IV diagnoses was conducted for all participants. As a result, 69 participants with schizophrenia spectrum disorder (57 schizophrenia, 2 schizophreniform, 8 schizoaffective and 2 delusional disorder) were identified for the study. The study sample selection process is presented in Figure 1.
The association between parental psychiatric disorders and outcome of psychosis in the NFBC1986 (III)

The study population is based on the Northern Finland Birth Cohort 1986, which comprises individuals with an expected date of birth between 1st of July 1985 and 30th of June 1986 in two Northern provinces of Finland; Oulu and Lapland (Järvelin et al., 1993). The cohort included 99% of all births in the area totalling 9,432 live-born children.

Cohort members with psychosis were searched using the CRHC (inpatient treatments until 2013), the Finnish outpatient registers (specialised care 1998-2013; primary care 2011-2013), the SII registers (patients entitled to reimbursable medicines; until 2005) and the Finnish Centre for Pensions (FCP) register (disability pensions until 2013). Based on these registers 189 individuals with psychosis were identified for the study. Although the CRHC, Finnish outpatient registers and FCP register had information available until 2015, only information up to 2013 was utilised in searching for individuals with psychosis as the intention was to have a follow-up time of at least two years. The following psychosis
diagnoses were included: schizophrenia, persistent delusional disorders, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorders, mania with psychotic symptoms, bipolar affective disorder with psychotic symptoms, depressive disorder with psychotic symptoms, other nonorganic psychotic disorder and unspecified nonorganic psychosis, corresponding to the ICD-10 codes F20, F22-F29, F30.2, F31.2, F31.5, F32.3 and F33.3.

The association between parental psychosis and early predictors and outcome of schizophrenia in the NFBC1966 (IV)

The study sample is comprised of the NFBC1966. To detect individuals with schizophrenia the following registers were used:

1. The CRHC, which covers all mental and general hospitals and in-patient wards at local health centres and private hospitals, was used to detect individuals with schizophrenia diagnosed by the end of 2006.
2. Specialised Outpatient Care Register was used to detect individuals with schizophrenia diagnosed by the end of 2006.
3. The FCP register was used to detect individuals with schizophrenia diagnosed by the end of 2006.
4. The SII registers were used to detect individuals with schizophrenia diagnosed based on reimbursable medicine (information available until the end of 2005), disability pension (until the end of 2000) and sick leave (until the end of 1999).

Based on these registers 161 individuals with schizophrenia spectrum disorder (125 schizophrenia, 3 schizophreniform, 13 schizoaffective and 20 delusional disorder) were identified for the study.

5.2.2 Psychiatric diagnoses

Diagnostic systems

When gathering data from the registers for the NFBC1966 (Study II and IV), ICD-8, ICD-9, ICD-10 and DSM-IV were used. In Study II, also the Structured Clinical Interview for DSM-IV (SCID I – interview, First et al., 2002) resulting in DSM-IV diagnoses was conducted for all participants as a part of the interview process in
In order to validate the diagnoses. Only ICD-10 was used with the NFBC1986 (Study III). In the meta-analysis (Study I) a wider range of diagnostic systems was used; ICD-10, DSM-II, DSM-III, DSM-III-R, DSM-IV as well as some less commonly used diagnostic systems. In the additional meta-analysis DSM-III-R, DSM-IV and RDC were used.

**Schizophrenia and other psychoses**

The ICD-10 diagnoses included in the definition of psychosis in this thesis are the following: F20 schizophrenia, F22 persistent delusional disorders, F23 acute and transient psychotic disorders, F24 induced delusional disorder, F25 schizoaffective disorders, F28 other nonorganic psychotic disorders, F29 unspecified nonorganic psychosis, F30.2 mania with psychotic symptoms, F31.2 & F31.5 bipolar affective disorder with psychotic symptoms, F32.3 & F33.3 depressive disorder with psychotic symptoms. Schizotypal disorder (F21) was not included in psychosis in NFBC1966 (Study II and IV) or NFBC1986 (Study III). The corresponding ICD-9 diagnoses are: 295, 2961E, 2962E, 2963E, 2964E, 2967 and 297–299. The corresponding ICD-8 diagnoses are: 295–299.

In this thesis the term schizophrenia usually refers to ‘schizophrenia spectrum disorder’, which includes the following ICD-10 diagnoses: F20 schizophrenia, F22 delusional disorder and F25 schizoaffective disorder. The schizophrenia spectrum disorder includes also the ICD-9 and ICD-8 code 2954 schizophreniform disorder, which does not exist in the ICD-10.

**Other psychiatric disorders**

In Study II and Study III ‘any psychiatric disorder’ included all psychiatric diagnoses, with the exception of organic mental disorders, mental retardation, disorders of psychological development, behavioural and emotional disorders with onset usually occurring in childhood and adolescence, and unspecified mental disorders. This included the following ICD-10 codes: F1x1, F1x2 mental and behavioural disorders due to psychoactive substance use (where x refers to a specific substance), F20-F29 psychotic disorders, F30-F39 mood (affective) disorders, F40-F48 neurotic, stress-related and somatoform disorders, F50-F59 behavioural syndromes associated with physiological disturbances and physical factors and F60-F69 disorders of adult personality and behaviour. The
corresponding ICD-9 diagnoses are: 295-298, 300-309, 312 and 314. The corresponding ICD-8 diagnoses are: 295-307 and 7902.

In Study II, all psychiatric diagnoses of relatives collected from the interviews, excluding organic mental disorders, were included. In practice, the inclusion criteria from the interviews were quite similar to the registers, because the interviewee rarely reported childhood-related problems of relatives.

5.2.3 Predictors of outcome

The association between family history of psychiatric disorders and outcome of schizophrenia in the NFBC1966 (II)

Family history of psychosis and family history of any psychiatric disorder were used as predictors of outcome. The diagnoses of parents and siblings were investigated. The following information sources were used to gather data regarding psychiatric diagnoses of the subjects’ relatives:

1. The CRHC (available until 2012), and primary (2011–2012) and specialised (1998–2012) health care outpatient registers were used to gather diagnoses of the subjects’ parents.
2. The register of disability pensions from the FCP was used to gather diagnoses of the subjects’ parents until 2011.
3. Two interviews, approximately at the ages of 34 (1999–2001) and 43 (2008–2011), were used to gather diagnoses of the subjects’ parents and siblings. At the interview, the interviewer filled in a semi-structured questionnaire including the following questions regarding first-degree relatives: description of the illness (i.e. diagnosis); symptoms; onset and duration of the symptoms; and treatment history.

The association between parental psychiatric disorders and outcome of psychosis in the NFBC1986 (III)

Parental psychosis and any psychiatric disorder were used as predictors of outcome. To find information regarding the psychiatric diagnoses of the subjects’ parents the following registers were used:

1. The CRHC (inpatient treatments 1972-2015).
3. The FCP register (disability pensions 1964-2016).

The association between parental psychosis and early predictors and outcome of schizophrenia in the NFBC1966 (IV)

Parental psychosis was used as predictor of outcome. In addition, several predictors related to pregnancy, birth and early stages of life (i.e. early predictors) were used as predictors of outcome. These early predictors were selected based on earlier literature describing factors that increase the risk of schizophrenia (Keskinen et al., 2013; Keskinen et al., 2015). The following predictors were used:

1. Maternal age (< 20, 20–35 or > 35 years); data gathered from the population register.
2. Wantedness of pregnancy (wanted/mistimed or unwanted); data gathered by interviewing the mother during pregnancy.
3. Grand multiparity (< 6 children or ≥ 6 children); data gathered by interviewing the mother during pregnancy.
4. Birth weight (< 2500g, 2500-4500g or > 4500g) and height at birth (≤ 46cm, 47-53cm, or ≥ 54cm); data gathered from delivery records.
5. Age of achievement of standing up, standing up without support and walking without support in months as a continuous variable; data gathered from records of regular visits to Finnish child welfare clinics.

To find information regarding the psychosis diagnoses of the subjects’ parents the following registers were used:

1. The CRHC (inpatient treatments 1972-2012).
5.2.4 Background variables

The association between family history of psychiatric disorders and outcome of schizophrenia in the NFBC1966 (II)

The following background variables were analysed:

1. Gender.
2. Educational level (low, middle or high); data gathered from interview at age 43.
3. Marital status (married/cohabiting or unmarried/divorced/widow); data gathered from interview at age 43.
4. Age at onset of schizophrenia; data gathered from hospital notes or register data.
5. Duration of illness.
6. Schizophrenia diagnosis (schizophrenia or schizophreniform/schizoaffective/delusional disorder).
7. Remission (based on the criteria by Andreasen et al. (2005) utilising PANSS); data gathered from interview at age 43.
8. Social class of father at birth of the child in 1966 (unskilled workers or others); data gathered from questionnaire to parents.

The association between parental psychiatric disorders and outcome of psychosis in the NFBC1986 (III)

The following background variables were analysed:

1. Gender.
2. Psychosis diagnosis; data gathered from registers.
3. Age at onset of psychosis; data gathered from registers.
4. Duration of illness.

The association between parental psychosis and early predictors and outcome of schizophrenia in the NFBC1966 (IV)

The following background variables were analysed:

1. Gender.
2. Age at onset of schizophrenia (< 20, 20–35 or > 35 years); data gathered from registers.
3. Mother’s education (0–8 or ≥ 9 years); data gathered by interviewing the mother during pregnancy.
4. Mother’s marital status (married or single/divorced/widowed); data gathered by interviewing the mother during pregnancy.

5.2.5 Outcome data

The association between family history of psychiatric disorders and outcome of schizophrenia in the NFBC1966 (II)

The interview at age 43 included a SCOS interview, PANSS interview and SOFAS assessment, which were used to assess the outcome. The questions of the SCOS interview were grouped into four different outcome categories: social outcome (questions 1 and 2); occupational outcome (questions 3 and 4); clinical outcome (questions 5 and 6); global outcome (questions 1–9). In the PANSS interview the following five symptom dimensions were analysed: positive, negative, emotional, excitement, and disorganisation (van der Gaag et al., 2006).

The association between parental psychiatric disorders and outcome of psychosis in the NFBC1986 (III)

Register information regarding work activity, disability pension and hospital treatments due to psychiatric cause were used to assess the outcome. Work activity was assessed by measuring the cumulative number of work days in 2014 and 2015 (i.e. minimum of two years after onset of illness); this information was received from the FCP register. The study subjects were divided into two classes based on work history; less than 25% of working days at work, and more than 25% of working days at work. The information regarding disability pension at the end of 2015 (i.e. at the end of the follow-up, at age 29-30) was also received from the FCP register. The psychiatric hospital treatments were assessed using the CRHC (inpatient treatments until 2015). The number of hospital treatment days, number of treatment episodes and proportion of time spent in hospital due to any psychiatric cause (since onset of psychosis) were measured.
The association between parental psychosis and early predictors and outcome of schizophrenia in the NFBC1966 (IV)

Occupational outcome was studied using information on disability pension and working days during the last two years of the follow-up period. In Finland, a person receiving disability pension may work for a limited amount (Disability Pension, 2018). The employment status was defined as ‘employed’ if the person had been working for at least 25% of working days, and ‘not employed’ if there were less working days. The data regarding disability pension was gathered from the FCP (information available until the end of 2011) and SII registers (information available until the end of 2000), and data regarding working days from the FCP register (information available until the end of 2011).

Hospitalisation was studied analysing psychiatric hospitalisations during the last two years of follow-up. All treatment periods with any psychiatric diagnosis in psychiatric hospitals were included. The data was gathered from the CRHC until the end of 2011.

The two above-mentioned outcomes were combined and this combination outcome was considered ‘good’ if the person was working for at least 25% of working days and had no hospitalisations during the last two years of the follow-up period.

5.2.6 Statistical methods

The association between family history of psychiatric disorders and outcome of schizophrenia in the NFBC1966 (II)

The associations between family history of psychiatric disorders and background variables were analysed using a chi-square test and independent sample t-test as appropriate. Mann-Whitney U test was used to analyse the associations between family history and outcomes. Descriptive statistics are presented using frequency distributions, means with standard deviations (normally distributed variables) and medians with interquartile ranges (skewed variables). P-values of < 0.05 were considered statistically significant. Multivariate analyses were not performed as none of the background variables associated with parental psychiatric disorders. Statistical analyses were carried out using IBM SPSS Statistics version 22 (IBM corp., 2013).
The association between parental psychiatric disorders and outcome of psychosis in the NFBC1986 (III)

The associations between parental psychiatric disorders and background variables were analysed using a chi-square test and independent sample t-test as appropriate. The associations between parental psychiatric disorders and outcomes were analysed using the Mann-Whitney U test and chi-square test as appropriate. Multivariate analyses were not performed as none of the background variables associated with parental psychiatric disorders. Statistical analyses were conducted with IBM SPSS Statistics version 24 (IBM corp., 2016).

The association between parental psychosis and early predictors and outcome of schizophrenia in the NFBC1966 (IV)

Cross-tabulation, the chi-square test, Fisher’s exact test and t-test for independent samples were used to analyse the associations of background variables and predictors with outcome. McNemar’s test was used to verify the results of the t-tests, due to the skewedness of continuous variables in some cases. Binary logistic regression models were used to study the associations between predictors and outcome after adjustment for gender and onset age. Statistical analyses were carried out using IBM SPSS Statistics version 22 (IBM corp., 2013).
6 Ethical considerations and personal involvement

6.1 Ethical considerations

Data protection of the NFBC1966 and NFBC1986 has been approved by the Finnish Privacy Protection Agency and the Ministry of Social Affairs and Health. The Ethical Committee of the Northern Ostrobothnia Hospital District has approved the study designs. Written informed consent has been obtained from each participant of the follow-up studies of NFBC1966. All cohort members have the right to decline the use of their data, and those who have decided to do so have been excluded from the study. The participants have been assigned an ID-number and their identities are not revealed.

6.2 Personal involvement

I planned this thesis together with my supervisors Professor Jouko Miettunen and Docent Erika Jääskeläinen. I did most of the work for the literature searches: I analysed the abstracts, read the full text articles, selected the eligible studies and contacted authors for unpublished data. The database searches were conducted by informatician Noora Hirvonen, M.A., Ph.D. and Professor Jouko Miettunen. I participated in the planning of the original Studies I, II and III together with my supervisors, I interpreted the results and was the corresponding author and responsible for writing these articles. I also organised the submission, rewriting and resubmission of these manuscripts. I conducted the statistical analyses of the original Study III, and a professional statistician helped with Study II and the additional meta-analysis. Professor Jouko Miettunen conducted the statistical analyses of Study I. I was a second author in the original Study IV; I participated in the planning, conducted the majority of the background literature searches, and contributed to writing the manuscript. I did not participate in collecting the original data for the NFBC1966 and NFBC1986 studies. However, I read and analysed the data of the interviews at age 43 of the NFBC1966 regarding family history of mental disorders and converted the data into a format that could be used in the statistical analysis.
7 Results

7.1 Meta-analyses of family history of psychosis and outcome in schizophrenia (Study I and additional meta-analysis)

7.1.1 Study I

The database searches identified 4,081 unique records. Eight studies from the systematic literature search met all of our inclusion criteria and were accepted for the analysis. In addition, six studies found from manual searches were included, resulting in a total of 14 accepted studies. More details regarding the filtering process of the study selection is presented in the original publication (Study I, Figure 1).

Study characteristics

The 14 included studies were published between 1939 and 2013, had altogether 1,660 study subjects, and had an average follow-up time of 12.6 years (standard deviation (SD) 5.8; range 3–25). The number of study subjects in the original studies varied from 39 to 290. The included studies did not use any statistical method to account for attrition in the analyses. Several diagnostic systems were used: DSM-IV (n = 3), DSM-III-R (n = 4), DSM-III (n = 2), DSM-II (n = 1), ICD-10 (n = 1), and other (n = 3). Information on family history of psychosis was often obtained from multiple sources (n = 3) or interviews (n = 4), less often using only a register (n = 1) or medical records (n = 1), and five studies did not report the source of this information. Interview (n = 11), register (n = 1) or both (n = 2) were used to assess outcome. Only one study reported information about possible confounders, and none of the studies adjusted the analyses.

Family history of psychosis and outcome in schizophrenia

Family history of psychosis had a small but statistically significant association with poorer occupational outcome in schizophrenia (n = 3; r = 0.17, 95% CI 0.05-0.29; p = 0.008). The results are shown in Figure 2. There were no studies that focused solely on social outcome. However, three studies were included that studied combined social and occupational outcome. Family history of psychosis had no
effect on combined social and occupational outcome in schizophrenia (n = 3; r = -0.05, 95% CI -0.16-0.07; p = 0.40). The results are shown in Figure 3. Family history of psychosis had a small but statistically significant association with poorer global outcome in schizophrenia (n = 11; r = 0.13, 95% CI 0.05–0.21; p = 0.002). The results are shown in Figure 4. Egger’s test for small-study effects was conducted only for global outcome, as the number of studies was low in other outcomes. The test found no indication of publication bias for global outcome (t = 1.62, p = 0.14). The funnel plots were done for all results, and there was no indication of publication bias.

Fig. 2. Correlations between family history of psychosis and occupational outcome in schizophrenia (Study I, Figure 2). Positive correlation indicates that presence of psychosis in the family is associated with poorer outcome.
Fig. 3. Correlations between family history of psychosis and combined social and occupational outcome in schizophrenia (Study I, Figure 3). Positive correlation indicates that presence of psychosis in the family is associated with poorer outcome.

Fig. 4. Correlations between family history of psychosis and global outcome in schizophrenia (Study I, Figure 4). Positive correlation indicates that presence of psychosis in the family is associated with poorer outcome.
7.1.2 Additional meta-analysis

The database search identified 946 records. After analysing the abstracts there were 28 studies left that potentially fulfilled the inclusion criteria. The most common reasons for exclusion (which accounted for > 90% of exclusions) during abstract screening were that the article did not study schizophrenia or the association between family history of psychosis and outcome. The remaining 28 articles were read in full. Five studies met the inclusion criteria and were included for qualitative analysis. Two of the studies (Caseiro *et al.*, 2012; Morley *et al.*, 2008) had only a qualitative result and were thus excluded from the quantitative analysis. Also, in two studies (Ergül & Üçok, 2015; Gee *et al.*, 2016) the results were reported in a way that could not be included in the quantitative analysis and were thus excluded. As a result, only one study (Esterberg & Compton, 2012) from the literature search was included in the quantitative analysis.

In addition, all of the 12 studies from the meta-analysis by Esterberg *et al.* (2010) that studied the association between family history of psychosis and symptoms in schizophrenia were reviewed. Two of the studies (Feldman *et al.*, 2001; Borkowska & Rybakowski, 2002) were excluded, since they studied family history of any psychiatric disorder instead of family history of psychosis. Chen *et al.* (2005) was excluded because we did not have access to the unpublished data that Esterberg *et al.* (2010) had received. Thus, nine studies were included for quantitative analysis.

Consequently, the total number of studies included for the meta-analysis was ten. The filtering process of the studies is presented in Figure 5.
Study characteristics

The ten included studies were published between 1994 and 2012 and had a total of 1053 study subjects. The number of study subjects in the original studies varied from 24 to 196. The follow-up time varied between 0-23 years, and three articles did not report the follow-up time. The following diagnostic systems were used: DSM-IV ($n = 6$), DSM-III-R ($n = 3$) and RDC ($n = 1$). Information on family history of psychosis was obtained from interview of the patient or relatives ($n = 8$), from interview and medical notes ($n = 1$), and from register ($n = 1$). The outcome was
assessed by interview in all studies. Two studies reported information about possible confounders, and one study adjusted the analyses.

The ten included studies are presented in Table 3 with the following information: study reference, diagnostic system, sample size, attrition rate, definition and assessment of family history of psychosis, follow-up time, confounders, outcomes, and main results and comments.
Table 3. Study characteristics of the included studies for the additional meta-analysis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnostic system (country)</th>
<th>Sample size (males/females)</th>
<th>Sample size (male/females)</th>
<th>Attrition rate</th>
<th>Definition of familial risk</th>
<th>Data source for family history of psychosis</th>
<th>Follow-up time, years</th>
<th>Confounders</th>
<th>Outcome(s)</th>
<th>Main results and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arajärvi et al., 2006 (Finland)</td>
<td>DSM-IV (N)</td>
<td>196 (132/64)</td>
<td>[63/133]</td>
<td>0%</td>
<td>1st degree relative psychotic disorder</td>
<td>Register</td>
<td>&gt; 23</td>
<td>No</td>
<td>SAPS, SANS</td>
<td>FH+ patients had more severe positive and negative symptoms.</td>
</tr>
<tr>
<td>Esterberg and Compton, 2012 (USA)</td>
<td>DSM-IV (non-affective psychosis)</td>
<td>152 (114/38)</td>
<td>[23/129]</td>
<td>0%</td>
<td>1st degree relative non-affective psychosis</td>
<td>Interview (patient, relatives)</td>
<td>Not reported</td>
<td>Yes</td>
<td>PANSS</td>
<td>No difference between FH+ and FH− patients in positive or negative symptoms.</td>
</tr>
<tr>
<td>Malaspina et al., 2000 (USA)</td>
<td>DSM-III-R (N)</td>
<td>99 (not reported)</td>
<td>[39/60]</td>
<td>0%</td>
<td>1st or 2nd degree relative schizophrenia related psychosis</td>
<td>Interview (relatives)</td>
<td>&gt; 12</td>
<td>No</td>
<td>PANSS</td>
<td>FH+ patients had more severe negative symptoms; no difference in positive symptoms.</td>
</tr>
<tr>
<td>Malaspina et al., 2004 (USA)</td>
<td>DSM-IV (N)</td>
<td>26 (16/10)</td>
<td>[10/16]</td>
<td>0%</td>
<td>1st or 2nd degree relative non-affective psychosis</td>
<td>Interview (relatives)</td>
<td>&gt; 11</td>
<td>No</td>
<td>PANSS</td>
<td>FH+ patients had more severe negative symptoms; no difference in positive symptoms.</td>
</tr>
<tr>
<td>Martin Reyes et al., 2004 (Spain)</td>
<td>DSM-IV (N)</td>
<td>150 (not reported)</td>
<td>[82/88]</td>
<td>Not reported</td>
<td>Schizophrenia in the family</td>
<td>Interview (relatives)</td>
<td>Not reported</td>
<td>No</td>
<td>PANSS</td>
<td>FH+ patients had more severe negative symptoms; no difference in positive symptoms.</td>
</tr>
<tr>
<td>Norman and Malla, 2001 (England)</td>
<td>DSM-III-R (N)</td>
<td>24 (20/4)</td>
<td>[12/12]</td>
<td>0%</td>
<td>1st or 2nd degree relative schizophrenia</td>
<td>Interview (patient, relatives)</td>
<td>Not reported</td>
<td>No</td>
<td>SAPS, SANS</td>
<td>No difference between FH+ and FH− patients in positive or negative symptoms.</td>
</tr>
<tr>
<td>Reference (country)</td>
<td>Diagnostic system (diagnosis)</td>
<td>Sample size (males/females) [FH+/FH−]</td>
<td>Attrition rate</td>
<td>Definition of familial risk</td>
<td>Data source for family history of psychosis</td>
<td>Follow-up time, years</td>
<td>Confounders</td>
<td>Outcome(s)</td>
<td>Main results and comments</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>---------------------------------------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Norman et al., 2007 (Canada)</td>
<td>DSM-IV (B)</td>
<td>56 (38/18) [28/28]</td>
<td>0%</td>
<td>1st degree relative schizophrenia spectrum disorder</td>
<td>Interview (patient, relatives, medical records)</td>
<td>&gt; 2</td>
<td>No</td>
<td>SAPS, SANS</td>
<td>No difference between FH+ and FH− patients in positive or negative symptoms.</td>
<td></td>
</tr>
<tr>
<td>Ritsner et al., 2005 (Israel)</td>
<td>DSM-IV (N)</td>
<td>148 (121/27) [69/79]</td>
<td>0%</td>
<td>1st or 2nd degree relative schizophrenia related psychosis</td>
<td>Interview (patient, relatives)</td>
<td>15</td>
<td>Yes</td>
<td>PANSS</td>
<td>FH+ patients had more severe negative symptoms; no difference in positive symptoms.</td>
<td></td>
</tr>
<tr>
<td>Roy et al., 1994 (USA)</td>
<td>DSM-III-R (N)</td>
<td>130 (86/44) [68/62]</td>
<td>0%</td>
<td>1st degree relative schizophrenia</td>
<td>Interview (relatives)</td>
<td>&gt; 11</td>
<td>No</td>
<td>CASH</td>
<td>FH− patients had more severe positive symptoms; no difference in negative symptoms.</td>
<td></td>
</tr>
<tr>
<td>Sautter et al., 1994 (USA)</td>
<td>RDC (B)</td>
<td>72 (54/18) [37/35]</td>
<td>0%</td>
<td>1st or 2nd degree relative psychotic disorder</td>
<td>Interview (relatives)</td>
<td>≤ 2</td>
<td>No</td>
<td>SAPS, SANS</td>
<td>No difference between FH+ and FH− patients in positive or negative symptoms.</td>
<td></td>
</tr>
</tbody>
</table>

DSM = Diagnostic and Statistical Manual of Mental Disorders, RDC = Research Diagnostic Criteria.

1 Diagnostic criteria, and distribution of schizophrenia diagnoses: B = broad schizophrenia (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder), N = narrow schizophrenia (schizophrenia). 2 FH+ = presence of family history of psychosis, FH− = no family history of psychosis.
**Association between family history of psychosis and symptoms in schizophrenia**

Family history of psychosis had a small but statistically significant association with negative symptoms in schizophrenia (n = 10; SMD 0.39, 95% CI 0.16-0.61; p = 0.003). The results are shown in Figure 6. Family history of psychosis had no association with positive symptoms in schizophrenia (n = 9; SMD 0.01, 95% CI -0.15-0.16; p = 0.356). The results are shown in Figure 7. Egger's test for small-study effects was conducted to assess publication bias, and no indication of publication bias was found (t = 0.22 and p = 0.832 for negative symptoms; t = 0.97 and p = 0.364 for positive symptoms).

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (95% CI)</th>
<th>%Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roy et al. (1994)</td>
<td>-0.11 (-0.46, 0.23)</td>
<td>12.13</td>
</tr>
<tr>
<td>Saudet et al. (1994)</td>
<td>-0.03 (-0.49, 0.43)</td>
<td>9.90</td>
</tr>
<tr>
<td>Esteberg and Compton 2012</td>
<td>0.13 (0.32, 0.57)</td>
<td>10.23</td>
</tr>
<tr>
<td>Ritsner et al. (2005, 2007)</td>
<td>0.39 (0.06, 0.71)</td>
<td>12.35</td>
</tr>
<tr>
<td>Arjaiivi et al. (2006)</td>
<td>0.42 (0.12, 0.72)</td>
<td>12.96</td>
</tr>
<tr>
<td>Norman et al. (2007)</td>
<td>0.43 (-0.10, 0.96)</td>
<td>8.76</td>
</tr>
<tr>
<td>Norman and Matta (2001)</td>
<td>0.56 (-0.26, 1.38)</td>
<td>5.26</td>
</tr>
<tr>
<td>Malaspina et al. (2000)</td>
<td>0.57 (0.17, 0.98)</td>
<td>10.90</td>
</tr>
<tr>
<td>Malaspina et al. (2004)</td>
<td>0.86 (0.03, 1.69)</td>
<td>5.17</td>
</tr>
<tr>
<td>Martin Reyes et al. (2004)</td>
<td>0.94 (0.60, 1.28)</td>
<td>12.17</td>
</tr>
<tr>
<td>Overall (I-squared = 53.8%; p = 0.003)</td>
<td>0.39 (0.16, 0.61)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Fig. 6. Association between family history of psychosis and negative symptoms in schizophrenia. Positive effect size indicates that presence of psychosis in the family is associated with poorer outcome. SMD = standardised mean difference.
Fig. 7. Association between family history of psychosis and positive symptoms in schizophrenia. Positive effect size indicates that presence of psychosis in the family is associated with poorer outcome. SMD = standardised mean difference.

7.2 The association between family history of mental disorders and outcome in the NFBC1966 (II)

7.2.1 Characteristics of the sample

Of the 69 study subjects 37 (54%) were male. The average duration of illness was 16.9 years (SD 6.5; range 1.7–26.8 years). Fifty-four individuals (78.3%) had a family history of any psychiatric disorder: 21 individuals (30.4%) had psychosis, 27 individuals (39.1%) had mood disorder, 22 individuals (31.9%) had substance abuse disorder, and 42 individuals (60.9%) had other psychiatric disorders in the family. Family history of psychiatric disorders had no significant association with any of the background variables.
7.2.2 Family history of psychosis and outcome in schizophrenia

Family history of psychosis was not associated with outcomes. The results are shown in Table 4.

Table 4. Association between family history of psychosis and outcome in schizophrenia (Study II, Table 3).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Family history of psychosis</th>
<th>P-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=48)</td>
<td>Yes (n=21)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Strauss-Carpenter²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social outcome</td>
<td>7.0 (5.0-8.0)</td>
<td>7.0 (5.0-8.0)</td>
</tr>
<tr>
<td>Occupational outcome</td>
<td>3.0 (2.0-6.6)</td>
<td>3.0 (0.0-6.3)</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>7.0 (6.0-7.0)</td>
<td>6.0 (4.0-7.0)</td>
</tr>
<tr>
<td>Global outcome</td>
<td>24.0 (18.0-29.0)</td>
<td>22.0 (15.0-30.0)</td>
</tr>
<tr>
<td>Strauss-Carpenter²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social outcome</td>
<td>7.0 (5.0-8.0)</td>
<td>7.0 (5.0-8.0)</td>
</tr>
<tr>
<td>Occupational outcome</td>
<td>3.0 (2.0-6.6)</td>
<td>3.0 (0.0-6.3)</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>7.0 (6.0-7.0)</td>
<td>6.0 (4.0-7.0)</td>
</tr>
<tr>
<td>Global outcome</td>
<td>24.0 (18.0-29.0)</td>
<td>22.0 (15.0-30.0)</td>
</tr>
<tr>
<td>Symptom dimensions of PANSS³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>17.0 (11.0-27.0)</td>
<td>15.5 (10.0-28.3)</td>
</tr>
<tr>
<td>Positive</td>
<td>15.0 (9.0-20.0)</td>
<td>13.5 (9.5-22.8)</td>
</tr>
<tr>
<td>Disorganised</td>
<td>23.0 (13.0-33.0)</td>
<td>20.0 (15.3-34.5)</td>
</tr>
<tr>
<td>Excitement</td>
<td>14.0 (11.0-18.0)</td>
<td>14.0 (10.3-20.5)</td>
</tr>
<tr>
<td>Emotional</td>
<td>17.0 (13.0-23.0)</td>
<td>15.5 (13.0-25.0)</td>
</tr>
<tr>
<td>SOFAS⁴</td>
<td>45.0 (36.0-63.0)</td>
<td>46.0 (32.0-67.0)</td>
</tr>
</tbody>
</table>

IQR = interquartile range.

¹ Statistical significance based on Mann-Whitney U test. ² Strauss-Carpenter Outcome Scale –interview (Strauss & Carpenter, 1977) (higher scores indicating better outcome). ³ Positive and Negative Syndrome Scale, factors based on van der Gaag et al. (2006) (higher scores indicating more severe symptoms). ⁴ Social and Occupational Functioning Assessment Scale (Spitzer et al., 2000) (higher scores indicating better functioning).

7.2.3 Family history of any mental disorder and outcome in schizophrenia

Individuals with a family history of any psychiatric disorder had more severe positive (median 11.0 vs. 16.0, p = 0.046) and emotional (median 13.0 vs. 17.5, p = 0.041) symptoms in PANSS. The results are shown in Table 5.
Table 5. Association between family history of any psychiatric disorder and outcome in schizophrenia (Study II, Table 2).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Family history of any psychiatric disorder</th>
<th>P-value$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=15)</td>
<td>Yes (n=52)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Strauss-Carpenter$^2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social outcome</td>
<td>6.0 (4.0-7.0)</td>
<td>5.0 (7.0-8.0)</td>
</tr>
<tr>
<td>Occupational outcome</td>
<td>4.0 (2.0-7.0)</td>
<td>3.0 (0.0-6.0)</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>6.5 (4.0-8.0)</td>
<td>6.5 (5.0-7.0)</td>
</tr>
<tr>
<td>Global outcome</td>
<td>26.0 (18.0-30.0)</td>
<td>23.5 (17.0-29.0)</td>
</tr>
</tbody>
</table>

Symptom dimensions of PANSS$^3$

|                           |                                            |             |
|                           | No (n=15)                                  | Yes (n=52)  |
|                            | Median (IQR)                               | Median (IQR)|
| Negative                   | 19.0 (10.0-28.0)                           | 15.5 (11.0-26.8)| 0.757 |
| Positive                   | 11.0 (8.0-18.0)                            | 16.0 (11.0-20.0)| 0.046 |
| Disorganised               | 18.0 (11.0-33.0)                           | 21.5 (15.3-34.5)| 0.335 |
| Excitement                 | 14.0 (11.0-20.0)                           | 14.0 (11.0-18.0)| 0.928 |
| Emotional                  | 13.0 (12.0-18.0)                           | 17.5 (13.0-25.0)| 0.041 |

SOFAS$^4$

|                        |                                            |             |
|                        | No (n=15)                                  | Yes (n=52)  |
|                        | Median (IQR)                               | Median (IQR)|
| Global outcome         | 50.0 (38.8-80.0)                           | 45.0 (35.0-63.3)| 0.279 |

IQR = interquartile range.

$^1$ Statistical significance based on Mann-Whitney U test. $^2$ Strauss-Carpenter Outcome Scale – interview (Strauss & Carpenter, 1977) (higher scores indicating better outcome). $^3$ Positive and Negative Syndrome Scale, factors based on van der Gaag et al. (2006) (higher scores indicating more severe symptoms).

$^4$ Social and Occupational Functioning Assessment Scale (Spitzer et al., 2000) (higher scores indicating better functioning). Statistically significant p-values in **bold**.

### 7.3 The association between parental mental disorders and outcome in the NFBC1986 (III)

#### 7.3.1 Characteristics of the sample

Of the 189 study subjects 101 (53%) were male. The psychosis diagnoses of the 189 study subjects were distributed as follows: 44 individuals (23%) had schizophrenia, 15 individuals (8%) had schizophreniform, schizoaffective or delusional disorder, 47 individuals (25%) had depressive or bipolar disorder with psychotic symptoms and 83 individuals (44%) had other psychosis. The average age at onset of psychosis was 21.2 years (SD 4.0), and the average duration of illness 8.8 years (SD 4.0; range 2.1-20.7). The parental psychiatric diagnoses were distributed as follows: 88 individuals (47%) had parental (any) psychiatric disorder, 20 individuals (11%) had parental psychosis, 65 individuals (34%) had parental...
mood disorder and 34 individuals (18%) had parental substance abuse disorder. The parental psychiatric disorders did not associate with any of the background variables.

### 7.3.2 Parental psychosis and outcome in psychotic disorders

Parental psychosis was not associated with outcome. The results are shown in Table 6.

**Table 6. Association between parental psychosis and outcome in psychotic disorders (Study III, Table 2).**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Parental psychosis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=169)</td>
<td>Yes (n=20)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Hospital treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days at hospital</td>
<td>43 (2-169)</td>
<td>45 (2-185)</td>
</tr>
<tr>
<td>Number of hospitalisations</td>
<td>2.0 (1.0-5.0)</td>
<td>2.0 (1.0-3.8)</td>
</tr>
<tr>
<td>Proportion of time spent at hospital</td>
<td>1.6% (0.0-5.9%)</td>
<td>1.7% (0.2-4.5%)</td>
</tr>
<tr>
<td>Disability pension</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>No</td>
<td>137 (81)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Yes</td>
<td>32 (19)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Cumulative number of work days in 2014-2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 25% of work days</td>
<td>104 (62)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>&gt; 25% of work days</td>
<td>65 (38)</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>

IQR = interquartile range. ¹ Statistical significance based on Mann-Whitney U test. ² Statistical significance based on chi-square test.

### 7.3.3 Any parental mental disorder and outcome in psychotic disorders

Individuals with any parental psychiatric disorder spent a higher number of days at hospital and had a higher number of hospitalisations due to psychiatric cause. The results are shown in Table 7.
Table 7. Association between any parental psychiatric disorder and outcome in psychotic disorders (Study III, Table 3).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Any parental psychiatric disorder</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=101)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Hospital treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days at hospital</td>
<td>26 (0-147)</td>
<td>0.0351</td>
</tr>
<tr>
<td>Number of hospitalisations</td>
<td>2.0 (0.0-4.5)</td>
<td>0.0391</td>
</tr>
<tr>
<td>Proportion of time spent at hospital</td>
<td>0.8% (0.0-5.6%)</td>
<td>0.0851</td>
</tr>
<tr>
<td>Disability pension</td>
<td></td>
<td>0.2292</td>
</tr>
<tr>
<td>No</td>
<td>85 (84)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (16)</td>
<td></td>
</tr>
<tr>
<td>Cumulative number of work days in 2014-2015</td>
<td></td>
<td>0.1282</td>
</tr>
<tr>
<td>≤ 25% of work days</td>
<td>58 (57)</td>
<td></td>
</tr>
<tr>
<td>&gt; 25% of work days</td>
<td>43 (43)</td>
<td></td>
</tr>
</tbody>
</table>

IQR = interquartile range.

1 Statistical significance based on Mann-Whitney U test. 2 Statistical significance based on chi-square test.

7.4 The association of parental psychosis and early predictors with outcome in the NFBC1966 (IV)

7.4.1 Characteristics of the sample

Of the 161 individuals with schizophrenia 90 (56%) were male. Eighteen (11.2%) were employed and 36 (22.4%) were hospitalised during the last two years of follow-up. Analysing the specific diagnoses revealed that individuals with schizophrenia were less often employed (6.4%) and more often hospitalised (27.2%) than individuals with schizophreniform disorder (66.7% employed, 0% hospitalised), schizoaffective disorder (30.8% employed, 0% hospitalised) and delusional disorder (20.0% employed, 10.0% hospitalised) during the last two years of follow-up.
7.4.2 Parental psychosis and outcome in schizophrenia

Parental psychosis was not associated with outcome. The results are shown in Table 8.

Table 8. Association between parental psychosis and outcome in schizophrenia.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Parental psychosis</th>
<th>P-value1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=270)</td>
<td>Yes (n=52)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>13 (9.6)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Not employed</td>
<td>122 (90.4)</td>
<td>21 (80.8)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalised</td>
<td>32 (23.7)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Not hospitalised</td>
<td>103 (76.3)</td>
<td>22 (84.6)</td>
</tr>
</tbody>
</table>

1 Statistical significance based on Fisher’s exact test.

7.4.3 Pregnancy, birth and early development related factors and outcome in schizophrenia

None of the early factors were associated with employment status in individuals with schizophrenia. Only one of the early factors was associated with hospitalisation: young maternal age was related to higher probability of being hospitalised in individuals with schizophrenia (47% of individuals whose mother was under 20 years old during pregnancy were hospitalised, whereas only 18-26% of individuals whose mother was of an older age group during pregnancy were hospitalised) after adjusting for gender and onset age. The rest of the results are presented in the original article (Study IV).
8 Discussion

8.1 Main findings

In the meta-analysis (Study I), the presence of family history of psychosis had a small but statistically significant association with poorer long-term occupational and global (i.e. combined occupational, social and clinical) outcome in schizophrenia. The search did not find any studies that focused on social outcome, and there was no association between family history of psychosis and combined social and occupational outcome. The number of studies was small (n = 3 for occupational outcome; n = 3 for combined social and occupational outcome) or moderate (n = 11 for global outcome) and there was a fairly high amount of heterogeneity in the quality aspects of the studies, and therefore more studies with large sample size and proper quality assessment are required to gain more reliable results. There was no indication of publication bias. This is the first meta-analysis to investigate the association between family history of psychosis and social, occupational and global outcome in schizophrenia. In the additional meta-analysis the presence of family history of psychosis had a small but statistically significant association with more severe negative symptoms in schizophrenia. There was no association between family history of psychosis and positive symptoms. The number of studies was moderate (n = 10), and there was no indication of publication bias.

In NFBC1966 (Study II), family history of any psychiatric disorder was associated with a higher amount of positive and emotional symptoms in schizophrenia. There was no association between family history of psychosis and outcomes. Given the somewhat high number of tested parameters (n = 20) and the small significance of the associations found, the association between family history of psychiatric disorders and outcome seems small according to this study.

In NFBC1986 (Study III), the presence of any parental psychiatric disorder was associated with a higher number of days spent at hospital and a higher number of hospitalisations in psychotic disorders. There was no association between parental psychosis and outcomes. Similarly to the NFBC1966, the results for NFBC1986 on the whole indicate that the association between parental psychiatric disorders and outcome seems quite small.

In NFBC1966 (Study IV), none of the pregnancy, birth and early development related factors were associated with employment in schizophrenia. Only one
predictor was associated with hospitalisation: young maternal age was related to higher probability of being hospitalised for schizophrenia. Parental psychosis did not associate with hospital treatment. The studied variables are known risk factors for schizophrenia, but most of them do not seem to be prognostic factors.

All studies combined, family history of any psychiatric disorder was associated with positive and emotional symptoms in schizophrenia and hospitalisation in psychotic disorders based on the cohort studies (Study II and III). The majority of the tested outcomes had no association with family history of any psychiatric disorder. Family history of psychosis was associated with occupational, global and clinical (negative symptoms) outcome in schizophrenia based on the findings of the two meta-analyses. Family history of psychosis was not associated with outcomes based on the cohort studies (Study II, III and IV). The results are summarised in Table 9.

Table 9. Association between family history of psychiatric disorders and outcome in schizophrenia and other psychoses.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Meta-analyses (Study I and additional analysis)</th>
<th>NFBC1966 (Study II)</th>
<th>NFBC1986 (Study III)</th>
<th>NFBC1986 (Study IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical outcome</td>
<td>FHP associated with clinical outcome (negative symptoms)¹</td>
<td>N.S.P</td>
<td>N.S.P</td>
<td>N.S.P</td>
</tr>
<tr>
<td></td>
<td>FHA associated with positive and emotional symptoms¹</td>
<td>FHA associated with hospitalisation¹</td>
<td>FHA associated with hospitalisation¹</td>
<td>FHA associated with hospitalisation¹</td>
</tr>
<tr>
<td>Occupational outcome</td>
<td>FHP associated with occupational outcome¹</td>
<td>N.S.P</td>
<td>N.S.P</td>
<td>N.S.P</td>
</tr>
<tr>
<td>Social outcome</td>
<td>No articles found²</td>
<td>N.S.P</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Global outcome</td>
<td>FHP associated with global outcome¹</td>
<td>N.S.P</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

FHP = presence of family history of psychosis, FHA = presence of family history of any psychiatric disorder, N.S.P = no significant association between family history of psychosis and outcome, N.S.A = no significant association between family history of any psychiatric disorder and outcome.

¹Patients with family history of psychosis or any psychiatric disorder had worse outcome. ²No association between family history of psychosis and combined social and occupational outcome in schizophrenia.
The meta-analyses had several significant associations and the cohort studies had mostly non-significant associations. Markedly, the cohort studies showed no significant association between family history of psychosis and outcome. One possible explanation is the small number of individuals with a family history of psychosis (n = 26 in Study II; n = 20 in Study III, n = 21 in Study IV) in the cohort studies, i.e. the negative finding may be due to lack of power. However, as presented in the next section, varying results were also produced in the earlier studies, and therefore this finding is not surprising.

8.2 Comparison to earlier studies

8.2.1 Clinical outcome

Association between family history of psychosis and outcome

Clinical outcome in the NFBC1966 (Study II and IV) was assessed based on hospital treatment, PANSS and SCOS interview (questions 5. Duration of non-hospitalisation and 6. Absence of symptoms). There was no association between family history of psychosis and these outcomes. In the NFBC1986 (Study III), clinical outcome was assessed based on hospital treatment, and parental psychosis did not associate with outcome. The additional meta-analysis combined studies from the meta-analysis by Esterberg et al. (2010) (n = 9) and a newer literature search (n = 1), resulting in the finding that the presence of family history of psychosis is associated with more severe negative symptoms in schizophrenia. Five studies found and five studies did not find an association between family history of psychosis and negative symptoms. In two studies family history of psychosis was associated with more severe positive symptoms, but overall there was no effect. In addition to the ten studies included in the quantitative analysis, there were two studies with only a qualitative result: family history of psychosis was not associated with symptoms (Caseiro et al., 2012; Morley et al., 2008). Furthermore, the results of two studies were of a nature that could not be included in quantitative analysis, namely: patients with family history of psychosis had either more severe and stable negative symptoms or more severe and decreasing negative symptoms (Gee et al., 2016); and patients with family history of psychosis had higher motivation-pleasure deficit (i.e. higher anhedonia-asociality and avolition-apathy scores) based on SANS (Ergül and Üçok, 2015).
Regarding earlier studies, according to the meta-analysis by Esterberg et al. (2010) family history of psychosis has a small but statistically significant association with more severe negative symptoms based on PANSS and there is no association with positive symptoms. In the additional meta-analysis of this thesis the studies of the meta-analysis by Esterberg et al. (2010) were combined with updated literature search, and the result remained the same. Family history of schizophrenia or psychosis has been associated with more frequent or longer hospitalisation in schizophrenia in several original studies (Erlenmeyer-Kimling et al., 1969; McGlashan, 1986; Suvisaari et al., 1998; Dadić-Hero et al., 2013).

In summary, the additional meta-analysis showed a small association, whereas both of the original studies showed no association, which indicates that there is evidence for a small association between family history of psychosis and clinical outcome in schizophrenia, although the results were not very consistent. The results are in line with previous findings.

**Association between family history of any psychiatric disorder and outcome**

Family history of any psychiatric disorder was associated with a higher amount of positive and emotional symptoms in PANSS in schizophrenia (Study II), a higher number of days spent at hospital, and a higher number of hospitalisations in psychotic disorders (Study III).

In earlier studies, family history of any psychiatric disorder has been associated with more severe psychopathological symptoms (based on GAS and BPRS), a higher amount of negative symptoms (based on PANSS), more frequent rehospitalisation and higher risk of relapse in schizophrenia (Feldmann et al., 2001; Borkowska & Rybakowski, 2002; Ciudad et al., 2012) and, in one study, the number of relapses in a seven-year follow-up period was not associated with psychiatric family history (Altamura et al., 2001).

In the cohort studies (Study II and III), family history of any psychiatric disorder was associated with only three of the several tested outcomes, and therefore the association seems either small or non-significant as a whole. Thus, the results of the present study are somewhat in line with previous slightly inconsistent findings.
8.2.2 Occupational outcome

Association between family history of psychosis and outcome

In the meta-analysis (Study I), only three studies regarding occupational outcome met the inclusion criteria and were included in the analysis. Family history of psychosis was associated with slightly worse occupational outcome in schizophrenia. One study found and two studies did not find an association between family history of psychosis and occupational outcome. In the NFBC1966 (Study II and IV), occupational outcome was assessed based on amount of work days, disability pension, the SCOS interview (questions 3. Amount of useful employment and 4. Quality of work function) and SOFAS, and family history of psychosis was not associated with occupational outcome in schizophrenia. In the NFBC1986 (Study III), occupational outcome was assessed based on number of work days and disability pension, and parental psychosis was not associated with occupational outcome.

The level of social security and the criteria for disability pension vary between countries, therefore comparing studies that have used disability pension as a measure of work ability is problematic. For example, in Finland disability pension can be granted until further notice as a full or a partial disability pension, or for a temporary period as a full or partial cash rehabilitation benefit if there is a chance that the ability to work might be restored (Disability Pension, 2018). In Finland, disability pension can be granted if an individual’s working capacity has been reduced for at least one year, but working for limited pay is allowed under both full and partial disability pension.

Besides the studies mentioned above, I am not aware of any other studies examining the association between family history of psychosis and occupational outcome in schizophrenia. Consequently, there seems to be small or no association between family history of psychosis and poorer occupational outcome in schizophrenia.

Association between family history of any psychiatric disorder and outcome

Family history of any psychiatric disorder was not associated with occupational outcome in schizophrenia or psychotic disorders (Study II and III). I am not aware of previous studies regarding the matter. Therefore there is no evidence of
association between family history of any psychiatric disorder and occupational outcome in schizophrenia or psychotic disorders.

### 8.2.3 Social outcome

In the meta-analysis (Study I), no articles specifically studying social outcome were found. There was no association between family history of psychosis and combined social and occupational outcome in schizophrenia (three studies). In the NFBC1966 (Study II), social outcome was assessed based on the SCOS interview (questions 1. Frequency of social contacts and 2. Quality of social relationships) and SOFAS, and neither family history of psychosis nor family history of any psychiatric disorder were associated with these outcomes. To my knowledge, this was the first study to investigate the association between family history of psychosis or any psychiatric disorder and social outcome in schizophrenia. In conclusion, there is no evidence of an association between family history of psychosis or any psychiatric disorder and social outcome in schizophrenia.

### 8.2.4 Global outcome

In the meta-analysis (Study I), eleven studies of global outcome were included in the analysis. Family history of psychosis was associated with slightly worse global outcome in schizophrenia. Four studies found and seven studies did not find an association between family history of psychosis and global outcome. In the NFBC1966 (Study II), global outcome was assessed with a SCOS interview, which is a global outcome measure, and also the PANSS and SOFAS combined serve as a global outcome measure. Neither family history of psychosis nor family history of any psychiatric disorder was associated with the SCOS or SOFAS results.

Besides the studies mentioned above, I am not aware of other studies regarding the association between family history of psychosis or any psychiatric disorder and global outcome in schizophrenia. As a result, the findings regarding the association between family history of psychosis and global outcome in schizophrenia indicate a small association. There is no evidence of an association between family history of any psychiatric disorder and global outcome in schizophrenia.
8.2.5 Other outcomes

According to earlier literature, family history of psychosis has also been associated with lower cognition (Walker & Shaye, 1982; Wolitzky et al., 2006; Goldberg et al., 2011), higher risk of homelessness (Ran et al., 2006) and higher risk of suicide (Björkenstam et al., 2014) in schizophrenia or psychotic disorders. Although these outcomes do not directly relate to the outcomes of this thesis, the direction of effect is similar to the present thesis; family history of psychosis is associated with poorer outcome.

8.2.6 Comparison of predictors

Table 10 presents some predictors of outcome in psychotic disorders and their magnitude (effect size) for comparison. Although the majority (60%) of predictors in Table 10 have a small effect size, there are also medium (20%) and large (20%) effect sizes. Consequently, the strength of association between family history of psychosis and outcome in schizophrenia found in this thesis (small effect size) does not seem very strong when compared to some other predictors of outcome, but it is in line with the majority of other outcome predictor studies. Interestingly, all of the studies in Table 10 regarding NFBC1966 (Miettunen et al., 2006; Lauronen et al., 2007; Juola et al., 2013) also had a small effect size.

Table 10. Predictors of outcome in psychotic disorders.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Predictor</th>
<th>Result</th>
<th>Effect size (magnitude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezeme et al., 2016</td>
<td>Family relationship</td>
<td>Satisfactory family relationship increases the likelihood of good response to antipsychotics treatment</td>
<td>$X^2 = 15.5$ (medium)</td>
</tr>
<tr>
<td>Ezeme et al., 2016</td>
<td>Onset age</td>
<td>Late onset age increases the likelihood of good response to antipsychotics treatment</td>
<td>$X^2 = 27.6$ (large)</td>
</tr>
<tr>
<td>Ezeme et al., 2016</td>
<td>Marital status</td>
<td>Being married increases the likelihood of good response to antipsychotics treatment</td>
<td>$X^2 = 27.6$ (large)</td>
</tr>
<tr>
<td>Ezeme et al., 2016</td>
<td>Occupation</td>
<td>Acquisition of skilled occupation increases the likelihood of good response to antipsychotics treatment</td>
<td>$X^2 = 5.5$ (small)</td>
</tr>
<tr>
<td>Ran et al., 2011</td>
<td>Gender</td>
<td>Poor work functioning is significantly associated with male gender</td>
<td>$X^2 = 8.9$ (small)</td>
</tr>
<tr>
<td>Ran et al., 2011</td>
<td>Age</td>
<td>Poor work functioning is significantly associated with older age</td>
<td>Cohen d = 0.59 (medium)</td>
</tr>
<tr>
<td>Reference</td>
<td>Predictor</td>
<td>Result</td>
<td>Effect size (magnitude)</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Ran et al., 2011</td>
<td>Education</td>
<td>Poor work functioning is significantly associated with higher level of education</td>
<td>$X^2 = 10.2$ (small)</td>
</tr>
<tr>
<td>Ran et al., 2011</td>
<td>Family economic status</td>
<td>Poor work functioning is significantly associated with lower family economic status</td>
<td>$X^2 = 12.4$ (small)</td>
</tr>
<tr>
<td>Ran et al., 2011</td>
<td>Caregivers</td>
<td>Poor work functioning is significantly associated with lack of caregivers</td>
<td>$X^2 = 8.3$ (small)</td>
</tr>
<tr>
<td>Levine et al., 2014</td>
<td>Pre-natal exposure to environmental adversities</td>
<td>Pre-natal exposure to environmental adversities increases the risk of rehospitalisation</td>
<td>HR = 2.28 (medium)</td>
</tr>
<tr>
<td>Penttilä et al., 2014</td>
<td>Duration of untreated psychosis (DUP)</td>
<td>Long DUP predicts poor general symptomatic outcome, more severe positive and negative symptoms, lesser likelihood of remission and poor social functioning and global outcome in schizophrenia</td>
<td>Correlations = 0.13–0.18 (small)</td>
</tr>
<tr>
<td>Lauronen et al., 2007</td>
<td>School marks</td>
<td>Individuals without remission had significantly lower school marks compared to those with remission</td>
<td>OR = 4.7 (small)</td>
</tr>
<tr>
<td>Lauronen et al., 2007</td>
<td>Father's social class</td>
<td>Father's low social class protected from having poor outcome in terms of hospitalisations</td>
<td>OR = 0.19 (small)</td>
</tr>
<tr>
<td>Mittunen et al., 2006</td>
<td>Short first hospitalisation</td>
<td>A short (1-14 days) first hospitalisation predicted rehospitalisation within 2 years</td>
<td>OR = 6.39 (small)</td>
</tr>
<tr>
<td>Juola et al., 2013</td>
<td>Single at onset</td>
<td>Being single at onset predicted more negative, disorganisation, excitement and emotional symptoms and a lack of remission</td>
<td>OR = 0.2 (small)</td>
</tr>
<tr>
<td>Wolitzky et al., 2006</td>
<td>Family history of psychosis</td>
<td>Individuals without family history of psychosis performed better in WAIS-R performance IQ subtest (object assembly)</td>
<td>Cohen d = 0.35 (small)</td>
</tr>
<tr>
<td>Ran et al., 2006</td>
<td>Family history of psychosis</td>
<td>Individuals with family history of psychosis had higher risk of homelessness</td>
<td>RR = 2.4 (small)</td>
</tr>
<tr>
<td>Xiao et al., 2013</td>
<td>DRD2 gene 141C insertion</td>
<td>DRD2 gene 141C insertion increased positive symptoms</td>
<td>Cohen d = 0.92 (large)</td>
</tr>
<tr>
<td>Tsang et al., 2013</td>
<td>SNPs in GABRB2 gene</td>
<td>Single nucleotide polymorphisms (SNPs) in GABRB2 gene were associated with more severe positive symptoms</td>
<td>Correlations 0.25-0.31 (medium)</td>
</tr>
<tr>
<td>Bishop et al., 2011</td>
<td>SNPs in GRM3 gene</td>
<td>SNPs in the GRM3 gene were associated with more severe psychotic symptoms</td>
<td>Cohen d = 0.91-1.88 (large)</td>
</tr>
</tbody>
</table>
8.3 Theoretical discussion

When analysing the association between psychiatric family history and outcome, the essential question is whether the found effect is a result of genetics or environment. According to a recent study, among those with a family history of serious mental illness, childhood neglect significantly raised the risk of negative symptoms of schizophrenia (Gallagher et al., 2016b). Several interesting findings have been made regarding the connection between genetics and risk of schizophrenia (The International Schizophrenia Consortium, 2008; Agerbo et al., 2015; Singh et al., 2016) as well as between genetics and outcome in schizophrenia (see section 3.2.4). Schizophrenia has been associated with epigenetic modifications in certain brain regions, and environmental factors may affect these epigenetic mechanisms resulting in altered gene expression during development and adulthood resulting in progression of schizophrenia (Maric & Svrakic, 2012; Ibi et al., 2015; Shorter et al., 2015), which provides an interesting aspect to the pathophysiology and prognosis of the disease. Healthy individuals with a family history of psychosis show higher amount of positive and negative symptoms, functional impairment (Janssens et al., 2016) and neurocognitive deficits (Agnew-Blais & Seidman, 2013) compared to healthy individuals without a family history of psychosis, which supports the hypothesis that there is an association between family history of psychosis and outcome.

Families play a key role in facilitating help-seeking for people with first-episode psychosis; the family may have, for example, introduced a stigma regarding the disorder which may decrease the help seeking (Connor et al., 2016). Medication adherence may be influenced by the same reasons. Family interventions may reduce rehospitalisation and increase medication adherence (Bird et al., 2010; Pharoah et al., 2010). Thus, family history of psychiatric disorders may have an effect on outcome in schizophrenia also by means other than genetics and adverse environment, i.e. family history may also affect the treatment process.

Consequently, the complex interaction of genetics and environment may have a significant role in the outcome of schizophrenia, and the simple presence or absence of family history of psychiatric disorders alone may not be a substantial factor. As our understanding of genetics increases, new possibilities for research will be opened up in the future. The accuracy of findings will also increase as genetic testing and more detailed information on environmental history are added to the analysis.
8.4 Strengths and limitations

The meta-analysis (Study I) is based on a comprehensive literature search including a systematic search of several databases and an extensive manual search from a range of scientific journals. The studies were collected from a long-term period (1939–2013). No language restrictions were applied to the search, although we were unable to translate one article. Variables such as onset age, gender and environmental aspects may have an effect on the association between family history and outcome, and therefore it would be important to control for these variables, which was not done in any of the included articles. The results of older studies may not be comparable with the situation today due to changes e.g. in treatment, clinical assessments, and expectations of occupational and global functioning. The total number of study subjects (n = 1660) in the meta-analysis was satisfactory, but the number of studies (n = 14) could be larger considering that several different outcomes were studied. There was no evidence of publication bias based on Egger's test and funnel plots.

In the additional meta-analysis only one database (Pubmed) was used, which is a limitation. The number of studies (n = 10) is moderate, and the total number of study subjects (n = 1053) is reasonable. Only two studies presented information about confounders, and only one study adjusted the analyses. There was no evidence of publication bias based on the Egger's test. The negative finding regarding publication bias needs to be assessed with caution as the statistical test for this is not very powerful in detecting bias with relatively small number of included studies.

The NFBC1966 (Study II and IV) is a general population-based cohort study with high coverage and unique data sources from several national registers and interviews. The follow-up period was quite long; an average of 17.5 years in Study II and 16.9 years in Study IV. Information regarding the diagnoses of the subjects and subjects’ relatives was collected from several different sources. The outcome was assessed rather comprehensively using several different measures. The small number of individuals with a family history of psychosis (n = 21 in Study II; n = 26 in Study IV) decreases the reliability, leaving a possibility for type II error (lack of study power to show significant associations), and there were several tested parameters leaving a possibility for type I error (significant results by chance). The average power to detect medium effect sizes (Cohen d ≥ 0.5) was 48% (p < 0.05) for Study II and 64% for Study IV, and the power to detect large effect sizes (Cohen d ≥ 0.8) was 86% for Study II and 93% for Study IV. In Study II, only 69 (39.4%)
of the 175 invited individuals participated in the interviews, and the participants had a higher level of education and were more often employed than the non-participants, raising the possibility that the participants were not very representative of the total schizophrenia group.

The NFBC1986 (Study III) is based on a general population cohort study with high coverage and a reliable register data. Disability pension and work activity from the FCP register and psychiatric hospital treatments from the CRHC can be considered fairly good measures of outcome. The total sample size \( n = 189 \) is reasonable, but the small number of individuals with parental psychosis \( n = 20 \) is a limitation. The average power to detect medium effect sizes \( (\text{Cohen} \ d \geq 0.5) \) was 56\% \( (p < 0.05) \) and 88\% for large effect sizes. The average follow-up period of 8.8 years is satisfactory. The relatively young age of the study subjects (29-30 years at the end of the follow-up) is a limitation, since some individuals may not yet have completed their education, or may have only recently entered working life and may therefore be unemployed due to reasons other than capability to work. The study population consists of schizophrenia and other non-organic psychoses, and therefore the results are not fully comparable to the other studies of the thesis (Study I, II and IV), which only included individuals with schizophrenia spectrum disorders in the study population.

One drawback regarding the study materials (meta-analyses, NFBC1966 and NFBC1986) is that there is no information as to whether the study subjects with a family history of psychiatric disorder were raised by the affected relative, and therefore reasoning regarding environmental exposure cannot be made. Moreover, as discussed in section 2.5.1, studying only the presence or absence of mental disorder in the family provides a limited understanding of the situation as the family is a dynamic entity with a fluctuating environment resulting in subjective experience, which is difficult to objectively measure.

The methods used also have a limitation in estimating genetic association, as the actual transmission of affected genes is not controlled for. Therefore, the current study has a clear limitation compared to genetics studies. Quantification of familial risk (i.e. using a familial loading method which takes into account family size and age structure) could be a more accurate measure of genetic loading compared to the present approach where only presence or absence of family history was observed. Using an adoption design, i.e. comparing adopted and biological children, would also help to differentiate the genetic and environmental effect and would therefore be a more reliable method. Investigating a cohort of children born to high-risk families would help to discover the interactions between genetics and environment.
9 Conclusions

9.1 Main conclusions

The results regarding the association between family history of mental disorders and outcome in schizophrenia are not explicit. Overall, there seems indication that such an association exists, but a large proportion of the studies show no association. In those studies that found a statistically significant association between family history of psychosis or other mental disorders and outcome in schizophrenia, the results mainly show that the presence of mental disorder in the family is associated with poorer outcome. The evidence is strongest for the association between family history of psychosis and poorer negative symptoms and poorer global outcome in schizophrenia, but the associations are small. Nevertheless, other outcome predictors also typically have only a small association with outcome. If the association between family history and negative symptoms is real, it could also explain some of the other results such as the association between family history and poorer work performance and higher amount of hospital treatment identified in some studies. There is less research regarding the association between family history of any mental disorder and outcome in schizophrenia but, based on the cohort studies, family history of any mental disorder could be an even stronger outcome predictor than family history of psychosis.

Family history of psychosis is a strong risk factor for schizophrenia, and based on this study it seems to also have a small effect on the outcome after illness onset. The other studied risk factors of schizophrenia, i.e. pregnancy, birth and early development related factors, do not seem to substantially affect later outcome after onset of schizophrenia.

9.2 Clinical relevance of the study

Patients with a family history of mental disorders are a potential target group for interventions. Based on this thesis, there is no evidence of strong correlation between family history of mental disorders and outcome in schizophrenia, and thus using this information in making estimates of the patients’ prognosis is not trivial, and therefore conclusions regarding the rationality of interventions are not straightforward. Nevertheless, as there is indication of small such an association,
this information could be valuable as a predictor of prognosis when combined with other significant information regarding the patient’s background.

Currently the family history of mental disorders is often inquired from the patient or relatives, but this information is not being systematically taken into consideration when deciding treatment options. As this study does not provide any new straightforward proposals, it offers no significant influence on the treatment practice of schizophrenia. However, there is demand among patients and relatives to know how a family history of mental disorders might affect the illness course, and therefore this study may have some clinical relevance in terms of its informative value.

9.3 Future research

As this study showed an association between family history of psychosis and outcome in schizophrenia, and since affecting outcome has a central role in psychiatry, it would be worthwhile to compare the effect of antipsychotics medication and therapy between those with and without a family history of psychosis. Since there is considered to be a genetic connection between different mental disorders, studying the association between outcome and family history of other mental disorders such as mood (affective) disorders, neurotic, stress-related and somatoform disorders could provide interesting results. Studying the association between familial mental disorders and cognition could help to understand more about the nature of the association between family history of mental disorders and outcome, as lower cognition could, for example, explain poorer work performance. The association between familial mental disorders and brain structure and activity, and how these brain findings affect outcome, is also a fascinating topic. Furthermore, more thorough examination of the association between environment and outcome could be valuable, i.e. gathering more detailed information regarding the subjective experience of family relationships, family support and adverse events. Further investigation into the effect of family history on treatment adherence could also have clinical relevance, since treatment adherence is a substantial predictor of outcome. Comparison of family history with other predictors of outcome within the same study population would also be of interest. Fascinating new areas of investigation are also set to emerge as our knowledge of genetics increases. For example, as more risk genes of schizophrenia are being found, studying the association between these genes (polygenic loading) and outcome in schizophrenia could help us understand the difference between
genetic and environmental effect on outcome in the familial form of schizophrenia. Using an adoption design would also help in differentiating genetic and environmental effects on outcome.
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StataCorp. (2013). *Stata Statistical Software: Release 13*. College Station: StataCorp LP.


List of original publications


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


1449. Kajula, Outi (2018) Periytyvän rintasyöpäalttiusmutaation (BRCA1/2) kantajamiesten hypoteettinen perinnöllisyysneuvontamalli


1452. Capra, Janne (2018) Differentiation and malignant transformation of epithelial cells: 3D cell culture models

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FAMILY HISTORY OF MENTAL DISORDERS AND LONG-TERM OUTCOME IN SCHIZOPHRENIA