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Emmi Keskinen

PARENTAL PSYCHOSIS, RISK FACTORS AND PROTECTIVE FACTORS FOR SCHIZOPHRENIA AND OTHER PSYCHOSIS

THE NORTHERN FINLAND BIRTH COHORT 1966

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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PARENTAL PSYCHOSIS, RISK FACTORS AND PROTECTIVE FACTORS FOR SCHIZOPHRENIA AND OTHER PSYCHOSIS

The Northern Finland Birth Cohort 1966

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium F202 of the Faculty of Medicine (Aapistie 5 B), on18 December 2015, at 12 noon

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Abstract

The aim of this study was to investigate whether risk factors for psychosis are different among those with and without parental psychosis, and to study the interaction between parental psychosis and risk factors. Protective factors for psychosis were also examined. Data from the Northern Finland Birth Cohort 1966 (N = 10,458) was used.

Biological risk factors in particular increased the risk for schizophrenia and other psychosis among those with parental psychosis. In the same group, the risk for schizophrenia was increased if the achievement of holding the head up and touching the thumb with the index finger was delayed. A new born's large size, advanced maternal age and mother's antenatal depressed mood had interactions with parental psychosis regarding risk for schizophrenia and the mother's smoking during pregnancy regarding risk for other psychosis. Parental psychosis and delayed touching the thumb with the index finger had an interaction regarding risk for schizophrenia and other psychosis. Several variables were associated with the decreased risk for psychosis in the total sample. In the parental psychosis group, only a mother's non-depressed mood and a mother's working outside the home or studying associated to remaining unaffected.

This study is one of the few studies to investigate risk factors for psychosis among those with and without parental psychosis and to examine interactions between parental psychosis and risk factors. This study showed that many risk factors increased the risk for schizophrenia and other psychosis only among those with parental psychosis. Hence, parental psychosis might even explain part of the association between some risk factors. Surprisingly few protective factors were found among those with parental psychosis. Further studies on the protective factors for psychosis are important in order to prevent psychosis in individuals at high risk.

Keywords: birth cohort, parental psychosis, protective factor, psychosis, risk factor, schizophrenia

Keskinen, Emmi, Vanhemman psykoosi sekä skitsofrenian ja muiden psykoosien riski- ja suojaavat tekijät. Pohjois-Suomen vuoden 1966 syntymäkohortti

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

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Tiivistelmä

Tämän tutkimuksen tavoitteena oli selvittää, eroavatko psykoosien riskitekijät henkilöillä, joiden vanhemmalla oli psykoosi verrattuna niihin joiden vanhemmalla ei ollut psykoosia sekä tutkia vanhemman psykoosin ja riskitekijöiden yhdysvaikutusta. Myös psykoosilta suojaavia tekijöitä tutkittiin. Tutkimusaineistona oli Pohjois-Suomen vuoden 1966 syntymäkohortti (N = 10458).

Erityisesti biologiset tekijät lisäsivät skitsofrenian ja muiden psykoosien riskiä henkilöillä, joiden vanhemmalla oli psykoosi. Viivästynyt pään kannattelun ja pinsettiotteen oppiminen lisäsivät skitsofreniariskiä henkilöillä joiden vanhemmalla oli psykoosi. Vastasyntyneen suurella koolla, äidin korkealla iällä ja raskaudenaikaisella masentuneella mielialalla oli yhdysvaikutus vanhemman psykoosin kanssa skitsofreniariskin osalta ja äidin raskaudenaikaisella tupakoinnilla muiden psykoosien riskin osalta. Vanhemman psykoosilla ja viivästyneellä pinsettiotteen oppimisella oli yhdysvaikutus sekä skitsofrenian että muiden psykoosien riskin osalta. Koko aineistossa useat tekijät liittyivät alentuneeseen psykoosiriskiin. Vain äidin ei-masentunut mieliala ja työskentely kodin ulkopuolella tai opiskelu suojasivat psykoosilta henkilöitä, joiden vanhemmalla oli psykoosi.

Tämä on yksi harvoista tutkimuksista, jossa on tutkittu psykoosien riskitekijöitä erikseen henkilöillä, joiden vanhemmalla oli tai ei ollut psykoosia sekä vanhempien psykoosin ja riskitekijöiden yhdysvaikutusta. Useat riskitekijät lisäsivät skitsofreniariskiä ainoastaan henkilöillä, joiden vanhemmalla oli psykoosi, joten vanhemman psykoosi voisi selittää osan psykoosien riskitekijöistä. Psykoosilta suojaavia tekijöitä löydettiin yllättävän vähän niillä, joiden vanhemmalla oli psykoosi. Suojaavien tekijöiden tutkiminen on tärkeää, jotta suuressa psykoosiriskissä olevien sairastumista voidaan ennaltaehkäistä.

Asiasanat: psykoosi, riskitekijä, skitsofrenia, suojaavatekijä, syntymäkohortti, vanhemman psykoosi

To my lovely mother

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Oulu, November 2015 Emmi Keskinen

Main definitions

Antenatal

Synonym for prenatal; time before labour, i.e. pregnancy

Any biological factor

Biological risk factors may directly affect foetal development. This thesis included birth weight, birth length, gestational age, birth weight / gestational age, mother's smoking during pregnancy, paternal and maternal age at the time of birth as biological risk factors.

Any psychosocial factor

Psychosocial risk factors may affect foetal development in several ways or they might also be proxies for parental mental illness. This thesis included mother's antenatal depressed mood, wantedness of the pregnancy, family type, father's social class, mother's education and grand multiparity as psychosocial risk factors.

Body Mass Index (BMI)

Anthropometric measure defined as weight in kilograms divided by the square of height in metres

Clinical high risk

Indicates an imminent risk for psychosis and is based on two complementary approaches: the ultra-high risk (UHR) and basic symptoms (BS) criteria

Developmental milestone

An important point in the progress or development, e.g. learning to walk in motor development

Incidence

The number of new cases of a condition, symptom, death or injury within a population over a given time period (e.g. one year)

Interaction

Interaction occurs when a relation between at least two independent variables is modified by at least one other variable. In other words, the strength or the direction of a relation between at least two variables is different depending on the value of some other variable(s).

Other psychosis

Including other psychosis than schizophrenia, e.g. schizophreniform disorder, delusional disorder, brief psychotic disorders, schizoaffective disorder, other non-organic psychosis, unspecified non-organic psychosis and affective psychoses (bipolar disorder and depression with psychotic symptoms)

Parental psychosis

A parent (mother and/or father) having any non-organic psychosis

Perinatal

The period from 20 gestational weeks to 1-4 weeks after birth

Population attributable risk

An estimate of how many cases of a disorder could be prevented if a particular risk factor was completely removed from a population

Premorbid

Time before the onset of the illness

Prenatal

Synonym for antenatal; time before labour, i.e. pregnancy

Prevalence

The proportion of subjects with specific characteristic present within a given population in a certain time period

Prevention

Actions aimed at eradicating, eliminating or minimising the impact of a disease and disability or retarding the progress of a disease and disability

Prodromal

Early symptoms or signs that may indicate the start of an illness before the specific symptoms occur

Prospective study

Usually implies a study population selected in the present and followed into the future

Protective factor

Characteristic(s) that enhance the likelihood of positive outcomes and reduce the negative effect of adversity on the outcome

Risk factor

Any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury

Abbreviations

95% CI	95% Confidence Interval
BMI	Body Mass Index
BS	Basic Symptoms state
CBT	Cognitive Behavioural Therapy
CHR	Clinical High Risk
CNV	Copy Number Variant
CRCH	Care Register for Health Care
DSM	Diagnostic and Statistical Manual of Mental Disorders
DUP	Duration of Untreated Psychosis
GWAS	Genome Wide Association study
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IQ	Intelligence Quotient
LCA	Latent Class Analysis
NFBC 1966	Northern Finland Birth Cohort 1966
NNT	Number Needed to Treat
OR	Odds Ratio
PAR	Population Attributable Risk
RR	Risk Ratio
SNP	Single Nucleotide Polymorphism
UHR	Ultra-High Risk
WHO	World Health Organization

List of original publications

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

I Keskinen E, Miettunen J, Koivumaa-Honkanen H, Mäki P, Isohanni M & Jääskeläinen E (2013) Interaction between parental psychosis and risk factors during pregnancy and birth for schizophrenia–the Northern Finland 1966 Birth Cohort study. Schizophr Res 145(1-3): 56–62.

II Keskinen E, Marttila A, Marttila R, Jones P, Murray G, Moilanen K, Koivumaa-Honkanen H, Mäki P, Isohanni M, Jääskeläinen E & Miettunen J (2015) Interaction between parental psychosis and early motor development and the risk of schizophrenia in a general population birth cohort. Eur Psychiatry 30(6): 719–727.

III Keskinen E, Marttila R, Koivumaa-Honkanen H, Moilanen K, Keinänen-Kiukaanniemi S, Timonen M, Isohanni M, McGrath J, Miettunen J & Jääskeläinen E (2015). Search for protective factors for psychosis–A population based sample with special interest in unaffected individuals with parental psychosis. Manuscript.

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

Contents

1 Introduction

There are descriptions of psychosis throughout recorded history in every society and culture. Schizophrenia was first introduced by *Eugen Bleuler* in 1911, when he described the disorder as a fragmentation of the mind. Earlier *Emil Kraepelin* had called the disorder *dementia preacox* referring to a state similar to premature dementia starting in early life, developing progressively and leading to chronicity.

Psychoses are commonly considered as *the most severe psychiatric disorders* and out of them schizophrenia is the most common and the most severe. It affects more than 26 million people worldwide (WHO 2008) and no society or culture has been found to be free of schizophrenia (McGrath *et al.* 2004, Saha *et al.* 2005). While the incidence of the disorder is rather low, schizophrenia is one of the main contributors of the global burden of disease (WHO 2008) and one of the leading causes of years lost due disability (WHO 2008, Wittchen *et al.* 2011, Global Burden of Disease Study 2013 Collaborators 2015).

The characteristic features of schizophrenia are the presence of psychotic symptoms (e.g. hallucinations, delusions, thought disturbances), decline in cognitive, social and occupational functioning and the certain duration of the disorder. Psychotic symptoms are characteristic to all psychotic disorders but cognitive decline in other psychosis is not usually as severe as in schizophrenia and the duration of the active disorder is usually shorter than in schizophrenia. (WHO 1992, APA 2013).

The course of schizophrenia is very individual and usually chronic. The two extremities; full recovery and permanent hospitalization, are rare courses of the disorder (Jääskeläinen *et al.* 2013). Psychosocial interventions in adjunct to antipsychotic treatment have been shown to prevent a transition to psychosis in people at clinical high risk state (Preti & Cella 2010) and decrease symptom severity in psychosis (Bird *et al.* 2010).

There are several aetiological models for schizophrenia. The vulnerability-stress model and two hit hypothesis, both suggest that genetic factors or perinatal risk factors result in increased vulnerability to later environmental risk factors, which trigger the psychotic symptoms if the threshold of psychosis is met. The progressive neurodevelopmental model of schizophrenia suggests that schizophrenia is a result of insufficient brain development starting from the foetal period of life (Rapoport *et al.* 2012) and affecting brain maturation in a way that is different from healthy aging (Douaud *et al.* 2014, Nour & Howes 2015).

The inheritance model of psychoses has been suggested to be *multifactorial* where many genes and environmental factors, each insufficient to cause the disorder on their own, have an interactive effect on risk when they exist together in the same individual (Mittal *et al.* 2008, Cardno & Owen 2014). Psychoses are an aetiologically heterogeneous group of disorders with overlapping symptomatology, genetics and risk processes (Lichtenstein *et al.* 2009, Cross-Disorder Group of the Psychiatric Genomics Consortium 2013, Domschke 2013, Reininghaus *et al.* 2013 Cardno & Owen 2014, Caspi *et al.* 2014). Schizophrenia is found to be polygenic with more than 100 genes, each with a small effect size, contributing to disease risk (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

Several risk factors for schizophrenia have been found and the family history of psychosis is considered the most powerful risk factor (Matheson *et al.* 2011, Rasic *et al.* 2014). There are many studies on parental psychosis and also of risk factors for schizophrenia, but only few studies have investigated their interaction. Risk factor studies may be particularly valuable, as the exposure of population to such risk factors can be decreased. There are even fewer studies focusing on the *protective factors of psychosis* even if they are needed in order to find ways of preventing psychosis among individuals at high risk.

The purpose of this thesis was to investigate whether risk factors during pregnancy, birth and in childhood for schizophrenia and other psychosis are different between individuals with and without parental psychosis, and also to find interactions between parental psychosis and risk factors. In addition, factors associating with unaffected status in the total sample and among those with parental psychosis were investigated. The study population was the general-population based Northern Finland Birth Cohort 1966 decreasing selection bias and enabling comparison between those with parental psychosis and the total sample. The prospective design of the study minimises recall bias and long-term follow-up enables studying causations.

2 Schizophrenia and other psychosis

Schizophrenia is a complex, often chronic and very severe psychiatric disorder and one of the leading causes of disability worldwide (WHO 2008). It is considered rather a diagnostic entity than one single disorder (Carpenter 2008). It has remarkable, life-long consequences on affected individuals and their families. The onset of schizophrenia is usually at the threshold of productive life, i.e. in late adolescence or early adulthood, disrupting social and educational development (van Os & Kapur 2009). While the majority of individuals with schizophrenia manage to overcome the psychotic episodes with optimal treatment, cognitive, functional and emotional impairments often remain persistent with progressive course or stable deficit (Farangou 2008, Jääskeläinen *et al.* 2013).

Schizophrenia causes both direct (e.g. medical costs) and indirect costs (e.g. lost income due to disability and mortality) with total cost per affected individual estimated to be the highest among psychiatric disorders (Gustavsson *et al.* 2011).

Other psychosis than schizophrenia include schizophreniform disorder, delusional disorder, induced delusional disorder, brief/acute and transient psychotic disorders, schizoaffective disorder, other non-organic psychosis, unspecified non-organic psychosis, bipolar disorder with psychotic symptoms and depression with psychotic symptoms. Hereafter the group of other psychosis than schizophrenia is named as "other psychosis" in this thesis.

2.1 Symptoms and diagnosis of schizophrenia and other psychosis

With a lack of biological tests, the diagnosis of schizophrenia and other psychosis relies on the examination of the mental state by observation and interview. No single symptom is specific to schizophrenia and therefore the differential diagnostics of the psychotic disorders is difficult, particularly in the early stages of the illness. Characteristic features of the active phase of psychoses are impairments in perception, thinking, behaviour, and emotions. In schizophrenia there is also a decline in social, cognitive and occupational functioning below the level prior to the disorder. A certain duration of the disorder is required for all of the psychosis diagnoses. (WHO 1992, APA 2013).

There have been several attempts to gain systematic, evidence-based diagnoses and nosology for mental disorders (Bhati *et al.* 2013). At the moment, the 5th Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by the American

Psychiatric Association (APA 2013) and 10th International Statistical Classification of Diseases and Related Health Problems (ICD-10) by the World Health Organization (WHO 1992) are the most often used classification guidelines in diagnosing schizophrenia and other psychosis. In Finland, clinicians use ICD-10 whereas the DSM-system is more common in research.

2.1.1 Symptoms of psychosis

The core feature of psychosis is loss of contact with reality. In schizophrenia, psychotic symptoms are divided into positive and negative. Positive psychotic symptoms include hallucinations, delusions and dissociative speech and behaviour. Negative symptoms include apathy, restricted affects, passive social withdrawal and anhedonia. (WHO 1992, APA 2013).

The Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983), and Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987) are widely used tools for evaluating psychotic symptoms. Certain positive symptoms (auditory hallucinations, delusions of control, delusional perception, thought withdrawal, insertion or broadcasting) do seem more likely to be associated with schizophrenia than other psychotic disorders, and were named as first-rank symptoms by Kurt Schneider (Schneider 1959). However, the scientific evidence for first-rank symptoms as the main differentiating symptoms of schizophrenia from other psychosis is very unclear (Nordgaard *et al.* 2008). Thus, DSM-5 has downplayed the importance of Schneider's first-rank symptoms in diagnosing schizophrenia (APA 2013).

Schizophrenia usually leads to decreased performance in cognitive, social and occupational functions (Magliano *et al.* 2005, Seidman *et al.* 2010, Tuulio-Henriksson *et al.* 2011) and cognitive deficits are already established before the onset of the disorder (Bora & Murray 2014). The decline in function is milder or absent in other psychosis than schizophrenia (APA 2013).

Several subclinical symptoms and signs of the illness, such as anxiety, depression, sleep disturbances and also attenuated psychotic symptoms, have been noticed before the onset of full-blown psychosis and the period is often called the prodromal state or clinical high-risk state (Du 2015). The course of psychotic disorders can be either continuous, or episodic with a progressive or stable deficit, or there can be one or more episodes with complete or incomplete remission (Farangou 2008, Jääskeläinen *et al.* 2013).

2.1.2 Diagnosis of schizophrenia

The diagnostic criteria of schizophrenia have been under constant revision during the last century and there have been great differences between the contents of the revisions as well as between different guidelines. With time, the diagnostic criteria of the DSM and ICD have become more congruent; however, the most differentiating feature is the time that the psychotic symptoms are required to persist. The Structured Clinical Interview for DSM (SCID-I) is commonly used in making DSM-diagnoses (Spitzer *et al.* 1989).

The ICD-10 and DSM-III-R (revised version of the DSM III) (APA 1987) are the main diagnostic guidelines used in this doctoral thesis. DSM-5 is the current version of the DSM-guidelines (APA 2013). The main differences between DSM-III-R and DSM-5 are: the duration of the active psychotic symptoms is extended from at least one week in the DSM-III-R to at least one month in the DSM-5 (the duration of the disturbance is at least 6 months in both), subtypes of schizophrenia are eliminated and negative symptoms are added to the characteristic symptoms in the DSM-5 (Tandon *et al.* 2013). In ICD-10 the subtypes of schizophrenia (e.g. paranoid, hebephrenic, catatonic, undifferentiated, simple, residual, unspecified and other schizophrenia) are still left. In Table 1, the diagnostic criteria of schizophrenia are presented according to both the diagnostic guidelines used in this doctoral thesis and also DSM-5.

Table 1. The diagnostic criteria of schizophrenia according to ICD-10, DSM-III-R and DSM-5.

Description	ICD-10 (WHO 1992)	DSM-III-R (APA 1987)	DSM-5 (APA 2013)
Diagnosis code:	F20	295 (except 295.4 and 295.7)	295 (except 295.4 and 295.7)
Duration of the characteristic symptoms:	≥ 1 month	≥ 1 week	≥ 1 month
Characteristic symptoms and signs:	At least one of the following a) Thought echo, thought insertion/withdrawal, thought broadcasting b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception c) Hallucinatory voices commenting or voices conversing or voices coming from some part of the body d) Persistent bizarre delusions	Criterion A At least two of the following 1. Bizarre delusions (e.g. being controlled, thought broadcasting, thought insertion/withdrawal) 2. Somatic, grandiose, religious, nihilistic or other delusions without persecutory or jealous content 3. Delusions with persecutory or jealous content if accompanied with hallucinations of any type 4. Auditory hallucinations (commenting voices or voices conversing) 5. Auditory hallucinations on several occasions with content of more than one or two words, having no apparent relation to depression or elation	Criterion A At least two of the following (at least one must be 1, 2 or 3): 1. Delusions 2. Hallucinations 3. Disorganised speech 4. Grossly disorganized or catatonic behavior 5. Negative symptoms

Description	ICD-10 (WHO 1992)	DSM-III-R (APA 1987)	DSM-5 (APA 2013)
		6. Incoherence, marked loosening of associations, markedly illogical thinking, or marked poverty of content of speech if associated with blunted, flat or inappropriate affect/delusions or hallucinations/catatonic or other grossly disorganized behaviour	
	Or at least two of the following a) Persistent hallucinations in any modality b) Neologisms, thought disorder, incoherence or irrelevant speech c) Catonic 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)	Criterion B Deterioration from a previous level of functioning in such areas as work, social relations and self-care	Criterion B Disturbances in at least one major area of social/occupational functioning
		Criterion C Continuous signs of the disturbance persist for at least 6 months, including active phases of criterion A-symptoms for at least one week, with or without prodromal or residual symptoms	Criterion C Continuous signs of the disturbance persist for at least 6 months, including active phases of criterion A symptoms for at least one month

Description	ICD-10 (WHO 1992)	DSM-III-R (APA 1987)	DSM-5 (APA 2013)
	.	Criterion D The full depressive or manic syndrome, if present, developed after any psychotic symptoms or was brief in duration relative to the duration of the psychotic symptoms in A Criterion E Onset of the prodromal or active phase of the illness before age of 45.	
	Exclusion criteria Schizoaffective disorder or mood disorder, Drug/Alcohol intoxication or withdrawal, Overt brain disease	Exclusion criteria Criterion F: Organic mental disorder or mental retardation	Exclusion criteria Criterion D: Schizoaffective disorder and mood disorder (depression or bipolar disorder) with psychotic symptoms Criterion E: Substance use or other medical condition Criterion F: Relation to Global Developmental Delay or Autism Spectrum Disorder- the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least one month

2.1.3 Diagnosis of other psychosis

In addition to schizophrenia, other non-affective psychoses include schizophreniform disorder, delusional disorder, induced delusional disorder, brief psychotic disorders, schizoaffective disorder, other non-organic psychosis and unspecified non-organic psychosis. All of the above mentioned, except brief psychotic disorder and induced delusional disorder, are called together also as schizophrenia spectrum disorders. Affective psychoses include bipolar disorder with psychotic symptoms and depression with psychotic symptoms.

According to the DSM-5, *schizophreniform disorder* has similar symptoms than in schizophrenia but the duration of the symptoms is shorter, i.e. at least one month but less than 6 months (APA 2013). According to this criterion, schizophreniform disorder is included in schizophrenia in ICD-10. The diagnosis of schizophreniform disorder does not require a decline in functioning as in schizophrenia (Bhati *et al.* 2013).

In the ICD-10, *delusional disorder* is defined by the presence of one or more delusions that are not totally impossible or culturally inappropriate at least for three months with no other psychotic symptoms. ICD-10 divides delusional disorders into subtypes of persecutory, litiginous, self-referential, grandiose, hypochondriacal (somatic), jealous and erotomanic type. In DSM-5, the delusions no longer have to be non-bizarre and the required time of delusions to be present for is at least a month. There are no impairments in functions outside the specific impact of the delusion. In *induced (ICD-10)/shared (DSM-5) delusional disorder* the developed delusional system is originally held by someone else, who is in close contact with the patient. In DSM-5, shared delusional disorder is not separated from delusional disorder (APA 2013).

In *brief psychotic disorder* (called acute and transient psychosis in ICD-10) psychotic symptoms are present for at least one day but less than one month and there is no decline in function according to DSM-5. In ICD-10, the time interval from the first appearance of psychotic symptoms to full-blown psychosis should not exceed two weeks and the symptoms should be present for not more than three months.

In *schizoaffective disorder* the individual fulfils both the schizophrenia-like psychotic symptom criteria and moderate or severe degree depressive or manic diagnostic criteria, the mood disorder being present for at least half of the illness duration. According to DSM-5 -criteria, the individual experiences hallucinations

or delusions for at least two weeks in the absence of a depressive or manic episode. In ICD-10, the psychotic symptoms are required to be present most of the time during a period of at least two weeks.

Schizotypal disorder is included in psychoses in ICD-10, but not in DSM-5. In this study it is not included in other psychosis.

According to ICD-10, *affective psychoses* meet the criteria of mania, severe depression or bipolar disorder with psychotic symptoms, other than those listed as typically schizophrenic (delusions that are not completely impossible or culturally inappropriate or hallucinations that are not in the third person or giving a running commentary). With mania, the commonest examples of delusions are grandiose, self-referential, erotic or persecutory content. With depression, the examples of delusions are depressive, guilty, hypochondriacal, nihilistic, self-referential, persecutory content or depressive stupor. The criteria of schizophrenia or schizoaffective disorder must not be met.

Other non-organic psychotic disorders cover those psychoses that do not meet the criteria of schizophrenia, delusional disorder of affective psychoses, but can be otherwise specified, e.g. persistent hallucinatory disorder. *Unspecified non-organic psychosis* cannot be specified otherwise and do not meet the criteria for any other psychosis diagnosis according to ICD-10 (WHO 1992). In DSM-5, *unspecified schizophrenia spectrum and other psychotic disorder* are grouped to same diagnosis code and are assigned to individuals with psychotic symptoms but do not meet the diagnostic criteria of schizophrenia or any other specified psychotic disorder (APA 2013).

Psychosis diagnoses should not be made during active brain disease or serious metabolic disturbances affecting the central nervous system or while under drug/alcohol intoxication, dependence or withdrawal. (WHO 1992, APA 2013).

2.2 Epidemiology of schizophrenia and other psychosis

Schizophrenia afflicts all known human societies and cultures but the incidence of schizophrenia and other psychosis varies markedly across and within populations (McGrath *et al.* 2004).

Incidence means the number of new cases of a disorder within a population over a given time period (Last 2001). In a review of over 150 studies drawn from 33 countries McGrath *et al.* (2004) reported on incidence data for schizophrenia from 1965 to 2001. The annual mean incidence rate for persons was 15.2 per

100,000 with a 5.6-fold variance across regions. Incidence was higher in densely populated urban areas and in some migrant and minority ethnic groups (McGrath *et al.* 2004) and this pattern of existence is common also in other psychosis. The finding on incidence of schizophrenia was similar to that of recent systematic review of studies conducted between years 1950–2009 in England, which reported incidence for schizophrenia to be 15.2 per 100,000 person-years (Kirkbride *et al.* 2012). The incidence of all psychoses was 31.7 per 100,000 person-years, non-affective psychoses 23.2 per 100,000 person-years and affective psychoses 12.4 per 100,000 person-years (Kirkbride *et al*. 2012).

Prevalence means the proportion of subjects who, during some point, period or during their lifetime has ever had the specific characteristic (Last 2001). The worldwide median prevalence of schizophrenia is around 0.3% for 1-year prevalence and 0.4% for lifetime prevalence (Saha *et al.* 2005). Lifetime morbid risk is 0.7% (Saha *et al.* 2005). The prevalence of schizophrenia is higher in migrants compared to native-born individuals, the median migrant-to-native-born ratio being 1.8 (95% confidence interval 0.9-6.4). Prevalence estimates from the least developed countries have been significantly lower than those from emerging or developed countries, but there does not seem to be significant difference in prevalence between urban, rural and mixed sites. (Saha *et al.* 2005).

Incidence, but not prevalence, is higher in males than in females with a 1.4-fold ratio (Aleman *et al.* 2003, McGrath *et al.* 2004, Saha *et al.* 2005). Males also tend to have an earlier onset of illness than females and the pattern is similar in all psychotic disorders (Häfner 2003, Kirkbride *et al.* 2012, Sutterland *et al.* 2013). The highest incidence of schizophrenia for men occurs in the age band of 20 to 24 years and for women in the age band of 25 to 29, but a greater rise in the incidence of psychoses among women older than 40 than among men has been found (Kirkbride *et al.* 2006). This gender difference is suggested to be related to the neuroprotective and antidopaminergic effect of oestrogen among premenopausal women (Hayes *et al.* 2012). Affective psychoses occur equally in men and women (Kirkbride *et al.* 2006, Kirkbride *et al.* 2012) and the onset age is older (mean 40.7, range 16-81) than that of schizophrenia (Baldwin *et al.* 2005).

In the Finnish Health 2000 Study, the life-time prevalence was 0.87% for schizophrenia, 0.32% for schizoaffective disorder, 0.07% for schizophreniform disorder and 0.18% for delusional disorder among over 30 year-old Finns. The life-time prevalence for any psychotic disorder was 2.99% when, in addition to the above mentioned, affective psychoses, substance-induced psychotic disorders and psychotic disorders due to a general medical condition were taken into account.

(Perälä *et al.* 2007). The prevalence of schizophrenia varied geographically in Finland and was highest in Eastern and Northern Finland (Perälä *et al*. 2008).

Outcomes of schizophrenia

The recovery rates are conflicting depending on the definition of the recovery. Recent meta-analysis revealed the median recovery rate of schizophrenia to be 13.5% when the definition of recovery included both clinical and social/functional dimensions and the duration of the recovery was for at least two years. The median annual recovery rate was 1.4% (Jääskeläinen *et al.* 2013). Earlier it has been shown that rates for complete recovery in schizophrenia have varied between 11–33% and for social recovery 22–53%, though there was no criterion for the duration of the recovery in these definitions (Warner 2004). Recovery rates have not improved over decades (Hegarty *et al.* 1994, Warner 2004).

In Finland, only 6.9% of individuals with schizophrenia were employed according to the Finnish Health 2000 Study, whereas the percentage for controls was 56.7%, for other non-affective psychosis than schizophrenia 19.8% and any psychotic disorder 20.7% (Perälä *et al.* 2008). In the Northern Finland Birth Cohort (NFBC) 1966, 56% of people with schizophrenia were on disability pension (Miettunen *et al.* 2007) and only 3.4% had completely recovered at the age of 34 (Lauronen *et al.* 2005).

Mortality in schizophrenia

The systematic review of studies from 25 different countries revealed that people with schizophrenia have approximately 2.5-times higher risk for death in all causes compared to the general population, including 2.4-fold risk for death from natural causes and 12.9-fold risk for dying of suicide compared to the general population. The standardised mortality ratio; SMR (ratio of observed to expected deaths) does not significantly vary between high-income countries and emerging economy countries. (Saha *et al.* 2007). Mortality in schizophrenia is high in all age groups, resulting in decreased life-expectancy of approximately 20 years compared to the general population (Laursen *et al.* 2014).

In Finland, mortality is 4.5-times higher among people with first-episode schizophrenia than in the general population within a five-year follow-up (Kiviniemi *et al.* 2010). The mortality gap between individuals with schizophrenia

and the general population has widened during the past decades (Laursen *et al.* 2014), but in the Nordic countries this gap has slightly diminished (Wahlbeck *et al*. 2011). In the NFBC 1966, case fatality rate (number of suicides divided by number of schizophrenia cases) was 7% until 2005 (Alaräisänen *et al.* 2009).

2.3 The models of the aetiology of schizophrenia

Several theories of the aetiology of schizophrenia have been emerged within years of psychosis research. However, the aetiology has remained elusive. The attention has shifted to disease models involving multiple factors, since no single genetic or environmental risk factor has been proven to be either sufficient or necessary to cause the onset of the illness (Maynard *et al.* 2001, Cardno & Owen 2014).

The vulnerability-stress model of mental health demonstrates how vulnerability to psychosis interacts with environmental protective or risk factors contributing to a normal development or psychopathology (Zubin & Spring 1977). This model suggests that an individual's vulnerability to a disorder arises from genetic risk factors or early perinatal risk factors (e.g. pregnancy and birth complications) and can be increased by environmental risk factors, e.g. stressful life events, infections, head trauma or substance abuse. Resilience may be understood as the opposite of vulnerability towards psychosis and includes positive adaptation in the face of adversity, coping mechanisms and social skills that may protect against mental illnesses (Marulanda & Addington 2014). If the individual is resilient or has low vulnerability for a particular disorder, it would take high levels of stress to trigger symptoms of that disorder. On the other hand, if the individual has high vulnerability towards the disorder, then it would take lower levels of stress for symptoms to appear. (Zubin & Spring 1977). However, protective factors can safeguard vulnerable persons. Vulnerability to psychosis itself is insufficient to cause the disorder and other risk factors or stresses are needed for psychosis onset (Cardno & Owen 2014). If the combination of vulnerability and later risk factors exceeds a disease threshold, the person will develop psychosis (Maynard *et al.* 2001).

Vulnerability-stress model suggests that genetically vulnerable individuals are more sensitive to environmental risk factors, which is supported by *the gene-environment interaction model* of schizophrenia (Maynard *et al.* 2001, Rutter *et al.* 2001, Tsuang *et al.* 2004, Wan *et al.* 2008a, van Os *et al.* 2008, Maric & Svrakic 2012). Gene-environment interaction appears when the environmental effects on psychosis risk differ according to a person's genetic liability, or person's genetic

predispositions are expressed differently in different environments (Tsuang *et al.* 2004).

The two hit hypothesis of psychosis supports the vulnerability-stress model, since in this model early perinatal genetic or environmental "first hit" disrupts some aspects of foetal brain development and produces long-term vulnerability to "second hit" that then leads to the development of the disorder (Maynard *et al.* 2001). On the other words, the first hit primes the nervous system to the second, which then precipitates the disease symptoms and neither of the events is itself sufficient to cause schizophrenia (Maynard *et al.* 2001).

The hybrid model of psychosis indicates that vulnerable individual can move in any direction between asymptomatic and symptomatic state along the psychosis continuum. Other models of psychosis are more irreversible and unidirectional and suppose evolution from asymptomatic state via certain stages to frankly psychotic state (Yung & McGorry 1996, Salokangas *et al.* 2001). In the hybrid model, individual's progression to psychosis can stop, decelerate, or even turn around with prevention and early intervention (Salokangas *et al.* 2001, van Os *et al.* 2008).

The progressive neurodevelopmental model of schizophrenia proposes that the disorder results of abnormal neurodevelopmental processes that have started years before the illness onset, probably already during the foetal period of life (Rapoport *et al.* 2012), and the process of abnormal neurodevelopment continues throughout life (Andreasen 2010) in a way that is different from healthy aging (Douaud *et al.* 2014, Nour & Howes 2015). The onset of schizophrenia is usually in the second or third decade of life but studies have found several observable subclinical signs of neuropathology in infancy, childhood and adolescence (Niemi *et al.* 2003, Welham *et al.* 2008), e.g. deficits in cognitive function (Bora & Murray 2014) supporting the neurodevelopmental model.

2.4 Risk factors for schizophrenia and other psychosis

Risk factor is defined as any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury (Last 2001). Risk factors are suggested to be causally related to the outcome and are distinguished from risk markers, which denote increased risk but are not causative (Last 2001). Triggers, in turn, precipitate the effect of other risk factors. The most robust design to examine risk factors of illnesses is the birth cohort study (Brown 2011a).

Psychoses are shown to be highly heritable (Sullivan *et al.* 2003, Cardno & Owen 2014, Rasic *et al.* 2014). However, genetic risk alone does not explain the development of the disorder (Kirkbride & Jones 2011, Svrakic *et al.* 2013). Thus, there are a lot of studies emphasizing the crucial role of environmental factors in the development of psychosis (Matheson *et al.* 2011).

The risk factors for schizophrenia are largely studied and recognized almost in every period of the human lifespan. The list of potential risk factors is extensive and results are somewhat conflicting. However, replications and summarizations are made regularly. Systematic reviews and meta-analyses are the ways of summarizing the broad literature and making generalisable conclusions of the findings (Button *et al.* 2013).

Recent systematic meta-review listed the risk factors for schizophrenia spectrum disorders according to quality of the studies and of the evidence. The risk factors with the highest quality evidence, reporting medium effect sizes, were advanced paternal age, obstetric complications, and cannabis use. The strongest evidence among the putative antecedents was identified for motor dysfunction and low IQ. (Matheson *et al.* 2011). However, known risk factors explain only a small proportion of the vulnerability to psychosis. Table 2 presents some of the recent meta-analyses of risk factors for psychoses after the meta-review of Matheson *et al.* (2011).

The contribution of a risk factor to a disease is quantified using the population attributable risk (PAR), which is an estimate of a proportion of cases of a disease that could be prevented if a particular risk factor were completely removed from a population assuming that the risk factor is causative and all other contributing risk factors remain unaltered after the intervention (Last 2001, Brown & McGrath 2011).

Many of the risk factors are found to be non-specific for schizophrenia and to overlap with other psychotic disorders and also with non-psychotic disorders (Kessler *et al.* 2010, McLaughlin *et al.* 2010).

Table 2. Meta-analyses of risk factors for psychosis after Matheson's meta-review from 2011.

Author (year)	Number of studies[1], cases and controls[2]	Main topic		Results	Comments
		Exposure	Outcome		
Khandaker *et al.* (2012)	7 studies, (2,424 cases, > 1.2 million controls)	Central nervous system (CNS) infection during childhood	Non-affective psychosis	CNS viral infection increased the risk of non-affective psychosis (RR 1.70; 95% CI 1.13-2.55). CNS bacterial infections did not increase the risk of psychosis.	
Varese *et al.* (2012)	18 case-control studies, (2,048 cases, 1,856 controls), 18 population studies, (N=77,849)	Adversity and trauma (sexual, physical, psychological abuse, neglect, parental death, and bullying) in childhood	Psychosis	There was a significant association between adversity and psychosis (OR 2.78; 95% CI 2.34-3.31). The estimated population attributable risk was 33% (16%-47%).	
Vassos *et al.* (2012)	8 studies; (46,820 cases)	Urbanicity	Non-affective psychosis	The risk for schizophrenia in the most urban environment was estimated to be OR 2.4 (95% CI = 1.6–3.5) times higher than in the most rural environment.	There was large heterogeneity between studies.
Beards *et al.* (2013)	11 case-control studies, (861 cases; 1,602 controls), 5 population studies (N=18,846)	Adverse life events in adulthood	Psychosis or psychotic symptoms	Meta-analysis yielded an overall weighted OR of 3.19 (95% CI 2.15-4.75) for psychotic disorders/symptoms.	Methodological quality of the studies was low. Caution with causality of the life events and the onset of the illness.

Author (year)	Number of studies[1], cases and controls[2]	Main topic		Results	Comments
		Exposure	Outcome		
Dickson *et al.* (2012)	26 studies, (835 cases, 34,483 controls)	Deficits in cognitive or motor function in youth aged 16 years or younger	Schizophrenia or schizophrenia spectrum disorder (SSD)	By age 16, individuals who subsequently developed schizophrenia/SSD displayed significant deficits in IQ (d=0.51) and in motor function (d=0.56).	
Matheson *et al.* (2013)[a]	7 studies, (798 cases, 883 controls)	Adversity in childhood	Schizophrenia and other psychiatric disorders	Increased rates of childhood adversity in people with schizophrenia compared to controls (OR 3.60, 95% CI 2.08–6.23).	.
Matheson *et al.* (2013)[b]	6 studies, (177 cases, 3,651 controls)	Social withdrawal in childhood measured by the Child Behaviour Checklist (CBCL)	Schizophrenia	A large effect of increased social withdrawal in childhood among those with schizophrenia (standardized mean difference [SMD] score 1.04, (95% CI 0.30-1.77), with no indication of publication bias.	There was considerable heterogeneity between studies.
de Sousa *et al.* (2014)	20 studies, (890 parents of cases, 863 parents of controls)	Parental communication deviance (CD)	Schizophrenia	Parental CD increased the risk of offspring's schizophrenia (g 0.97; 95% CI 0.76-1.18). Pooled effect size was stable after controlling for methodological and demographic features.	There was considerable heterogeneity between studies.
Rasic *et al.* (2014)	33 studies, (3,863 high risk offspring, 3,158 control offspring)	Family history of severe mental illness (SMI), i.e. high risk	SMI, schizophrenia, major depressive disorder, bipolar disorder	Parental SMI increased the risk of offspring's schizophrenia (RR 3.94; 95% CI 2.03-7.63). Parental schizophrenia increased the risk of offspring's schizophrenia (RR 7.54; 4.02–14.13).	

Author (year)	Number of studies[1], cases and controls[2]	Main topic		Results	Comments
		Exposure	Outcome		
Roisko *et al.* (2014)	8 studies, (199 cases, 223 controls)	Parental communication deviance (CD)	Schizophrenia spectrum disorders	High level of parental CD was associated with schizophrenia spectrum disorders in the offspring. A large overall effect size (d=0.79) was found in the meta-analysis.	
Gutiérrez-Fernández *et al.* (2015)	25 studies, (2,178 cases, 4.141 controls)	Chlamydia pneumoniae, Toxoplasma gondii, Herpes simplex virus 1 and Human herpes virus 6 infections	Schizophrenia	C. pneumoniae DNA in blood and brain were more common in patients with schizophrenia (OR 5.96; 95% CI 3.42–10.39). There was association with parasitism by T. gondii (OR 2.50; 1.40–4.47) despite the existence of publication bias. No association with herpes viruses.	
Tortelli *et al.* (2015)	16 studies, (4,105 cases, >37 million controls)	Migration	Schizophrenia	The pooled IRR of schizophrenia in the African-Caribbean migrant-group was 4.7 (95 % CI 3.9-5.7).	No evidence of publication bias was observed.

[1]Number of studies included in meta-analysis, [2]Number of cases and controls included in meta-analysis. CI=confidence interval, N=number of people in study population, d=Cohen's d, g=Hedge's g, IRR=Incidence Rate Ratio, OR=Odds Ratio, RR=Risk Ratio.

2.4.1 Risk factors during pregnancy and birth

Perinatal risk factors, i.e. those occurring from 20 gestational weeks to 1–4 weeks after birth (Last 2001), have been considered more causative than factors appearing later in life, since the effect of the developing disorder in the individuals cannot influence the environmental milieu in utero and during delivery (Brown 2011a).

High paternal age

Several studies have shown that advanced paternal age at the time of birth increases the risk for schizophrenia in the offspring (Malaspina *et al.* 2001, Torrey *et al.* 2009, Miller *et al.* 2011a, McGrath *et al.* 2014). The putative mechanism behind this may be de novo mutations occurring during the repeated mitosis in the progenitor sperm cells as men age (Perrin *et al.* 2007, Torrey *et al.* 2009), and also epigenetic aberrations could be possible (Brown 2011a). Additionally, accumulated exposure to toxins over the life course is correlated with mutations in DNA (Yauk *et al.* 2008) making toxic influences more detrimental to older fathers (Schlosser *et al.* 2012).

Complications in pregnancy and birth

Complications in pregnancy such as maternal preeclampsia, bleeding, rhesus incompatibility and diabetes (Cannon *et al.* 2002) increase the risk for offspring's schizophrenia. Maternal preeclampsia may cause abnormal foetal blood flow leading to chronic hypoxia and malnutrition (Dalman *et al.* 1999, Gaillard *et al.* 2013). Bleeding during pregnancy could represent threatened spontaneous abortion or anoxia (Cannon *et al.* 2002). Autoimmune mechanisms could be designated in the association of rhesus incompatibility and maternal diabetes and also in the latter, the effect of impaired glucose metabolism and the toxic effect of hyperglycaemia in the foetal brain may be present (Cannon *et al.* 2002, Van Lieshout & Voruganti 2008). Rhesus incompatibility may also result into haemolytic disease of the foetus and lead to foetal hypoxia and neonatal hyperbilirubinemia, which has been found to increase the risk for schizophrenia among males (Hollister *et al.* 1996).

Also macro-and micronutrient deficiency during pregnancy may increase the risk for schizophrenia in the offspring (Hoek *et al.* 1998, Xu *et al.* 2009), due to lack of important nutrients in foetal growth and brain development. Several key

nutrients, including vitamin D, iron and folate are found to be important in brain development (McGrath *et al.* 2011).

Also, prenatal infections, i.e. infections during pregnancy (Last 2001), such as rubella, cytomegalovirus, herpes simplex, and Toxoplasma gondii are risk factors for schizophrenia resulting in the disruption of foetal brain development and causing congenital brain anomalies, neurocognitive dysfunction and behavioural disorders (Brown *et al.* 2004, Brown 2011b). Deficient foetal immune responses in maternal infections may also contribute to the risk for subsequent psychosis (Blomström *et al.* 2015).

Various birth-related events have been linked to foetal hypoxia such as asphyxia, uterine atony, emergency caesarean section (Cannon *et al.* 2002) increasing the risk for schizophrenia. The neurotoxic effect of hypoxia can lead to severe complications in prenatal growth, metabolism (Schlosser *et al.* 2012) and to premature cortical synaptic pruning (Rosso *et al.* 2000).

Risk factors associating with new born

Risk factors associating with the new born have been found also, e.g. low birth weight (Cannon *et al.* 2002) usually resulting from intrauterine growth retardation or prematurity, which both are found as risk factors for psychosis (Nosarti *et al.* 2012, Nielsen *et al.* 2013). Prematurity could relate to interrupted neurodevelopment (Nosarti *et al.* 2012) and an immature central nervous system is found to be especially vulnerable to neonatal brain injury (Volpe 2009). High birth weight may also increase the risk for schizophrenia (Gunnell *et al.* 2003, Bersani *et al.* 2007, Wegelius *et al.* 2011) with the risk of resulting possibly from prolonged labour and respiratory distress.

Risk factors associating with parents and family during pregnancy and birth

There is conflicting evidence of the impact of social class at the time of birth on the offspring's psychosis, since both low and high social class has been associated with an increased risk for psychosis (Kwok 2014). A large population-based birth cohort study in Jerusalem revealed only modestly increased risk for schizophrenia in the lowest social class (Corcoran *et al.* 2009).

Grand multiparity e.g. the mother having 5 or more births earlier may increase the risk for schizophrenia among female offspring (Lahti *et al.* 2014). The putative explanation for this association may be the increased levels of perinatal complications associating with grand multiparous pregnancies and births (Roman *et al.* 2004, Yasmeen *et al.* 2005, Teguete *et al.* 2012) and also exposure to early socioeconomic adversity and stress, which have been found to associate with grand multiparous-parenting (Lawson & Mace 2009).

Maternal stress during pregnancy increases the risk for psychosis in the child (Khashan *et al.* 2008, Malaspina *et al.* 2008) due to the harmful effect of maternal glucocorticoids in the developing foetal brain (Cotter & Pariante 2002). There is suggestion that the effect of a mother's stressful life events could be mediated by maternal psychopathology (Dorrington *et al.* 2014). Unwanted pregnancy represents a risk for schizophrenia and seems to relate to pregnancy stress (McNeil *et al.* 2009) as well as socio-economic factors.

Season of birth

There is evidence of an increased risk for schizophrenia with birth during winter and spring time; i.e. from January to April, in the northern hemisphere when compared to summer and autumn births (Davies *et al.* 2003, Disanto *et al.* 2012). The mechanism may be due to perinatal viral infections with excess exposure during the winter time (Brown 2011a) and vitamin D deficiency during the winter time (McGrath *et al.* 2010).

2.4.2 Risk factors during infancy and childhood

Early indicators of schizophrenia

Lower cognitive and motor performance (Sørensen *et al.* 2010, Clarke *et al.* 2011, Dickson *et al.* 2012), social deficiency (Schiffman *et al.* 2004), lower IQ (Khandaker *et al.* 2011, Dickson *et al.* 2012), neurological soft signs (Walker *et al.* 1994) and later speech development (Jones & Rodgers 1994) in the childhood have been noticed to precede subsequent schizophrenia. Individuals with later schizophrenia have also an increased prevalence of major and minor physical anomalies, especially on the craniofacial area, which are indicative of an in utero developmental disruption (McGrath *et al.* 2002, Waddington *et al.* 2008). In

addition, social withdrawal, anxiety, depression, deviant behaviour, social maladjustment and general psychopathology in childhood increases the risk for schizophrenia (Tarbox & Pogue-Geile 2008, Welham *et al.* 2009, Rubio *et al.* 2012).

Urbanicity

The association between urbanicity and schizophrenia and other psychosis is well established (Vassos *et al.* 2012, Padhy *et al.* 2014), also when potential confounders (e.g. cannabis use, belonging to ethnic minority) have been taken into account (van Os *et al.* 2010). The risk has been shown to elevate with rising levels of urbanicity and time lived in the urban area (Pedersen & Mortensen 2001). Explanations for this association include selective migration, exposure to infections and pollutants, poor diet (e.g. vitamin D deficiency) (Pedersen & Mortensen 2001, Vassos *et al.* 2012), social fragmentation and deprivation (Zammit *et al.* 2010a). It has been suggested that urbanization exerts its influence during development in childhood and adolescence and not around the time of illness (Pedersen & Mortensen 2001).

Childhood adversities

Low socioeconomic status in childhood increases the risk for psychosis and there is two competing hypotheses explaining this association: social causation versus social drift (Brown 2011a) where in the first low socioeconomic status increases the risk for psychosis and in the latter low socioeconomic status is a result of the subsequent psychotic disorder. Factors associating with social adversities in childhood such as the low socioeconomic status of the parents, parental unemployment, single parent family, living in a rented apartment and receiving social welfare benefits, increase the risk for later schizophrenia and other psychosis (Wicks *et al.* 2005). The association persisted even after controlling for several confounders such as urbanicity, parental substance abuse, parental psychotic illness, migration and paternal age (Wicks *et al.* 2005) supporting the social causation hypothesis. Further support for this hypothesis was offered when it was found that low social class at birth increases the risk for schizophrenia (Corcoran *et al.* 2009). Authors have explained this association by social exclusion and also by social stress (Wicks *et al.* 2005).

Separation from the either one or both parents increases the risk for psychosis with paternal separation presenting higher risk than maternal separation (Paksarian

et al. 2015a). Also, physical, sexual and psychological abuse in childhood increases the risk for schizophrenia and other psychosis (Matheson *et al.* 2013a).

Infections in childhood

An association between viral central nervous system infection in childhood and risk for non-affective psychosis in adulthood has been established (Khandaker *et al.* 2012). Also severe bacterial infections in childhood have been found to increase the risk for psychosis (Blomström *et al.* 2014). The mechanisms involved include the direct interference of viruses in brain development and immune activation resulting in functional and structural brain abnormalities (Khandaker *et al.* 2012).

Migration

Several studies have established migration as risk factor for schizophrenia (McGrath *et al.* 2004, Cantor-Graae & Selten 2005, Saha *et al.* 2005, Fearon *et al.* 2006, Bourque *et al.* 2011). Second-generation migration represents even greater risk than first-generation migration and the risk has been found to be higher when immigration is from developing countries to developed countries (Cantor-Graae & Selten 2005, Bourque *et al.* 2011).

Selective migration, i.e. the subsequent psychotic disorder causes the individuals to move from their birth origins, has been linked to this association, but selective migration cannot solely explain it (Selten *et al.* 2002), since second-generation migration represents an even greater risk (Cantor-Graae & Selten 2005). There are several possible explanations for this association including viral infections, vitamin D deficiency, discrimination and social defeat (Cantor-Graae & Selten 2005, Bourque *et al.* 2011). Even residential mobility within home country may increase the risk for schizophrenia (Paksarian *et al.* 2015b).

2.4.3 Risk factors during adolescence and adulthood

Cannabis

Cannabis use in adolescence increases the risk for schizophrenia, other psychosis and psychotic symptoms (Arseneault *et al.* 2002, Zammit *et al.* 2002, Moore *et al.* 2007) and dose-response relationship has also been observed (Zammit *et al.* 2002).

In most of the studies, cannabis use has preceded the onset of illness and the association has persisted after controlling for several confounders and the effect size has been moderate but consistent, arguing for the causal effect (Wilkinson *et al.* 2014). Additionally, cannabis use has been shown to associate with an earlier onset of psychosis (Large *et al.* 2011). The link between cannabis use and psychosis is moderated by age at the time of cannabis use (Wilkinson *et al.* 2014), where earlier use is associated with a greater risk for psychosis (Arseneault *et al.* 2002). One proposed pathophysiologic mechanism is that cannabis could alter dopaminergic signalling in the brain (Morrison & Murray 2009) but the specific mechanism has still remained uncovered (Sami *et al.* 2015).

School performance

A large population-based study from Sweden revealed poor school performance in youth among those with subsequent psychosis even after controlling for several biological and psychosocial confounding factors (MacCabe *et al.* 2008). Authors argued this finding to be more likely to be a risk marker than causative risk (MacCabe *et al.* 2008).

Stressful life events

There is suggestive literature for unfavourable life events in adult life increasing the risk for psychosis (Beards *et al.* 2013). But the association and mechanisms behind it need further investigation.

2.4.4 Risk factors for other psychosis

Risk factors for other psychosis have not been studied as extensively as risk factors for schizophrenia (Laurens *et al.* 2015). Schizophrenia spectrum disorders, i.e. schizophreniform disorder, delusional disorder and schizoaffective disorder, have commonly been included within studies of schizophrenia. Some of the studies have focused on affective disorders without the distinction of psychotic forms of them.

The history of obstetric complications, such as abnormal presentation of the foetus (Bain *et al.* 2000), non-spontaneus delivery (Sacker *et al.* 1995) and uterine atony (Hultman *et al.* 1999) increase the risk for affective psychosis. Tuberculosis or meningitis, neurological soft signs in childhood (Leask *et al.* 2002) and history

of winter/spring births (Hultman *et al.* 1999) increase the risk for affective psychosis as well as childhood adversities including sexual, physical and emotional abuse (Matheson *et al.* 2013a, Duffy *et al.* 2015). Disturbances in eating and hysterical symptoms in childhood may precede the onset of affective psychosis (Cannon *et al.* 2001).

Prematurity (Laursen *et al.* 2007, Mathiasen *et al.* 2011, Nosarti *et al.* 2012), prenatal stress (Zucchi *et al.* 2013), maternal smoking during pregnancy (Talati *et al.* 2013), prolonged parental separation, neglect, illicit substance use, recurrent physical illness and adverse life events (Smith *et al.* 2012), advanced parental age (Menezes *et al.* 2010), urbanicity (Laursen *et al.* 2007), excellent school performance (MacCabe *et al.* 2010), problems in attention and behaviour in childhood, psychopathology in youth, (Carlson & Weintraub 1993) and depressiveness in adolescence (Reichart *et al.* 2005) increase the risk for bipolar disorder, but there are not many studies focusing on the risk factors for the psychotic form of it.

Advanced paternal age (Lehrer *et al.* 2015), maternal exposure to influenza during pregnancy (Canetta *et al.* 2014) and impairments in neuropsychological performing in childhood (Seidman *et al.* 2013) increase the risk for bipolar disorder with psychotic symptoms. Female gender, young age of a mother, advanced paternal age, being born in a provincial town and the loss of a mother from unnatural causes increase the risk for depression with psychotic symptoms (Østergaard *et al.* 2013).

2.4.5 Risk factors in the Northern Finland Birth Cohort 1966

Risk factors and developmental pathways to schizophrenia are extensively investigated also in the Northern Finland Birth Cohort (NFBC) 1966 (Jääskeläinen *et al.* 2015). These studies have indicated that birth complications (Jones *et al.* 1998), deviant intrauterine growth in either direction (Moilanen *et al.* 2010), as well as a mother's antenatal depressed mood, i.e. during pregnancy (Mäki *et al.* 2010), unwanted pregnancy (Myhrman *et al.* 1996), grand multiparity (Kemppainen *et al.* 2000), viral central nervous system infections in childhood (Koponen *et al.* 2004) and high social class among girls (Mäkikyrö *et al.* 1997) increase the risk for schizophrenia.

Also the association between delay in learning to stand and walk and schizophrenia has been found (Isohanni *et al.* 2001). Delayed motor development correlated with poorer school performance at the age of 16 years (Isohanni *et al.*

2004) and lower educational level at the age of 31 (Taanila *et al.* 2005) and with later cognitive functioning (Ridler *et al.* 2006).

Population attributable risks (PAR) have been calculated for some of the found risk factors by age 34 in the NFBC 1966 with the highest PARs for parental psychosis (11%), being in lower or customised school class (15%), delayed toilet training (19%), later achievement of standing (24%) and walking milestones (33%) (Isohanni *et al.* 2006).

2.5 Family history of psychosis

Family, twin and adoption studies suggest substantial genetic influences on the liability to schizophrenia spectrum disorders, bipolar disorder and depression with psychotic symptoms. Hereditability, i.e. the proportion of variance explained by genetic factors, is suggested to be 60–80% for schizophrenia (Cardno *et al.* 1999, Sullivan *et al.* 2003, Cardno & Owen 2014), 58% for bipolar disorder (Song *et al.* 2015) and 39% for depression with psychotic symptoms (Domschke 2013).

Genetic overlap between psychotic disorders has been established in several studies (Lichtenstein *et al.* 2009, Cross-Disorder Group of the Psychiatric Genomics Consortium 2013, Domschke 2013, Cardno & Owen 2014). A recent meta-analysis (Rasic *et al.* 2014) showed that parental schizophrenia increases the risk for offspring's bipolar disorder and parental bipolar disorder increases the risk for offspring's schizophrenia, proposing shared genetics underlying schizophrenia and bipolar disorder. Bipolar disorder or schizophrenia of the parents also increases the risk for the offspring's depression with psychotic symptoms (Buoli *et al.* 2013, Østergaard *et al.* 2013).

Family history of psychosis has largely been used as an indirect measure of genetic risk (Van Os *et al.* 2008). It is considered the most powerful risk factor for schizophrenia and other psychosis also (Tsuang *et al.* 2004, Cardno & Owen 2014, Rasic *et al.* 2014), with a recently shown Risk Ratio (RR) of 7.5 for schizophrenia (Rasic *et al.* 2014). Roughly 10% of people with family history of psychosis will develop psychosis themselves (Liu *et al.* 2015). People with family history of psychosis tend to have an earlier onset age (Suvisaari *et al.* 1998, Esterberg *et al.* 2010), more severe negative symptoms (Esterberg *et al.* 2010) and poorer occupational outcome (Käkelä *et al.* 2014) when compared to people without family history of psychosis.

Any psychiatric disorder of a first-degree relative increased the risk for schizophrenia in the Danish longitudinal register study (Mortensen *et al.* 2010). In the same study, the risk for schizophrenia was highest with both parents having schizophrenia RR 37.5 (95% CI 19.9-70.9), second highest with the mother having schizophrenia; RR 9.0 (6.9-11.6), third with a sibling having schizophrenia; RR 7.5 (6.1-9.4) and last with the father having schizophrenia RR 6.6 (4.8-9.1) (Mortensen *et al.* 2010).

The risk for schizophrenia rises from 2–4% from a second-degree relative to 10–15% for a first-degree relative (Schwab & Wildenauer 2013). The concordance rates, i.e. the probability that a second twin will develop a disorder if the first one has it, is for monozygotic twins 40–45% and 0–10% for dizygotic twins regarding schizophrenia and schizoaffective disorder (Cardno & Owen 2014). The high discordance rate enables the assumption that environmental factors play a substantial role in the aetiology also.

In addition to increased risk by genetic vulnerability, children with parental psychosis are more likely to be exposed to stress (Walder *et al.* 2014), inadequate prenatal care and unhealthy habits during pregnancy (e.g. smoking, poor nutrition and substance abuse) (Lin *et al.* 2009, Matevosyan *et al.* 2011) and obstetric complications (Matevosyan *et al.* 2011, Preti *et al.* 2012). Psychotic disorder of the parents may also impair parenting, parent's sensitivity towards child's needs and child's attachment to parent (Wan *et al.* 2007, Wan *et al.* 2008b).

Approximately 50–70% of the offspring of parents with schizophrenia manifest a range of observable difficulties including socio-emotional (Tarbox & Geile 2008, Liu *et al.* 2015), cognitive (Seidman *et al.* 2013, Bora *et al.* 2014), neuromotor (Jones & Rodgers 1994, Erlenmeyer-Kimling 2000), speech and language problems (Jones & Rodgers 1994) and problems in school performance (Jundong *et al.* 2012).

In the high-risk studies, people with family history of schizophrenia (high-risk group) and matched healthy controls are compared. According to these, subjects with family history of psychosis and later schizophrenia differ in respect to neuropsychological, brain morphological and functional, neurological and developmental variables from high-risk people who remain unaffected and from healthy controls (Mednick *et al.* 1971, Ragins *et al.* 1975, Marcus *et al.* 1981, Fish 1987, Sameroff *et al.* 1987, Erlenmeyer-Kimling *et al.* 2000, Lawrie *et al.* 2001a, b, Byrne *et al.* 2003a, Johnstone *et al.* 2005, Smieskova *et al.* 2013, Thermenos *et al*. 2013, Ganzola *et al.* 2014). Studies have revealed that among people with family history of psychosis the cognitive performance, particularly verbal learning,

memory, executive functions, speed processing and attention, is intermediate between healthy controls and people with psychosis (Valli *et al.* 2012, Bora *et al.* 2014).

2.5.1 Genetics

During the 20th century, genome-wide genetic linkage studies revealed a range of chromosomal regions associating with schizophrenia, and genetic association studies that focused on specific genes found a range of significant associations, which have unfortunately been difficult to replicate consistently. More recently, the focus has turned to genome-wide association studies (GWAS), as these have become technically possible. GWAS are geared to detect commonly occurring genetic variants; single-nucleotide polymorphisms (SNPs) and large chromosomal structural variants, e.g. deletions and insertions, particularly copy number variants (CNVs). SNPs occur commonly and confer individually weak increments on risk. CNVs are rarer than SNPs but have a larger effect on risk when they occur. (Sullivan *et al.* 2012, Cardno & Owen 2014). The effect of rare CNVs varies from Odds Ratio (OR) 2 to OR 60, whereas common SNPs contribute only for OR <1.1 to schizophrenia risk (Rees *et al.* 2014, Pocklington *et al.* 2015).

The largest multi-stage GWAS study of schizophrenia, with a sample size more than 36,000 people with schizophrenia and more than 113,000 controls have revealed 128 independent SNP associations and 108 independent loci involved in schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Several genes of schizophrenia are expressed in the brain and involved in glutamatergic neurotransmission and synaptic plasticity. Also enriched associations among genes expressed in tissues with immune functions have been found, e.g. B-lymphocyte lineages involved in acquired immunity, supporting the role of immune dysregulation in schizophrenia. (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

Studies have found 11 CNVs as risk factors for schizophrenia (Rees *et al. 2014*, Kirov *et al.* 2015) but there still might be more to be revealed (Pocklington *et al.* 2015). CNVs may be especially important in sporadic (i.e. not inherited from parents) schizophrenia, since higher frequency of de novo mutations have been associated with CNVs (Schwab & Wildenauer 2013). Some larger deletions have been known already, for example the rare 22q11.2 micro-deletion syndrome with 20–25% transition rate to schizophrenia (Bassett *et al.* 2005). The most recent study

with over 11,000 people with schizophrenia and over 16,000 controls found enriched CNVs among genes involved in GABAergic neurotransmission and glutamatergic signalling (Pocklington *et al.* 2015). Many of the detected CNVs in schizophrenia have also been found in other neurodevelopmental disorders such as autism and mental retardation (Schwab & Wildenauer 2013, Kirov *et al.* 2015). There is also evidence of converge between SNPs and CNVs (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

Molecular genetic studies have shown that 50% of genetic determinants of schizophrenia overlap with bipolar disorder (Lichtenstein *et al.* 2009) and depression with psychotic symptoms have shared genetics with bipolar disorder, schizoaffective disorder, schizophrenia and depression (Domschke 2013).

2.6 Gene-environment interaction

Two epidemiological findings propose a gene-environment interaction in schizophrenia: firstly, there is geographic, temporal and ethnic variation in the incidence of schizophrenia emphasizing the role of environmental factors in the aetiology. Secondly, there is marked variability in people's responses to these environmental risk factors verifying the role of genes in the aetiology of schizophrenia. (van Os *et al.* 2008).

Interaction occurs when a relation between at least two independent variables is modified by at least one other variable. For example, gene-environment interaction occurs when environmental influences on psychosis risk differ according to a person's genetic predispositions, or a person's genetic predispositions are expressed differently in different environments (Tsuang *et al.* 2004). Interactions can exist between two or more genes, genes and the environment, and between two or more environmental risk factors (Yung *et al.* 2007, van Os *et al.* 2008).

Genes and environmental factors can interact together synergistically, so that the effect of the putatively causal factor is enhanced by the other factor or antagonistically, when the effect of the putatively causal factor is diminished by the other factor (Last 2001). Synergism is often referred to the additive model of interactions in which the combined effect of two or more factors on outcome is the sum of the effects (Last 2001, van Os *et al.* 2008). Interactions can also act multiplicatively, where the effect on outcome is multiplied with the factors co-occurring together (Last 2001, Zammit *et al*. 2010b, c). For complex multifactorial disorders, like schizophrenia, it seems likely that the co-exposure to two risk factors

will show greater than additive relationship in the disease risk (Zammit *et al.* 2010b, c). The gene-environment interaction should be distinguished from the gene-environment correlation (rGE), where genetic factors influence the probability of environmental exposures (van Os *et al.* 2008, Uher 2014). In the rGE model, the environmental exposure is more common among those with genetic liability to the disorder but may not be causally related to the liability (Mittal *et al.* 2008).

The science of epigenetics aims to overtake some of the mechanisms that mediate the interaction between genes and the environment. Epigenetic mechanisms refer to reversible regulation of various genomic functions that occur independently of DNA sequence. These mechanisms are mediated principally through changes in DNA methylation and chromatin structure and result in an altered gene expression during development and adulthood. (Rutten & Mill 2009, Shorter & Miller 2015). The absence of clear genetic effects in schizophrenia and other psychosis supports the epigenetic mechanisms on the basis of the genetics rather than solely on DNA sequence basis (Rutten & Mill 2009). Single-nucleotide polymorphisms and copy number variants may contribute to the high heritability of the disorder, but environmental factors that lead to epigenetic modifications may either reduce or exacerbate the expression of molecular phenotypes associated with schizophrenia and related disorders (Shorter & Miller 2015).

As an example of genes moderating sensitivity towards environmental factors, it has been shown that people with val/val- homozygosity in the Catechol-O-Methyltransferase (COMT)-gene at codon 158 are especially sensitive to cannabis effect in the risk for psychosis, whereas val/met-individuals have an elevated but lower risk and met/met-individuals have the lowest risk (Caspi *et al.* 2005).

2.6.1 The interaction between family history of psychosis and environmental risk factors in respect of psychosis

Family history of psychosis has been shown to modify the risk for psychosis with several environmental factors, showing some evidence of gene-environment interaction (Tsuang *et al.* 2004, van Os *et al.* 2008). Table 3 presents some of the interaction studies where family history of psychosis has been used as an indirect measure of genetic vulnerability to psychosis.

Siblings of African-Caribbean probands have higher risk for psychosis than siblings of white probands indicating gene-environment interaction between genetic risk and migration (Hutschinson *et al.* 1996). Interaction between family

history of psychosis and prenatal upper urinary tract infection of a mother in the risk for psychosis has been revealed (Clarke *et al.* 2009), as well as between parental psychosis and a mother's antenatal depressed mood (Mäki *et al.* 2010), cannabis use (McGuire *et al.* 1995), low IQ (Kendler *et al.* 2015) and between maternal psychosis and unwantedness of the pregnancy (McNeil *et al.* 2009) in respect of schizophrenia spectrum disorders. Synergistic effects between genetic vulnerability and urbanicity (van Os *et al.* 2004), and traumatic brain injury (Malaspina *et al.* 2001) in schizophrenia risk has been shown.

In the Swedish adoption study, the history of psychosis in the biological parents and social disadvantages (e.g. single-parent family, unemployment, and living in a rented apartment) in the adoptive family had significant interaction in psychosis risk (Wicks *et al.* 2010). Also, interaction between the history of psychosis in the biological family and impairments in the rearing of the adoptive family in the risk for schizophrenia spectrum disorders was found in the Finnish adoption study (Tienari *et al.* 2004, Wahlberg *et al.* 2004).

Table 3. The review of literature of interaction studies where family history of psychosis has been used as an indirect measure of genetic vulnerability for psychosis.

Author (year)	Sample	Main results	Comment(s)
McGuire *et al.* (1995)	23 first-episode psychosis patients with a cannabis positive urine screen and 46 cannabis negative first-episode psychosis patients in UK.	Those with cannabis positive psychosis were 10-times more likely to have family history of psychosis than those with cannabis negative urine toxicology.	There might be interaction between genetic liability and cannabis use in psychosis risk. Very small study population.
Malaspina *et al.* (2001)	565 members of schizophrenia pedigrees in USA.	Synergistic effect between traumatic brain injury and genetic liability in schizophrenia risk.	Possible interaction between genetic liability and traumatic brain injury. No controls without family history of psychosis.
Tienari *et al.* (2004)	Finnish Adoption study of 186 adopted offspring with high genetic risk and 203 control adoptees.	Adoptees with high genetic risk were more sensitive to adverse vs. healthy rearing patterns in adoptive families than were adoptees at low genetic risk.	Interaction between genetic liability and adoptive-family rearing patterns in psychosis risk.
van Os *et al.* (2004)	Population-based Danish cohort of 1,020,063 individuals.	Synergistic effects with family history of psychosis and urbanicity in schizophrenia risk.	Additive model used instead of multiplicative model.
Wahlberg *et al.* (2004)	109 adoptees from Finnish Adoption Study.	Genetic liability and communication deviance of the adoptive parents predicted significantly psychotic disorders of the adoptees, and the interaction was significant.	Interaction between genetic liability and communication deviance in the adoption family in psychosis risk.
Clarke *et al.* (2009)	Finnish national registers were used to identify 9,596 individuals exposed to maternal pyelonephritis and 13,808 control siblings.	The effect of prenatal exposure to pyelonephritis was 5-times greater in those who had a family history of psychosis compared to those who did not. A synergistic effect of prenatal pyelonephritis and genetic liability in risk of schizophrenia was found.	Synergistic effect between genetic liability and maternal prenatal upper urinary tract infection in the risk of psychosis.

Author (year)	Sample	Main results	Comment(s)
McNeil *et al.* (2009)	Swedish prospective study of 75 high-risk (HR) and 91 control offspring.	The effect of unwanted pregnancy in the risk of schizophrenia spectrum disorders was limited to the HR group and occurred in interaction with genetic risk.	Interaction between maternal psychosis and unwantedness of the pregnancy in the risk of schizophrenia spectrum disorders.
Gonzáles-Pinto *et al.* (2010)	Spanish cross-sectional study of 97 individuals with first-episode psychosis (44 with family history of psychosis) and 96 healthy controls.	A significant protective effect of a positive family environment for persons with a family history of psychosis. This effect was not seen in people without a family history of psychosis.	Interaction between family history of psychosis and positive family environment in the risk of psychosis.
Mäki *et al.* (2010)	The Northern Finland Birth Cohort 1966 Study (n=10,658).	The risk of schizophrenia was highest among those with both; parental psychosis and the mother's antenatal depressed mood than either of them alone.	Possible interaction between parental psychosis and mother's antenatal depressed mood in the risk of schizophrenia.
Wicks *et al.* (2010)	Swedish Adoption Study of 13,163 adopted children.	Social adversities increased the risk of non-affective psychosis but the risk was greater in children with a genetic liability for psychosis.	Interaction between genetic liability and social disadvantages in childhood in the risk of non-affective psychosis.
Kendler *et al.* (2015)	Swedish national sample of 1,204,983 males.	A robust interaction was seen between a genetic liability for schizophrenia and low IQ in predicting schizophrenia risk.	Interaction between genes and IQ in the risk of schizophrenia.

2.7 Protective factors for psychosis

Protective factors can be defined as characteristics of the child, family, and wider environment that improve the likelihood of positive outcomes and diminish the negative effect of adversity on an outcome (Masten & Reed 2002). One possibility to study the protective factors for psychosis is to focus on those with the highest risk for psychosis, e.g. those with family history of psychosis, and analyse how those who remain unaffected differ from those who develop psychosis.

There are only few studies that have been studying the protective factors for psychotic disorders, although they are needed in order to find ways to prevent the onset of psychosis. Previously, the Finnish adoption study showed that healthy rearing patterns (Tienari *et al.* 2004) and clear communication in the family (Wahlberg *et al.* 2004) lower the risk of schizophrenia in adoptees with family history of psychosis. Similarly, Gonzáles-Pinto *et al.* (2010) found that positive family environment lowers the risk for psychosis in families with a history of psychosis. Physical activity of low-moderate intensity is found to be protective against psychotic symptoms (Tao *et al.* 2007). Breastfeeding (Sørensen *et al.* 2005) and good school performace (MacCabe *et al.* 2008) may be protective against subsequent schizophrenia, while belonging to a minority group with high socioeconomic status and high social capital may be protective, especially among males (Suvisaari *et al.* 2014). One study suggests the protective effect of advanced maternal age in bipolar disorder with psychotic symptoms (Brown *et al.* 2013). Another study showed urbanicity protecting against affective psychoses (Kelly *et al.* 2010). Some propositions of the favourable effect of prenatal vitamin D, iron and folate substitution in prevention of schizophrenia have been made but randomised controlled trials are needed to support these suggestions (McGrath *et al.* 2011). Also, choline supply during pregnancy is possibly protective against mental illnesses (Freedman & Ross 2015), but needs to be further studied.

2.8 Prevention of psychosis

Prevention can simply be defined as action designed to reduce the likelihood that something harmful will occur, or to minimize that harm if it occurs. In public health, prevention strategies are commonly divided into *primary, secondary and tertiary prevention*. Primary prevention aims to limit the incidence of disease and disability

in the population by eliminating or reducing causes, controlling exposure to risk, and promoting factors that are protective for health. Secondary prevention aims to reduce the progression of disease through early detection and early intervention. Tertiary prevention aims to improve functions by minimizing the impact of established disease, and to prevent or delay complications through effective management and rehabilitation. (National Public Health Partnership 2006).

Preventive strategies can also be divided into *universal prevention* targeted at the general population*, selective prevention* targeted at people with risk factors but without signs or symptoms of the disorder, *indicated prevention* targeted at high-risk individuals with minimal signs of the disorder and *early intervention* to those with already diagnosable disorders aiming to decrease the severity of the illness, and reduce secondary morbidity (Yung *et al*. 2007, Kirkbride & Jones 2011).

Universal prevention strategies might be more cost-effective and efficient when focusing on preventing specific exposures at a universal level rather than focusing on any specific disorder, since many of the risk factors are non-specific (Kirkbride & Jones 2011). Reducing exposure to many disadvantages may result in a benefit to the whole population, e.g. reducing prenatal and obstetric complications may have broad preventive value for many mental and also physical disorders (Kirkbride & Jones 2011).

Selective prevention strategies involve the identification of subpopulations at a raised risk for psychosis (Yung *et al.* 2007). Selective preventive strategies exist for families with history of psychosis by improving social support, maternal care, enhancing parenting skills, reducing the psychotic symptoms by treating the parents well. Family-centred care and cognitive-remediation therapy have also been offered to children with parental history of psychosis. (Liu *et al.* 2015).

Indicated prevention strategies require the reliable identification of individuals at clinical high risk, in order to provide the most adequate strategies to prevent their transition to psychosis (Yung *et al.* 2007). Within time, two sets of criteria have been used to define the clinical high risk (CHR) state (also called prodromal state, attenuated psychosis syndrome or at risk mental state): the ultra high risk (UHR) and the basic symptoms (BS) criteria (van der Gaag *et al.* 2013, Ruhrmann *et al.* 2014, Schultze-Lutter *et al.* 2015). The UHR state requires one or more of the following: attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, or genetic risk and a marked decline in psychosocial functioning. The BS state requires subjectively experienced disturbances of different domains of functioning including, e.g. perception, thinking process, language and attention that are distinct from classical psychotic symptoms. (van der Gaag *et al*. 2013,

Ruhrmann *et al.* 2014). The European Psychiatric Association (EPA) recommends that high genetic risk with functional deficits should be used as an indicator of increased risk for pre-CHR for psychosis rather than clinical indicator of CHR state (Schultze-Lutter *et al.* 2015).

The indicated prevention strategies have included low doses of antipsychotics, antidepressants, omega 3-fatty acids, cognitive-behavioural therapy (CBT), cognitive remediation therapy, multifamily psychoeducation and social skills training (Yung *et al.* 2007, van der Gaag *et al.* 2012, Stafford *et al.* 2013). EPA recommends psychological treatments, particularly CBT, as a first choice of treatment and if proven ineffective, then low doses of second-generation antipsychotics should be offered to adult CHR-patients (Schmidt *et al.* 2015). The Finnish JERI-project found promising results with multi-professional, family-oriented and stress-reducing intervention in improving overall functioning, quality of life and reducing prepsychotic symptoms among adolescents at high risk for psychosis (Granö *et al.* 2009).

The objectives of *early intervention strategies* are minimising the duration of untreated psychosis (DUP), promoting recovery and minimising secondary morbidity and mortality (Yung *et al.* 2007). Early detection programs have aimed at improving the knowledge of psychosis by promoting help-seeking and the self-identification of risk. Those programs have also included targeted campaigns towards general practitioners, social workers and school health nurses to try to shorten the DUP (Wright *et al.* 2006, Yung *et al.* 2007), since long DUP associates with a poor outcome and more severe symptoms (Penttilä *et al.* 2014). Early intervention strategies have included psychosocial treatments (e.g. CBT, psychoeducation) aside with antipsychotic medications (Yung *et al.* 2007).

2.9 Summary of the risk factors, protective factors and prevention of psychosis

The aetiological models of psychosis propose that a family history of psychosis sets up vulnerability towards the offspring's psychosis and therefore increases the baseline risk (Tsuang *et al.* 2004, van Os *et al.* 2008, Cardno & Owen 2014, Rasic *et al.* 2014). The risk for psychosis can be elevated by several risk factors occurring from the perinatal period to adulthood and can be lowered by protective factors. An individual can move towards health or psychosis depending on the effect of risk factors or protective factors and prevention actions (Salokangas *et al.* 2001, van Os

et al. 2008). Psychotic symptoms appear if the threshold of psychosis is met (Maynard *et al.* 2001). Individuals with a family history of psychosis (Suvisaari *et al.* 1998, Esterberg *et al.* 2010) or accumulating environmental risk factors (Stepaniak *et al.* 2014) seem to develop the illness earlier than those without. Figure 1 illustrates the model of psychosis.

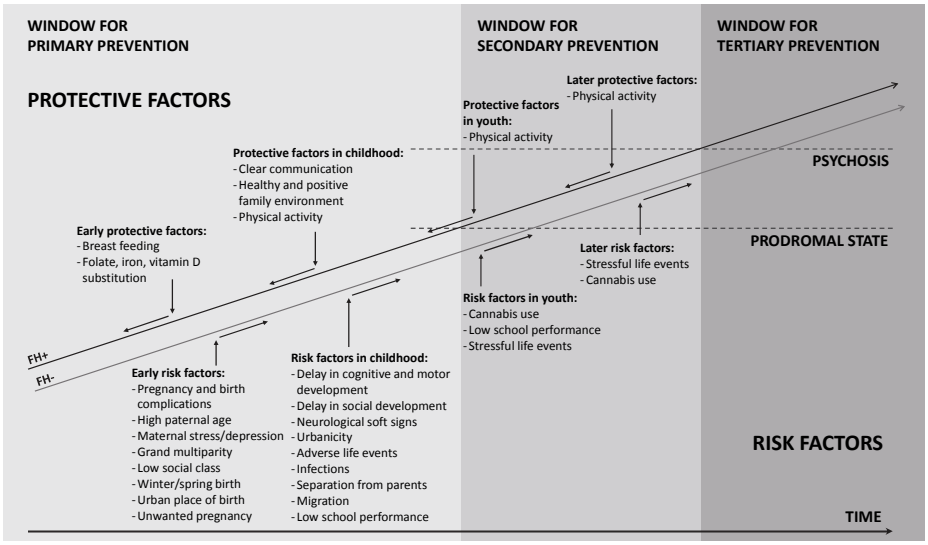

Fig. 1. An illustration of the model of risk and protective factors for psychosis and windows for the prevention of psychosis. FH+=family history of psychosis, FH-=no family history of psychosis.

3 Aims and hypotheses

The overarching aim of this thesis was to investigate whether risk factors for schizophrenia and other psychosis are different among individuals with and without parental psychosis.

3.1 Aims of the study

1. To study whether early risk factors, i.e. those related to pregnancy and birth, for schizophrenia and other psychosis are different among individuals with and without parental psychosis. In addition, the association between parental psychosis and early risk factors and also their interaction in respect of risk for schizophrenia and other psychosis was investigated.
2. To study whether the age of achievement of motor milestones associates differently with risk for schizophrenia and other psychosis among individuals with and without parental psychosis. In addition, the association between parental psychosis and the age of achievement of motor milestones and their interaction in respect of risk for schizophrenia and other psychosis was investigated.
3. To study the factors associated with unaffected status in the total study sample with special interest in those with parental psychosis.

3.2 Hypotheses of the study

1. The effects of early risk factors are different in the group with parental psychosis than among those without. There are interactions between parental psychosis and early risk factors in the risk for schizophrenia and other psychosis.
2. A delayed motor development increases the risk for schizophrenia and other psychosis differently in those with and without parental psychosis. There are interactions between parental psychosis and delayed motor milestones in the risk for schizophrenia and other psychosis.
3. Factors can be found to associate with unaffected status in the total sample and among those with parental psychosis. Those factors may be considered as protective factors.

4 Materials and methods

4.1 The Northern Finland Birth Cohort 1966

This study utilises data from the Northern Finland Birth Cohort 1966 (NFBC 1966), which is a prospective and unselected general-population based sample. The NFBC 1966 was founded by Professor Paula Rantakallio, who was interested in risk factors for low birth weight and perinatal death (Rantakallio 1969). The psychiatric sub-study of the NFBC 1966 was started in 1990 by Professor Matti Isohanni focusing on pre-and post-morbid development and the course of schizophrenia. The prospective nature of the study denotes that the collection of information on biological, socioeconomic and health conditions, living habits and family characteristics of the cohort members has been started since mid-pregnancy and the cohort members have been followed over time with most recent data being gathered in 2012.

The study population constitutes of 12,068 pregnant women in the provinces of Lapland and Oulu in Finland and their 12,058 live-born children with expected delivery dates during 1966. These births represent 96.3% of all births in this region. (Rantakallio 1969, Jääskeläinen *et al.* 2015). At the age of 16, there were 11,017 cohort members alive and living in Finland. Out of them, 84 denied permission to use their data leaving the number of cohort members at 10,933 suitable to study.

In the present study, all twins (n=258) are excluded, resulting in a number of 10,675 cohort members (50.8% boys, 49.2% girls). Further exclusion has been made for Studies II and III by excluding all individuals with an intellectual disability (ICD-8: 310–315, ICD-9: 317–319, ICD-10: F70–F79) (n=217) leaving the number of suitable cohort members at 10,458. In the Study I, the study population was 10,675 in the article, but results were re-analysed after the exclusion of individuals with intellectual disability for the summary part of this thesis, leaving the number of suitable cohort members at 10,458. In Figure 2, the number of cohort members after exclusions are presented.

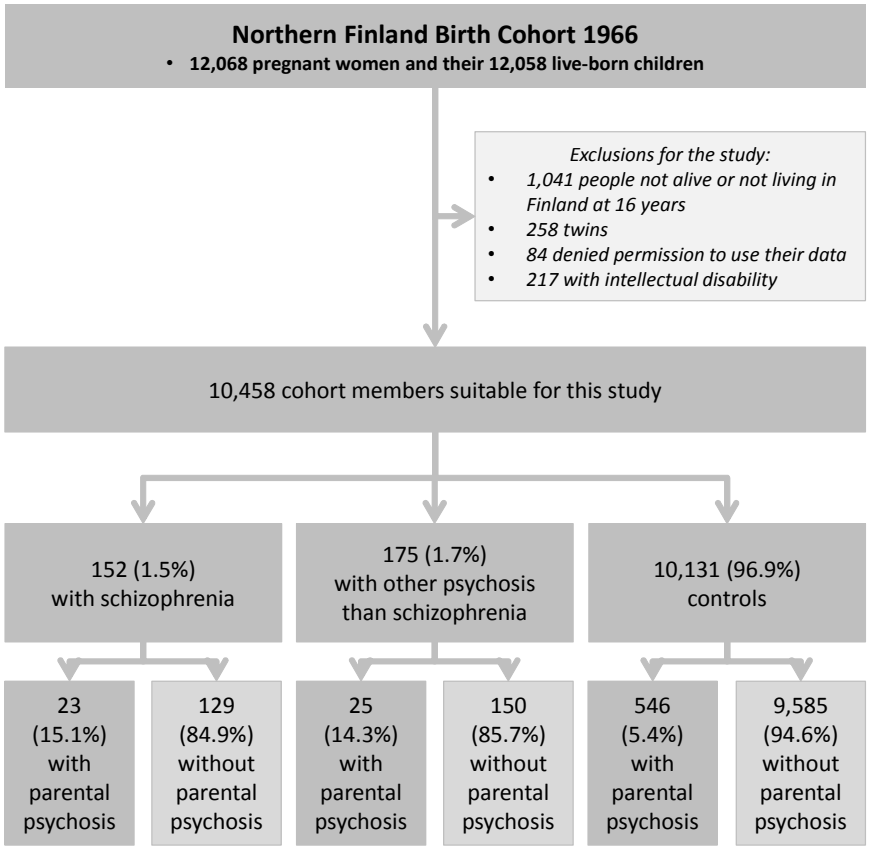

Fig. 2. Number of cohort members in different groups by diagnosis of psychosis and parental psychosis.

4.2 Diagnosis of parental psychosis

Parental psychosis was defined as present if a parent (mother and/or father) had any non-organic psychosis (ICD-8: 295–299; ICD-9: 295, 2961E, 2962E, 2963E, 2964E, 2967, 297–299; ICD-10: F20, F22–F29) at any time between years 1964–2005. The information on psychosis diagnosis was gathered from the nationwide Care Register for Health Care (formerly known as Finnish Hospital Discharge Register) and the disability pension register of the Finnish Centre for Pensions.

Care Register for Health Care (CRCH) includes all general and private hospitals and also wards in local health centres in Finland and contains the primary

ICD-diagnosis information, up to three secondary diagnoses and admission and discharge dates of the hospitals (Miettunen *et al.* 2011). The CRCH information has been available since 1972 and it includes also outpatient registers from special health care (since 1998).

The disability pension register of the Finnish Centre for Pensions includes diagnosis information on disability pension. It has been organized in year 1964 and parents appearing there are also included.

The parental information was available until 2012 but the limit was set to 2005, because possibly misdiagnosed organic psychoses (e.g. psychoses preceding dementia) were to be avoided or minimized. At the end of 2005, the parental age was 68.9 years on average (range 54.0-94.3). There were 355 (3.4%) cohort members with missing information on their father.

4.3 Diagnosis of schizophrenia and other psychosis of the cohort members

Several sources of data were used to define the diagnosis of schizophrenia and other psychosis (ICD-8: 295–299; ICD-9: 295, 2961E, 2962E, 2963E, 2964E, 2967, 297–299; ICD-10: F20, F22–F29 or DSM-III-R 295) of the cohort members:

- Care Register for Health Care (CRCH): inpatient data (1972–2012) and outpatient registers, including special health care (1998–2012) and primary health care (2011–2012)
- National registers of the Finnish Social Insurance Institute: sick days (1974–1999), disability pensions (1974–2000), reimbursable medications (1974–2005)
- Finnish Centre for Pensions: disability pension information (1974–2011)

The detected psychosis diagnoses (n=154, 47.1%) have been validated using the DSM-III-R criteria by the revision of hospital notes until 1997 (Isohanni *et al.* 2001, Moilanen *et al.* 2003). Later, two follow-up interviews at the age of 34 (1999–2001) (Lauronen *et al.* 2005) and at the age of 43 (2008–2011) have been conducted for a subsample to further verify the diagnoses and exclude organic psychoses. Schizophreniform disorder is included in schizophrenia in this study. Figure 3 illustrates the sources of diagnoses.

In the Study I, the psychosis information was available until 2010 at the time of preparing the article. Updated data on psychosis information until 2012 regarding the Study I has been added to summary part of the thesis.

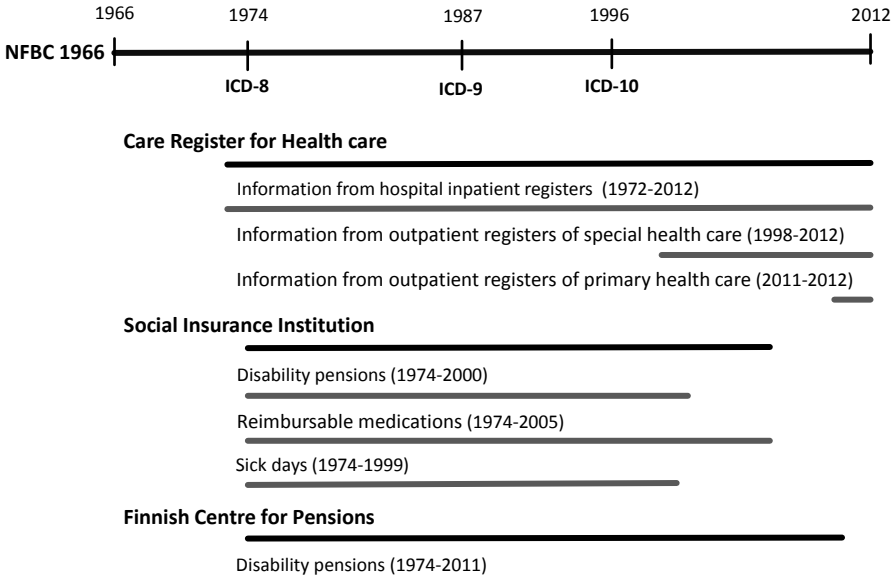

Fig. 3. Sources of information on schizophrenia and other psychosis in the NFBC 1966.

4.4 The information on cohort members

The data collection of all the variables used in Studies I–III is shown in Figure 4.

4.4.1 The information on pregnancy and delivery (I)

The data on socio-demographic characteristics of the mother and the family, and the information on pregnancy have been collected during the mother's visits to antenatal clinics where nurses interviewed the mothers using questionnaires. Mothers filled in the questionnaires on 24–28 weeks of gestation, but in some cases the questionnaire was filled in later on in pregnancy or after the delivery (10.1% of mothers).

The questionnaires (Q) contained information about the mother's health and habits and family characteristics. Information about the delivery and the new born was gathered from the mother's delivery reports (R) requested from delivery hospitals. Delivery reports included also information on maternal diabetes. The information on paternal age was collected from antenatal clinic questionnaires and

Finnish population registers. The studied variables are listed in Table 4. The variables have been divided into biological and psychosocial.

Table 4. Analysed potential risk factors for schizophrenia and other psychosis, and their sources (Study I, modified Table 1).

Risk factors	Description	Reference (source)
Biological risk factors		
Birth weight	Low (<2,500 g) vs. intermediate (2,500–4,500 g) vs. high (>4,500 g)	Moilanen *et al.* (2010) (R)
Birth length	Low (≤46 cm) vs. intermediate (47–53 cm) vs. high (≥54 cm)	Moilanen *et al.* (2010) (R)
Gestational age	<37 weeks (prematurity) vs. ≥37 weeks	Jones *et al.* (1998) (R)
Ratio: birth weight / gestational age	Low (>2 SD below the mean) vs. intermediate (within 2 SD below and above the mean) vs. high (>2 SD above the mean)	Moilanen *et al.* (2010) (R)
Mother's smoking after two months of pregnancy	Yes vs. no (including those who stopped smoking before 2 months of pregnancy)	Jones *et al.* (1998) (Q)
Paternal age at time of birth	Low (<25 years) vs. intermediate (25–40 years) vs. high (>40 years)	Miller *et al.* (2011b) (Q)
Maternal age at time of birth	Low (<20 years) vs. intermediate (20–35 years) vs. high (>35 years)	Miller *et al.* (2011b) (R)
Psychosocial risk factors		
Mother's antenatal depressed mood	Depressed or very depressed vs. not depressed	Mäki *et al.* (2010) (Q)
Wantedness of the child	Child being wanted at the time of pregnancy or later vs. child being unwanted	Myhrman *et al.* (1996) (Q)
Place of residence	Urban (Kajaani, Kemi, Oulu, Raahe, Rovaniemi, Tornio) vs. rural (other than before mentioned)	Isohanni *et al.* (2001) (Q)
Family type	Single-parent family vs. two-parent family	Mäkikyrö *et al.* (1997) (Q)
Father's social class at birth (determined from father's occupation and its prestige)	Unskilled workers (class IV) vs. others (class I=the highest prestige, usually required academic education, II= professional with shorter education than in class I, III=skilled workers, V=farmers)	Mäkikyrö *et al.* (1997) (Q)
Mother's education	Low (0–4 years) vs. intermediate (5–8 years) vs. high (≥9 years)	– (Q)
Grand multiparity	yes (mother has ≥ 6 earlier deliveries) vs. no	Kemppainen *et al.* (2000) (Q)

Q=questionnaire filled in during antenatal clinic visits, R= information on delivery records from delivery hospitals, SD=standard deviation.

4.4.2 The information on offspring's motor development (II)

The data on motor, neurological, social and lingual development of the children was collected during monthly visits to the Finnish child welfare clinics by nurses and doctors interviewing the parents and observing the children during infancy and early childhood (Pillas *et al.* 2014). This is normal procedure in Finnish public health care and was not organized particularly for research purposes. The mean number of contacts with child welfare clinics during the first year of life was 10 (Isohanni *et al.* 2001). Before 2007, information on motor milestones in the NFBC 1966 was a mixture of welfare card data on only walking and standing and parental responses to a questionnaire gathered at one year of age (Rantakallio *et al.* 1985, Isohanni *et al.* 2001, 2004). The welfare card information was obtained from 7,003 (67.0%) and one year questionnaire data from 8,876 (84.9%) cohort members. The previous incomplete milestone information was now merged with the completed welfare card data on all of the motor milestones so that the new information was taken into account in cases where the same cohort member had both; new and older information on milestone attainment. All of the children with parental psychosis and later schizophrenia were reared at home in the first year of life.

In the Study II, only the age of achievement of motor milestones (in months) was investigated as motor skills have been commonly associated with schizophrenia risk (Jones & Rodgers 1994, Sørensen *et al.* 2010, Clarke *et al.* 2011) and as this data in NFBC 1966 is more complete and detailed than that of other milestones (Isohanni *et al.* 2001, 2004).

The following motor milestones were examined: *being able to hold the head up, to grab an object, to turn from back to tummy, to sit without support, to touch the thumb with the index finger, to stand up, to stand without support and to walk without support.* The achievement times of each milestone, in months, were recorded on a separate welfare card in child welfare clinics. An illustration of the welfare card can be found from Appendix 1.

4.4.3 The information on variables in childhood and adolescence (III)

A postal questionnaire survey considering cohort member's family characteristics, hobbies, health and habits was sent to all children alive at 14 years of age and with a known postal address (Rantakallio 1988). The information of the mortality and addresses was gathered from the National Population Centre of Finland and Central

Statistical Office of Finland. If these authorities did not have the address information, it was obtained from church register offices.

The questionnaire was first sent to cohort members and if the child did not respond, the questionnaire was sent to a parent. If neither of them responded, the questionnaire was sent to regional school offices and school health nurses (Rantakallio *et al.* 1983). The postal questionnaire data was obtained from 9,903 (94.7%) cohort members including 287 parental responses and 220 responses from school health nurses (Rantakallio *et al.* 1983). Variables that were taken into account (in parenthesis is the source of information if other than 14-year postal questionnaire):

Variables considering pregnancy, birth and the first year of life

- Mother's antenatal depression (antenatal clinic data)
- Wantedness of pregnancy (antenatal clinic data)
- Grand multiparity (antenatal clinic data)
- Body Mass Index (BMI) of the mother in 1966 (antenatal clinic data)
- Breastfeeding (child welfare card data)

Variables considering family and childhood

- Working of the parents in 1980 (mother and father separately)
- Social class in 1980 (from the data on father's work)
- Moving hometown between 1966–1982 (from the Finnish population register)
- Family type 1966–1980 (from the antenatal clinic data and postal questionnaire, two-parent family if having the same two parents all the time)
- Parental somatic illness between 1966–1982 (mother and father separately) (from Care register for Health Care)

Variables considering health and habits at the age of 14

- Alcohol use
- Smoking
- BMI of the cohort member

Variables considering school performance

- School level at the age of 14 (postal questionnaire data and data from the National Board of Education for those who did not respond to the questionnaire)
- The following variables at the age of 16: grade of physical education, mean grade of non-theoretical school subjects (physical education, handicrafts, art, music) and mean grade of theoretical school subjects (history, biology, chemistry, physics, mathematics, geography, civics, religion, first foreign language, native language) (from the Finnish national application system for upper secondary education register)

Variables considering physical activity at the age of 14

- The frequency of sport hobbies
- Type of a sport hobby

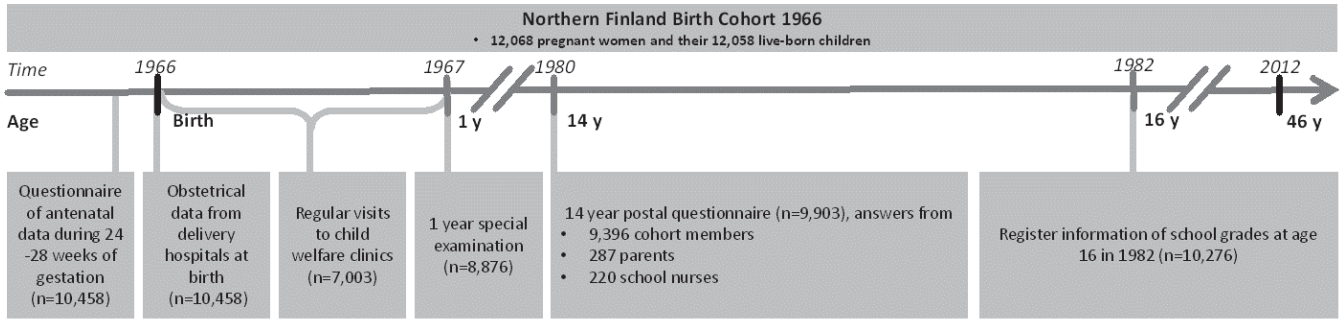

Fig. 4. The data collection within time in the NFBC 1966.

4.5 The amount of missing data

In Study I, antenatal and obstetrical data was gathered from 10,458 (100%) mothers. The amount of missing data on separate variables varied from 0% to 3.9% with the highest missing information concerning the mother's smoking from the antenatal clinic questionnaire. Among those with parental psychosis, missing data on the mother's smoking was 4.9% and among those without parental psychosis 3.9% (p=0.22). The amount of missing data on the mother's smoking information was 4.6% in the subsequent schizophrenia group and 3.9% without schizophrenia (p=0.53). Therefore, the amount of the highest missing data was not dependent on parental psychosis or subsequent schizophrenia.

In Study II, a total of 1,020 (9.8%) out of the 10,458 cohort members missed the information on motor development. Among those with parental psychosis, the missing milestone information (information on any of the milestones available) was 10.8% and among those without parental psychosis 9.7% (p=0.39). The amount of missing milestone information was 12.2% in the subsequent schizophrenia group and 9.7% without schizophrenia (p=0.13). Therefore, the amount of missing information on motor milestones was not dependent on parental psychosis or subsequent schizophrenia.

The amount of missing data regarding the separate milestone variables varied from 18.8% to 48.0%, except the variable "touching the thumb with the index finger" with missing data of 67.4%. The amount of missing data for the variable "touching the thumb with the index finger" was 69.4% in the parental psychosis group and 67.3% without parental psychosis (p=0.30). The amount of missing data regarding the variable "touching the thumb with the index finger" was 67.1% in the subsequent schizophrenia group and 67.4% without subsequent schizophrenia (p=0.93). Therefore, the amount of missing data was not dependent on parental psychosis or subsequent schizophrenia. The more complete data regarding variables "standing without support" and "walking with and without support" resulted from the combination of the one year questionnaire data with the new welfare card data.

In Study III, a total of 550 (5.3%) cohort members did not respond to the 14-year postal questionnaire. The amount of missing information was 5.9% in those with parental psychosis and 5.3% in those without parental psychosis (p=0.51), and 11.6% in those with later psychosis and 5.1% in those who remained unaffected

($p<0.001$). Therefore, the amount of missing data on postal questionnaire was not dependent on parental psychosis but was higher among those who developed psychosis later.

The amount of missing data regarding separate variables from the postal questionnaire varied from 5.3% to 12.4% with the highest missing information concerning the variable "father working outside home at 1980". The amount of missing data on father's working was 14.1% in the parental psychosis group and 12.3% in those without parental psychosis ($p=0.19$), and 19.0% among those who later developed psychosis and 12.2% among those who remained unaffected ($p<0.001$). Regarding all the variables used in the Study III, the variable "breastfeeding" missed information of 51.1% but it was obtained from the child clinic's welfare card data and not from postal questionnaire data. The amount of missing breastfeeding information did not differ statistically significantly between those with parental psychosis 51.5% and those without parental psychosis 51.0% ($p=0.22$) but differed between those with subsequent psychosis 59.3% and without subsequent psychosis 50.8% ($p=0.002$). Therefore, the amount of the highest missing data on father's work and breastfeeding was higher among those who developed psychosis subsequently.

4.6 Statistical analyses

In descriptive analyses, Pearson's chi square test was used to compare those with and without parental psychosis in all of the original studies when testing categorical variables. Also, Fisher's exact test was used whenever appropriate. Student's tests were used in case of normally distributed numerical variables, e.g. ages of reaching motor milestones. Cox regression analysis was used to test the association between parental psychosis and a specific risk factor in respect of schizophrenia and other psychosis and also their interaction in multiplicative model (parental psychosis × risk factor).

All of the results are presented as p-values, Hazard Ratios (HR) and their 95% confidence intervals (95% CI). The level of statistical significance was set to $p<0.05$. Cox regression analysis was the most suitable for this study as the study design is prospective and the effect of different factors on schizophrenia risk upon time was investigated. This technique took into account the time of migration and death as censoring points in analyses (Collet *et al.* 2003). The sample included 260 (2.5%) emigrants and 317 (3.0%) deaths (information from the Population Register

Centre until 2011). Statistical analyses were run using SPSS 17, 19–21, PASW 18, and Mplus 7.

4.6.1 Study I

Potential early risk factors for schizophrenia and other psychosis were studied separately in groups with and without parental psychosis, and the interaction between parental psychosis and risk factors was investigated using Cox regression analysis. Statistically significant biological risk factors were then combined into a composite variable "Any biological risk factor" and the same procedure was used for psychosocial risk factors to obtain "Any psychosocial risk factor". These composite variables took into account individuals having one or more statistically significant biological risk factors in case of "any biological risk factor" and significant psychosocial risk factors in case of "any psychosocial risk factor". The composite variables and their association to parental psychosis in respect of schizophrenia and other psychosis, in addition to their interactions, were then examined. The results were adjusted only for sex. Additional adjustment was made for maternal BMI assessed in the second trimester of pregnancy when studying birth weight, length and birth weight in relation to gestation age. The occurrence of maternal diabetes was also checked among mothers with psychosis.

4.6.2 Study II

The association between motor development and schizophrenia and other psychosis were studied separately in groups with and without parental psychosis, and the interaction between parental psychosis and the time (in months) of motor milestone achievement was investigated using Cox regression analysis. The results were reported for a one month delay in reaching each motor milestone. The covariates included sex, perinatal risk, antenatal maternal depression, family type and father's social class at the time of birth. Perinatal risk was a combined factor including any of the following: low gestational age (<37 weeks), low birth weight (≤2,500g) and perinatal brain damage (Jones *et al.* 1998). Antenatal maternal depression (depressed/very depressed vs no depression) (Mäki *et al.* 2010), family type (single-parent family vs two-parent family) (Mäkikyrö *et al.* 1997) and father's social class (unskilled workers vs others) (Mäkikyrö *et al.* 1997) were used as two-category variables.

After investigating every milestone variable separately, the motor development was scrutinized as a whole in respect of schizophrenia using a principal component analysis with one component model. The one principal component model explained 41.4% of the variation in the motor milestones, eigenvalue was 3.3, and communalities of the milestones varied between 0.34-0.76. The difference of principal component scores that described the overall motor development, in groups with and without parental psychosis and among those with and without subsequent schizophrenia, was tested with an analysis of the variance (ANOVA).

4.6.3 Study III

The difference in the prevalence of potential protective factors was tested using Pearson's chi square test (or Fisher's exact test) separately between (Fig. 5):

1. affected and unaffected individuals in the cohort
2. affected and unaffected individuals in parental psychosis group

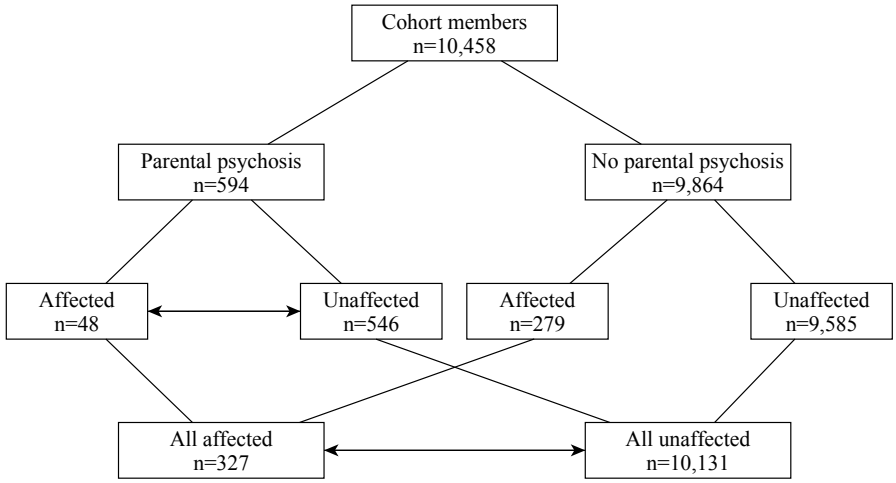

Fig. 5. An illustration of the performed pairwise comparisons (double-headed arrows). Affected = individual with later psychosis. Unaffected = individual remaining non-psychotic. (Study III, modified Figure 1).

Latent class analysis (LCA) was used to classify cohort members with parental psychosis by predictor variables. Only individuals with parental psychosis were included since they were of main interest. For LCA, one variable of interest was chosen from each predictor category and including too similar variables were tried to avoid: theoretical school performance from the school performance category, having a sports hobby from the category of physical activity, family type from the category relating to family and childhood, wantedness of the pregnancy and grand multiparity from the pregnancy and birth category and alcohol use from the health and habits category. Additionally, variables that had a statistically significant association with unaffected status among those with parental psychosis were chosen, i.e. mother working outside the home or studying and the mother's antenatal mood. Mplus 7 was used for LCA.

5 Ethical considerations and personal involvement

5.1 Ethical considerations

The permission to gather data for the NFBC 1966 was obtained from the Ministry of Social Welfare and Health Affairs in 1994. The Ethical Committee of the Northern Ostrobothnia Hospital district has approved the study and keeps it under review. Data protection has been scrutinised by the Privacy Protection Agency and by the principles from the Ministry of Health and Social Affairs. Written informed consent was obtained from every participant of the follow-up studies. All cohort members have the right to refuse the use of their data at any time and those who have denied permission to use their data, have been excluded from the study. Cohort members have been assigned an ID-number and their identities have not been revealed. The study design of this doctoral thesis was approved by the Postgraduate Research Committee of the Faculty of Medicine at the University of Oulu on 27th of October 2009.

5.2 Personal involvement

The author of this thesis has participated in the NFBC 1966 study as a researcher since 2008. Due to the longitudinal nature of the study, the author has not participated in collection of the data used in this dissertation study. The author has planned this doctoral thesis with her supervisors Professor Jouko Miettunen and Docent Erika Jääskeläinen. The author has participated in designing of all the original studies, selecting statistical methods, analysing the data and reporting the results. The author has made all of the statistical analyses of all of the studies and unpublished analyses in this thesis in consultation with a professional statistician. The author has conducted all literature searches and has written the first and final versions of all studies. In the Study II, medical student Anna Marttila helped with literature searches and wrote the first version of "Introduction"-chapter and started preparing the supplementary table of literature in the Study II as her advanced special studies in the medical school. The author has been the corresponding author in all of the studies. The author has coordinated submission, revision and resubmission processes for all of the studies.

6 Results

6.1 Demographics of the individuals with psychosis

Altogether, 327 (3.1%) individuals had psychosis in the NFBC 1966 until the end of 2012. Out of them, 152 (46.5%) had schizophrenia and 175 (53.5%) other psychosis. The distribution of diagnoses and other demographic information are presented in Table 5. Males developed schizophrenia and other psychosis more often than females, but the onset age of schizophrenia was surprisingly earlier among females (mean 26.1, min–max 16.9–38.8) than males (mean 27.6, 15.4–46.3). The onset age of other psychosis was later than in schizophrenia and was earlier among males (mean 36.6, 18.2–46.4) than among females (mean 38.1, 22.0–46.9).

6.2 The effect of parental psychosis in offspring

In total, 594 (5.7%) individuals had at least one parent with psychosis. Of them, 349 (58.7%) had a mother with psychosis, 257 (43.3%) a father with psychosis and 12 (2.0%) had both parents with psychosis. In the parental psychosis group, 48 (8.1%) suffered themselves from psychosis (23; 3.9% from schizophrenia) and out of the non-psychotic cohort members, 546 (5.4%) had parent(s) with psychosis.

The onset age of schizophrenia was earlier among those with parental psychosis (mean 25.8, min–max 15.4–46.3) than among those without it (mean 27.2, 16.2–39.1) but the difference was not statistically significant (p=0.41). The onset age of other psychosis was earlier also among those with parental psychosis (mean 36.7, 22.0–45.7) than among those without it (37.5, 18.2–46.9) (p=0.56).

Parental psychosis increased the risk for schizophrenia with HR 3.14 (95% confidence interval; CI 2.01–4.89) and the risk for any psychosis with HR 2.90 (1.90–4.43) and when adjusted for sex.

Table 5. Demographics of the individuals with schizophrenia, other psychosis and any psychosis.

	Schizophrenia (n=152)	Other psychosis (n=175)	Any psychosis (n=327)
Sex			
Male	93 (61.2%)	83 (47.4%)	176 (53.8%)
Female	59 (38.8%)	92 (52.6%)	151 (46.2%)
Parental psychosis			
No	129 (84.9%)	150 (85.7%)	279 (85.3%)
Yes	23 (15.1%)	25 (14.3%)	48 (14.7%)
Onset age (years)			
mean (min–max)	27.0 (15.4–46.3)	37.4 (18.2–46.9)	32.6 (15.4–46.9)
Diagnosis			
Schizophrenia	152 (100.0%)	-	152 (46.5%)
Delusional disorder	-	26 (14.9%) (one with both; delusional disorder and schizoaffective disorder)	26 (8.0%) (one with both; delusional disorder and schizoaffective disorder)
Schizoaffective disorder	-	19 (10.9%) (one with both; delusional disorder and schizoaffective disorder)	19 (5.8%) (one with both; delusional disorder and schizoaffective disorder)
Bipolar disorder with psychotic symptoms	-	23 (13.1%)	23 (7.0%)
Depression with psychotic symptoms	-	58 (33.1%)	58 (17.7%)
Brief psychotic disorder / acute and transient psychosis	-	17 (9.7%)	17 (5.2%)
Other psychosis	-	33 (18.9%)	33 (10.1%)

Min = minimum, max = maximum

6.3 Parental psychosis and risk factors during pregnancy and birth for schizophrenia and other psychosis (I)

6.3.1 The association between parental psychosis and risk factors during pregnancy and birth

Cohort members with parental psychosis had more often a mother with an antenatal depressed mood, were more often unwanted children at the time of pregnancy and

had more often low social class. Additionally, regarding other psychosis, those with parental psychosis lived more often in rural areas at birth (Table 6).

6.3.2 The association between parental psychosis and risk factors during pregnancy and birth in the risk for schizophrenia and other psychosis

In the group with parental psychosis high birth weight (HR 10.47; 95% CI 3.56–30.82) and length (HR 3.21; 1.09–9.58), high birth weight in relation to gestational age (HR 2.68; 1.05–6.84), advanced maternal age (HR 2.81; 1.23–6.43) and grand multiparity (HR 2.68; 1.05–6.79) increased the risk for schizophrenia. None of the mothers with psychosis had diabetes, which has been found to associate with the large size of a new born. Additional analysis was made for variables regarding the newborn's size in the parental psychosis group by adjusting for the mother's BMI. High birth weight remained significant (HR 8.64; 2.31–32.33) as well as high birth length (HR 3.80; 1.25–11.57), but high birth weight in relation to gestational age lost its statistical significance (HR 2.29; 0.79–6.58).

In the group without parental psychosis, low birth length (HR 2.25; 1.18–4.31), and maternal high level of education (HR 1.61; 1.12–2.31) increased the risk for schizophrenia.

The presence of "any biological risk factor" increased the risk for schizophrenia significantly only among those with parental psychosis (HR 3.21; 1.39–7.41), whereas the risk without parental psychosis was non-significant (HR 1.00; 0.69–1.45). Corresponding Hazard Ratios for the presence of "any psychosocial risk factor" were HR 2.47 (0.98–6.28) and HR 1.56 (1.09–2.23), respectively.

Regarding the risk for other psychosis, in the group with parental psychosis, maternal smoking increased the risk (HR 3.40; 1.41–8.22) and in the group without parental psychosis, low birth weight (HR 2.46; 1.25–4.83) increased the risk. The presence of "any biological risk factor" increased the risk for other psychosis significantly only among those with parental psychosis (HR 2.38; 1.03–5.52), whereas the risk without parental psychosis was non-significant (HR 1.38; 0.93–2.05). Results are presented in Tables 7 and 8. Figure 6 shows the effect of parental psychosis with any of the associated biological or psychosocial risk factors.

6.3.3 Interaction between parental psychosis and risk factors during pregnancy and birth in the risk for schizophrenia and other psychosis

There was a statistically significant interaction between parental psychosis and birth measurements: high birth weight (HR 8.34; 2.05–33.89) and high birth weight in relation to gestational age (HR 3.14; 1.04–9.46). The interaction between parental psychosis and high birth weight remained significant (HR 7.53; 1.64–34.64) when the mother's BMI was added as a covariate but interaction between parental psychosis and birth weight in relation to gestational age lost statistical significance (HR 2.70; 0.83–8.76) and the interaction between parental psychosis and high birth length became statistically significant (HR 3.88; 1.02–14.78). There was also significant interaction between parental psychosis and maternal advanced age (HR 2.63; 1.03–6.75) and maternal antenatal depressed mood (HR 2.83; 1.01–7.95). The interaction between parental psychosis and any biological risk was statistically significant (HR 3.25; 1.30–8.13), whereas between any psychosocial risk and parental psychosis was not.

There was one statistically significant interaction between parental psychosis and a mother’s smoking during pregnancy (HR 2.76; 1.04–7.37) in the risk for other psychosis (Tables 7 and 8).

Table 6. The association between parental psychosis and risk factors during pregnancy and birth (Study I, modified Table 2).

Variable	Schizophrenia					Other psychosis				
	Parental psychosis		No parental psychosis		p-value[1]	Parental psychosis		No parental psychosis		p-value[1]
	n	%	n	%		n	%	n	%	
Birth weight	569[2]		9,701[2]			571[2]		9,722[2]		
< 2,500g	17	3.0	243	2.5	0.49	17	3.0	246	2.5	0.54
2,500–4,500g	539	94.7	9,180	94.6	Ref.	544	95.3	9,199	94.6	Ref.
>4,500g	13	2.3	278	2.9	0.43	10	1.8	277	2.8	0.13
Birth length	567[2]		9,641[2]			569[2]		9,661[2]		
≤ 46 cm	29	5.1	372	3.9	0.13	30	5.3	372	3.9	0.09
47–53 cm	504	88.9	8,734	90.6	Ref.	509	89.5	8,755	90.6	Ref.
≥ 54 cm	34	6.0	535	5.5	0.60	30	5.3	534	5.5	0.86
Gestational age	543[2]		9,405[2]			544[2]		9,421[2]		
<37 weeks	25	4.6	409	4.3	0.78	24	4.4	411	4.4	0.96
≥ 37 weeks	518	95.4	8,996	95.7	Ref.	520	95.6	9,010	95.6	Ref.
Birth weight /gestational age	540[2]		9,362[2]			541[2]		9,379[2]		
>2 SD below mean	65	12	993	10.6	0.30	65	6.1	1,001	10.7	0.36
within the interval of 2 SD below and above mean	415	76.9	7,319	78.2	Ref.	420	77.6	7,327	78.1	Ref.
>2 SD above mean	60	11.1	1,050	11.2	0.96	56	10.4	1,051	11.2	0.62
Mother smoking during pregnancy	544[2]		9,338[2]			544[2]		9,356[2]		
Yes	81	14.9	1,387	14.9	0.98	86	15.8	1,395	14.9	0.57
No	463	85.1	7,951	85.1	Ref.	458	84.2	7,961	85.1	Ref.

Variable	Schizophrenia					Other psychosis				
	Parental psychosis		No parental psychosis		p-value[1]	Parental psychosis		No parental psychosis		p-value[1]
	n	%	n	%		n	%	n	%	
Paternal age at the time of birth	556[2]		9,368[2]			555[2]		9,391[2]		
< 25 years	111	20.0	2,078	22.2	0.30	113	20.4	2,082	22.2	0.41
25–40 years	369	66.4	6,160	65.8	Ref.	367	66.1	6,173	65.7	Ref.
>40 years	76	13.7	1,130	12.1	0.37	75	13.5	1,136	12.1	0.42
Maternal age at the time of birth	569[2]		9,691[2]			571[2]		9,712[2]		
< 20 years	51	9.0	926	9.6	0.78	53	9.3	931	9.6	0.90
20–35 years	410	72.1	7,140	73.7	Ref.	415	72.7	7,159	73.7	Ref.
>35 years	108	19.0	1,625	16.8	0.19	103	18.0	1,622	16.7	0.42
Mother's antenatal depressed mood	560[2]		9,468[2]			561[2]		9,489[2]		
No	447	79.8	8,222	86.8	Ref.	449	80.0	8,233	86.8	Ref.
Yes	113	20.2	1,246	13.2	**<0.001**	112	20.0	1,256	13.2	**<0.001**
Wantedness of the child	561[2]		9,460[2]			561[2]		9,482[2]		
Wanted at the time of pregnancy or later	476	84.8	8,387	88.7	Ref.	478	85.2	8,409	88.7	Ref.
Unwanted	85	15.2	1,073	11.3	**0.006**	83	14.8	1,073	11.3	**0.01**
Place of residence	569[2]		9,702[2]			571[2]		9,723[2]		
Urban	169	29.7	3,267	33.7	Ref.	167	29.2	3,273	33.7	Ref.
Rural	400	70.3	6,435	66.3	0.05	404	70.8	6,450	66.3	**0.03**
Family type	569[2]		9,714[2]			571[2]		9,735[2]		
One-parent	16	2.8	336	3.5	0.41	17	3.0	337	3.5	0.54
Two-parent	553	97.2	9,378	96.5	Ref.	554	97.0	9,398	96.5	Ref.
Father's social class at birth	567[2]		9,668[2]			569[2]		9,690[2]		
Low	165	29.1	2,165	22.4	**<0.001**	169	29.7	2,174	22.4	**<0.001**
Other	402	70.9	7,503	77.6	Ref.	400	70.3	7,516	77.6	Ref.

Variable	Schizophrenia					Other psychosis				
	Parental psychosis		No parental psychosis		p-value[1]	Parental psychosis		No parental psychosis		p-value[1]
	n	%	n	%		n	%	n	%	
Mother's education	560[2]		9,514[2]			561[2]		9,535[2]		
0–4 years	52	9.3	850	8.9	0.83	54	9.6	853	8.9	0.62
5–8 years	317	56.6	5,361	56.3	Ref.	317	56.5	5,398	56.6	Ref.
≥ 9 years	191	34.1	3,303	34.7	0.81	190	33.9	3,284	34.4	0.87
Grand multiparity	567[2]		9,699[2]			569[2]		9,721[2]		
Yes	68	12.0	1,127	11.6	0.79	66	11.6	1,129	11.6	0.99
No	499	88.0	8,572	88.4	Ref.	503	88.4	8,592	88.4	Ref.

[1]p-value from Pearson's chi square test, bolded results are statistically significant; Ref=reference category, SD=standard deviation. [2]Number of subjects with data on the variable.

Table 7. The updated hazard ratios for early biological factors for schizophrenia and other psychosis in groups with and without parental psychosis. Also the updated interaction results of parental psychosis and possible risk factor in respect of schizophrenia and other psychosis are presented. (Study I, modification of Tables 3 and 5).

Variable	Schizophrenia			Other psychosis		
	Parental psychosis	No parental psychosis	Interaction[1]	Parental psychosis	No parental psychosis	Interaction[1]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Birth weight						
< 2,500 g	NA	2.01 (0.88–4.56)	NA	NA	**2.46 (1.25–4.83)**	NA
2,500–4,500 g	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
> 4,500 g	**10.47 (3.56–30.82)**	1.30 (0.53–3.19)	**8.34 (2.05–33.89)**	2.19 (0.30–16.16)	0.98 (0.36–2.66)	2.29 (0.25–21.41)
Birth length						
≤ 46 cm	NA	**2.25 (1.18–4.31)**	NA	0.68 (0.10–5.04)	1.80 (0.95–3.43)	0.38 (0.05–3.06)
47–53 cm	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥ 54 cm	**3.21 (1.09–9.58)**	0.93 (0.43–2.01)	3.47 (0.92–12.99)	NA	0.75 (0.33–1.71)	NA
Gestational age						
< 37 weeks	0.90 (0.12–6.70)	0.93 (0.38–2.26)	0.98 (0.11–8.80)	NA	1.15 (0.54–2.47)	NA
37 weeks or more	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Birth weight / gestational age						
>2 SD below mean	0.43 (0.06–3.25)	0.86 (0.46–1.61)	0.50 (0.06–4.13)	0.30 (0.04–2.27)	1.30 (0.80–2.13)	0.23 (0.03–1.83)
within the interval of 2 SD below and above mean	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>2 SD above mean	**2.68 (1.05–6.84)**	0.86 (0.48–1.54)	**3.14 (1.04–9.46)**	0.76 (0.18–3.24)	0.93 (0.53–1.22)	0.81 (0.17–3.83)
Mother smoking during pregnancy						
Yes	0.93 (0.27–3.16)	0.90 (0.54–1.50)	1.03 (0.27–3.88)	**3.40 (1.41–8.22)**	1.23 (0.80–1.90)	**2.76 (1.04–7.37)**
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

Variable	Schizophrenia			Other psychosis		
	Parental psychosis	No parental psychosis	Interaction[1]	Parental psychosis	No parental psychosis	Interaction[1]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Paternal age at the time of birth						
< 25 years	0.43 (0.10–1.88)	1.14 (0.75–1.73)	0.38 (0.08–1.76)	0.99 (0.32–3.03)	1.11 (0.75–1.64)	0.89 (0.27–2.91)
25–40 years	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
> 40 years	1.58 (0.57–4.34)	0.98 (0.56–1.73)	1.61 (0.50–5.14)	1.54 (0.50–4.74)	1.18 (0.73–1.92)	1.31 (0.39–4.43)
Maternal age at the time of birth						
< 20 years	NA	0.99 (0.54–1.81)	NA	0.89 (0.21–3.88)	1.16 (0.70–1.93)	0.75 (0.16–3.54)
20–35 years	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
> 35 years	**2.81 (1.23–6.43)**	1.08 (0.68–1.70)	**2.63 (1.03–6.75)**	1.14 (0.42–3.07)	0.78 (0.48–1.25)	1.46 (0.49–4.39)

[1]Interaction between parental psychosis and risk factor, HR = Hazard Ratio, CI = confidence interval, Ref. = reference category, NA = Not applicable due to small sample size. The results are adjusted with sex, bolded results are statistically significant.

Table 8. The updated hazard ratios for early psychosocial factors for schizophrenia and other psychosis in groups with and without parental psychosis. Also the updated interaction results of parental psychosis and possible risk factor in respect of schizophrenia and other psychosis are presented. (Study I, modification of Tables 4 and 5).

Variable	Schizophrenia			Other psychosis		
	Parental psychosis HR (95% CI)	No parental psychosis HR (95% CI)	Interaction[1] HR (95% CI)	Parental psychosis HR (95% CI)	No parental psychosis HR (95% CI)	Interaction[1] HR (95% CI)
Mother's antenatal depressed mood						
Yes	2.21 (0.94–5.21)	0.78 (0.44–1.40)	**2.83 (1.01–7.95)**	1.69 (0.70–4.09)	1.25 (0.80–1.95)	1.36 (0.51–3.65)
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Wantedness of the child at the time of pregnancy						
unwanted	1.95 (0.77–4.94)	1.54 (0.95–2.48)	1.28 (0.45–3.64)	1.26 (0.43–3.70)	1.27 (0.79–2.03)	0.99 (0.30–3.20)
wanted at the time of pregnancy or later	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Place of residence						
rural	1.28 (0.54–3.03)	1.06 (0.74–1.52)	0.82 (0.32–2.08)	1.30 (0.52–3.26)	0.98 (0.70–1.37)	1.33 (0.50–3.53)
urban	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Family type						
one-parent	1.59 (0.21–11.80)	1.13 (0.46–2.77)	1.40 (0.16–12.55)	2.78 (0.66–11.79)	1.18 (0.52–2.66)	2.40 (0.46–12.61)
two-parent	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Father's social class at birth						
IV (low)	0.69 (0.26–1.86)	1.27 (0.86–1.88)	0.54 (0.19–1.57)	1.32 (0.58–2.98)	1.42 (1.0–2.03)	0.93 (0.38–2.26)
other	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

Variable	Schizophrenia			Other psychosis		
	Parental psychosis HR (95% CI)	No parental psychosis HR (95% CI)	Interaction[1] HR (95% CI)	Parental psychosis HR (95% CI)	No parental psychosis HR (95% CI)	Interaction[1] HR (95% CI)
Mother's education						
0–4 years	0.84 (0.19–3.71)	0.65 (0.28–1.51)	1.29 (0.23–7.06)	1.68 (0.55–5.11)	0.59 (0.30–1.17)	2.86 (0.78–10.54)
5–8 years	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥ 9 years	0.81 (0.33–2.02)	**1.61 (1.12–2.31)**	0.50 (0.19–1.34)	0.69 (0.27–1.80)	0.67 (0.46–0.96)	1.04 (0.37–2.91)
Grand multiparity						
yes	**2.68 (1.05–6.79)**	1.35 (0.83–2.19)	1.99 (0.70–5.70)	1.45 (0.50–4.22)	1.24 (0.78–1.97)	1.17 (0.36–3.74)
no	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Any biological risk						
yes	**3.21 (1.39–7.41)**	1.00 (0.69–1.45)	**3.25 (1.30–8.13)**	**2.38 (1.03–5.52)**	1.38 (0.93–2.05)	1.73 (0.68–4.38)
no	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Any psychosocial risk						
yes	2.47 (0.98–6.28)	**1.56 (1.09–2.23)**	1.59 (0.59–4.31)	-	-	-
no	Ref.	Ref.	Ref.	-	-	-

[1]Interaction between parental psychosis and risk factor, HR = Hazard Ratio, CI = confidence interval, Ref. = reference category. The results are adjusted with sex, bolded results are statistically significant.

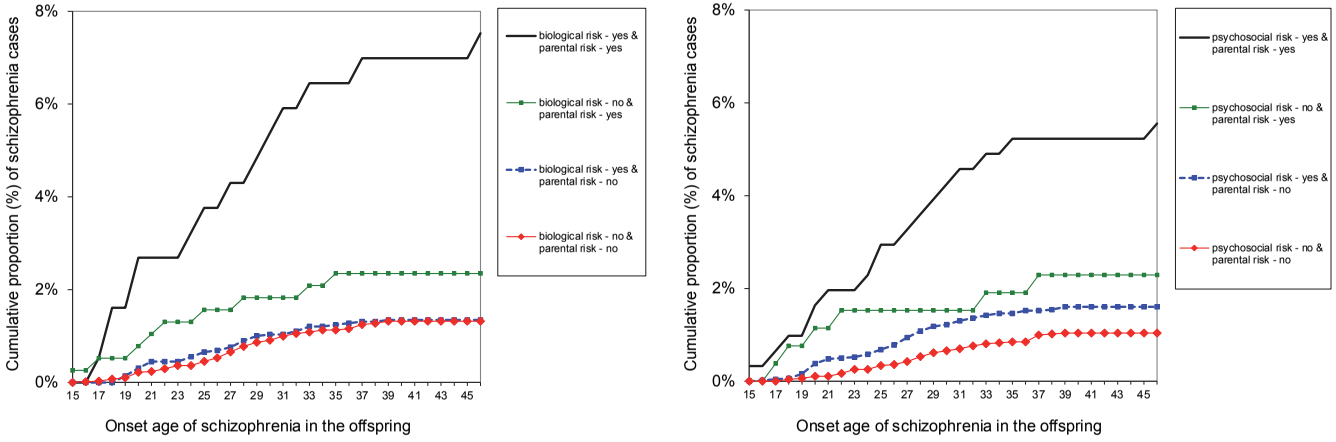

Fig. 6. Cumulative proportions of people with schizophrenia by the combined biological and psychosocial risk factors and parental psychosis (Study I, updated Figure 1).

6.4 Parental psychosis and delayed motor development in schizophrenia and other psychosis (II)

6.4.1 The association between parental psychosis and motor development

The cohort members with parental psychosis had, in general, a higher mean age of reaching each motor milestone compared to those without parental psychosis, except in turning from back to tummy. The difference was statistically significant in being able to hold the head up, in gripping on an object and in walking without support (Table 9).

6.4.2 The association between parental psychosis and delayed motor development in the risk for schizophrenia and other psychosis

In the parental psychosis group, later achievement of the following motor milestones was associated with an increased risk for schizophrenia: holding the head up (HR 2.46; 95% CI 1.07–5.66) and touching the thumb with the index finger (HR 1.84; 1.11–3.06). In the group without parental psychosis, later achievement of standing without support (HR 1.21; 1.06–1.39) and walking without support (HR 1.22; 1.10–1.37) increased the risk for schizophrenia (Table 10).

Regarding other psychosis, none of the delayed milestones increased the risk in the group with parental psychosis. In the group without parental psychosis, later achievement of standing without support (HR 1.17; 1.02–1.32) and walking without support (HR 1.19; 1.07–1.32) increased the risk for other psychosis (Table 11).

After adjusting the results for sex and every other covariate separately, and also in a fully adjusted model (sex, father's social class, perinatal risk, maternal antenatal depression and family type), the results stayed similar regarding the parental psychosis groups.

6.4.3 Interaction between parental psychosis and delayed motor development in the risk for schizophrenia and other psychosis

Parental psychosis had a statistically significant interaction with the later age of touching the thumb with the index finger regarding the risk for schizophrenia (HR 1.76; 95% CI 1.01–3.05) and the risk for other psychosis (HR 0.50; 0.27–0.92) (Tables 10 and 11).

The interaction between parental psychosis and touching the thumb with the index finger remained statistically significant when adjusting for every covariate separately and also in a fully adjusted model (gender, father's social class, perinatal risk, maternal antenatal depression and family type).

6.4.4 Principal component analysis results

Motor development as a whole was fastest in the group without parental psychosis and in those who did not develop schizophrenia and slowest in the group with parental psychosis and subsequent schizophrenia. However, the difference between groups was not statistically significant ($F=2.03$, $p=0.11$). Additionally, there was no interaction between parental psychosis and principal component in the risk for schizophrenia (HR 1.16; 95% CI 0.52–2.62). Figure 7 shows how the compared groups differ in motor development measured with the principal component analysis.

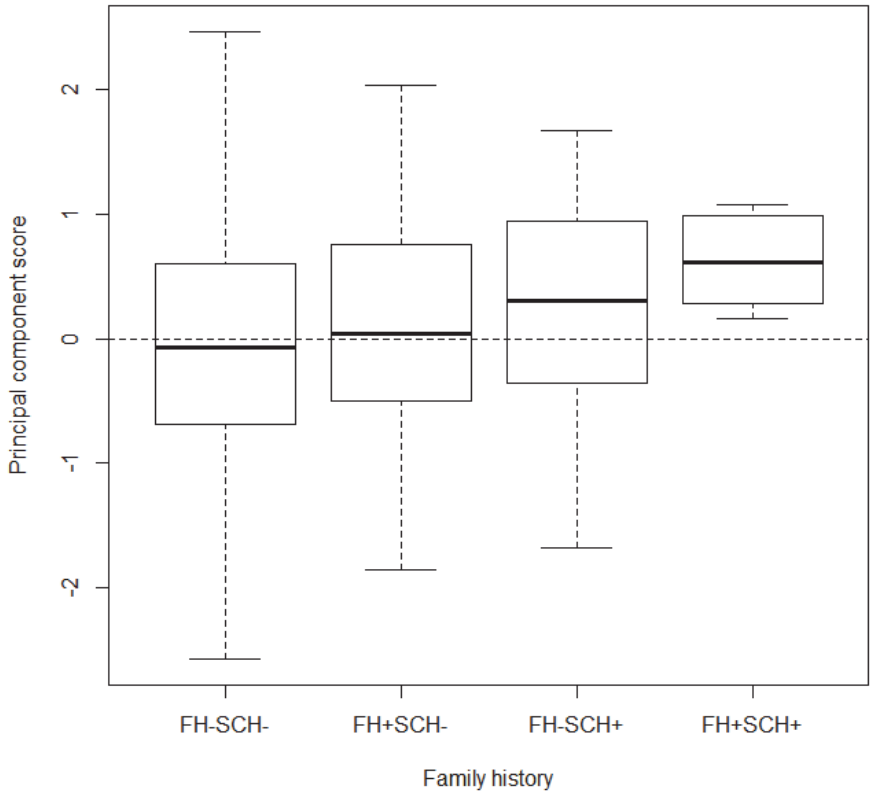

Fig. 7. Early motor development according to principal component analysis in different groups by parental psychosis and diagnosis of schizophrenia. FH= Family history of psychosis, i.e. parental psychosis in this study, SCH= Schizophrenia (Study II, Fig. 1).

Table 9. The associations between parental psychosis and the age (in months) of achievement of motor milestones (Study II, modified Table 1).

Variable	Schizophrenia					Other psychosis				
	Parental psychosis		No parental psychosis		p-value[1]	Parental psychosis		No parental psychosis		p-value[1]
	N	Mean (SD)	N	Mean (SD)		N	Mean (SD)	N	Mean (SD)	
Holding the head up	292	2.23 (0.71)	5318	2.13 (0.74)	**0.02**	292	2.22 (0.71)	5307	2.13 (0.74)	**0.04**
Gripping on an object	290	3.32 (0.68)	5088	3.23 (0.69)	**0.03**	287	3.34 (0.69)	5072	3.23 (0.69)	**0.01**
Turning from back to tummy	328	4.35 (1.19)	5716	4.37 (1.10)	0.79	326	4.35 (1.18)	5714	4.37 (1.10)	0.81
Sitting without support	279	7.33 (1.64)	5071	7.22 (1.13)	0.27	278	7.32 (1.62)	5069	7.22 (1.12)	0.30
Touching the thumb with the index finger	174	7.53 (1.22)	3175	7.40 (1.32)	0.21	172	7.45 (1.24)	3164	7.40 (1.32)	0.59
Standing up	292	8.58 (1.85)	5057	8.44 (1.38)	0.21	288	8.56 (1.86)	5040	8.43 (1.38)	0.28
Standing without support	440	10.48 (1.45)	7905	10.40 (1.34)	0.23	441	10.46 (1.46)	7916	10.40 (1.34)	0.38
Walking without support	436	11.74 (2.15)	7459	11.46 (1.50)	**<0.001**	438	11.69 (2.10)	7472	11.46 (1.51)	**0.03**

SD= standard deviation, [1]p-value from Pearson's chi-square test, bolded results are statistically significant

Table 10. The Hazard Ratios for the age (in months) of achievement of motor milestones and risk for schizophrenia in groups with and without parental psychosis (Study II, modified Table 2).

Variable	Schizophrenia	Parental psychosis		No parental psychosis		Interaction[1]
		Mean (SD)	HR (95% CI)	Mean (SD)	HR (95% CI)	HR (95% CI)
Holding the head up	No	2.21 (0.71)	Ref.	2.13 (0.74)	Ref.	Ref.
	Yes	2.70 (0.68)	**2.46 (1.07–5.66)**	2.16 (0.78)	1.06 (0.78–1.42)	2.38 (0.98–5.79)
Gripping on an object	No	3.33 (0.68)	Ref.	3.23 (0.69)	Ref.	Ref.
	Yes	3.25 (0.45)	0.85 (0.36–2.02)	3.24 (0.62)	1.02 (0.74–1.42)	0.84 (0.34–2.10)
Turning from back to tummy	No	4.35 (1.19)	Ref.	4.36 (1.10)	Ref.	Ref.
	Yes	4.38 (1.12)	1.02 (0.67–1.56)	4.55 (0.99)	1.16 (0.96–1.40)	0.88 (0.55–1.40)
Sitting without support	No	7.33 (1.65)	Ref.	7.22 (1.13)	Ref.	Ref.
	Yes	7.31 (1.49)	0.99 (0.71–1.38)	7.32 (1.16)	1.08 (0.87–1.33)	0.92 (0.62–1.35)
Touching the thumb with the index finger	No	7.49 (1.20)	Ref.	7.40 (1.32)	Ref.	Ref.
	Yes	8.57 (1.40)	**1.84 (1.11–3.06)**	7.49 (1.42)	1.05 (0.84–1.32)	**1.76 (1.01–3.05)**
Standing up	No	8.56 (1.87)	Ref.	8.43 (1.38)	Ref.	Ref.
	Yes	8.87 (1.60)	1.05 (0.87–1.27)	8.73 (1.42)	1.16 (0.99–1.37)	0.90 (0.70–1.16)
Standing without support	No	10.46 (1.46)	Ref.	10.40 (1.34)	Ref.	Ref.
	Yes	10.94 (1.16)	1.17 (0.93–1.48)	10.77 (1.40)	**1.21 (1.06–1.39)**	0.97 (0.74–1.27)
Walking without support	No	11.70 (2.13)	Ref.	11.46 (1.50)	Ref.	Ref.
	Yes	12.67 (2.30)	1.08 (0.99–1.18)	12.02 (1.83)	**1.22 (1.10–1.37)**	0.88 (0.76–1.01)

[1]Interaction between parental psychosis and milestone, SD=standard deviation, HR=Hazard Ratios for one month delay, adjusted for sex, CI=confidence interval, Ref=reference category, bolded results are statistically significant.

Table 11. The Hazard Ratios for the age (in months) of achievement of motor milestones and risk for other psychosis in groups with and without parental psychosis (Study II, modified Table 2).

Variable	Other psychosis	Parental Psychosis		No parental psychosis		Interaction[1]
		Mean (SD)	HR (95% CI)	Mean (SD)	HR (95% CI)	HR (95% CI)
Holding the head up	No	2.21 (0.71)	Ref.	2.13 (0.74)	Ref.	Ref.
	Yes	2.30 (0.82)	1.23 (0.51–2.97)	2.14 (0.70)	1.02 (0.74–1.41)	1.17 (0.47–2.93)
Gripping on an object	No	3.33 (0.68)	Ref.	3.23 (0.69)	Ref.	Ref.
	Yes	3.67 (0.71)	1.93 (0.83–4.50)	3.19 (0.78)	0.92 (0.63–1.34)	2.08 (0.83–5.22)
Turning from back to tummy	No	4.35 (1.19)	Ref.	4.36 (1.10)	Ref.	Ref.
	Yes	4.36 (0.92)	1.00 (0.62–1.61)	4.41 (1.20)	1.04 (0.85–1.28)	0.96 (0.56–1.63)
Sitting without support	No	7.33 (1.65)	Ref.	7.22 (1.13)	Ref.	Ref.
	Yes	7.08 (1.00)	0.89 (0.56–1.41)	7.30 (0.93)	1.06 (0.86–1.31)	0.84 (0.51–1.39)
Touching the thumb with the index finger	No	7.49 (1.20)	Ref.	7.40 (1.32)	Ref.	Ref.
	Yes	6.40 (1.95)	0.58 (0.34–1.00)	7.63 (1.56)	1.14 (0.87–1.49)	**0.50 (0.27–0.92)**
Standing up	No	8.56 (1.87)	Ref.	8.43 (1.38)	Ref.	Ref.
	Yes	8.45 (1.57)	0.96 (0.67–1.38)	8.67 (1.83)	1.12 (0.93–1.36)	0.86 (0.57–1.29)
Standing without support	No	10.46 (1.46)	Ref.	10.40 (1.34)	Ref.	Ref.
	Yes	10.53 (1.43)	1.03 (0.76–1.40)	10.69 (1.53)	**1.17 (1.02–1.32)**	0.88 (0.64–1.23)
Walking without support	No	11.70 (2.13)	Ref.	11.46 (1.50)	Ref.	Ref.
	Yes	11.55 (1.36)	0.96 (0.74–1.25)	11.93 (2.09)	**1.19 (1.07–1.32)**	0.81 (0.61–1.08)

[1]Interaction between parental psychosis and milestone, SD = standard deviation, HR=Hazard Ratios for one month delay, adjusted for sex, CI= confidence interval, Ref.= reference category, bolded results are statistically significant.

6.5 Protective factors for psychosis (III)

6.5.1 Factors associating with unaffected status in the total sample

The cohort members who remained unaffected differed from those who developed psychosis. The unaffected cohort members were more often wanted babies at the time of pregnancy and there was no grand multiparity in the family, their mother worked more often outside the home or was a student, and they more often had a two-parent family. The BMI of unaffected cohort members was more often in the highest quartile, grade in physical activity, and mean grades of non-theoretical school subjects and theoretical school subjects were more often good (≥9), and their school level was more often normal or upper than for same-aged cohort members who later developed psychosis. The unaffected cohort members had also more often a team sport hobby in their childhood. Table 12 shows the results for only statistically significant variables, and all results are represented in Appendix 2.

6.5.2 Factors associating with unaffected status among individuals with parental psychosis

In the parental psychosis group, unaffected individuals had a mother less often depressed during pregnancy (p=0.04) and more often working outside the home or studying (p=0.005) than individuals who developed psychosis subsequently (Table 12).

6.5.3 Latent class analysis results

Latent class analysis divided the cohort members with parental psychosis into two classes where Class 1 contained 453 (76.3%) and Class 2 contained 141 (23.7%) individuals. The affected individuals distributed differently to the two classes: in Class 1, 6.4% of individuals and in Class 2, 13.5% were affected. Thus Class 1 had most of the individuals who remained unaffected and the difference between the amount of affected individuals in Class 1 and 2 was statistically significant (χ^2=7.24, p=0.007). In Class 1, the probability of the subjects being wanted at the time of pregnancy, their mother being not depressed during the pregnancy, having a mother working outside the home or studying, having two-parent family and having no grand multiparity in the family was higher than in Class 2 (Fig. 8).

Table 12. Variables with statistically significant difference between unaffected individuals and individuals who developed psychosis subsequently (Study III, modified Table 3). All analysed variables are presented in Appendix 2.

Variable	Parental psychosis						No parental psychosis						Statistical comparisons[1]	
	Any psychosis						Any psychosis							
	Yes (A)		No (B)		Total (A+B)		Yes (C)		No (D)		Total (C+D)		A+C vs. B+D	A vs. B
	n	%	n	%	n	%	n	%	n	%	n	%	p-value	p-value
Variables considering pregnancy, birth and the first year of life														
Mother's antenatal depressed mood	47[3]		537[3]		584[3]		269[3]		9,344[3]		9,613[3]		0.19	**0.04**
Yes	15	31.9	105	19.6	120	20.5	36	13.4	1,233	13.2	1,269	13.2		
No	32	68.1	432	80.4	464	79.5	233	86.6	8,111	86.8	8,344	86.8		
Wantedness of the child	46[3]		538[3]		584[3]		268[3]		9,337[3]		9,605[3]		**0.02**	0.34
wanted at the time of pregnancy	23	50.0	308	57.2	331	56.7	159	59.3	6,048	64.8	6,207	64.6		
unwanted or mistimed	23	50.0	230	42.8	253	43.3	109	40.7	3,289	35.2	3,398	35.4		
Grand multiparity (≥6 siblings)	48[3]		544[3]		592[3]		278[3]		9,571[3]		9,849[3]		**0.04**	0.06
Yes	10	20.8	62	11.4	72	12.2	40	14.4	1,108	11.6	8,701	88.3		
No	38	79.2	482	88.6	520	87.8	238	85.6	8,463	88.4	1,148	11.7		
Variables considering family and childhood														
Mother working outside the home in 1980	42[3]		500[3]		542[3]		241[3]		8,894[3]		9,135[3]		**0.006**	**0.005**
Yes (working full-time or part-time, or studying)	10	23.8	230	46.0	240	44.3	127	52.7	5,093	57.3	5,220	57.1		
No (housewife, unemployed, on a sick leave or pensioned)	32	76.2	270	54.0	302	55.7	114	47.3	3,801	42.7	3,915	42.9		

Variable	Parental psychosis						No parental psychosis						Statistical comparisons[1]	
	Any psychosis						Any psychosis							
	Yes (A)		No (B)		Total (A+B)		Yes (C)		No (D)		Total (C+D)		A+C vs. B+D	A vs. B
	n	%	n	%	n	%	n	%	n	%	n	%	p-value	p-value
Family type in 1980	48[3]		546[3]		594[3]		279[3]		9,585[3]		9,864[3]		**0.04**	0.27
Single-parent family	16	33.3	142	26.0	158	26.6	60	21.5	1,744	18.2	1,804	18.3		
Two-parent family	32	66.7	404	74.0	436	73.4	219	78.5	7,841	81.8	8,060	81.7		
Variables considering health and habits at the of 14														
BMI	39[3]		474[3]		513[3]		230[3]		8,446[3]		8,676[3]		**0.04**	0.20
≤17.7 kg/m^2 (lowest 25th percentile)	5	12.8	122	25.7	127	24.8	75	32.6	2,078	24.6	2,153	24.8		
17.8–20.49 kg/m^2	23	59.0	244	51.5	267	52.0	115	50.0	4,248	50.3	4,363	50.3		
≥20.5 kg/m^2 (highest 25th percentile)	11	28.2	108	22.8	119	23.2	40	17.4	2,120	25.1	2,160	24.9		
Variables considering school performance														
School level in 1980	48[3]		546[3]		594[3]		279[3]		9,585[3]		9,864[3]		**0.03**	0.75[2]
Normal or upper class	45	93.8	515	94.3	560	94.3	262	93.9	9,234	96.3	9,496	96.3		
Below normal class or customised school	3	6.3	31	5.7	34	5.7	17	6.1	351	3.7	368	3.7		
Grade of physical education in 1982	45[3]		524[3]		569[3]		270[3]		9,403[3]		9,673[3]		**0.004**	0.46[2]
4–6	4	8.9	57	10.9	61	10.7	31	11.5	704	7.5	735	7.6		
7–8	33	73.3	332	63.4	365	64.1	179	66.3	5954	63.3	6133	63.4		
9–10	8	17.8	135	25.8	143	25.1	60	22.2	2745	29.2	2805	29.0		

Variable	Parental psychosis				No parental psychosis				Statistical comparisons[1]	
	Any psychosis				Any psychosis					
	Yes (A)		No (B)		Total (A+B)		Yes (C)		No (D)		Total (C+D)		A+C vs. B+D	A vs. B
	n	%	n	%	n	%	n	%	n	%	n	%	p-value	p-value
Mean grade of non-theoretical school subjects in 1982	45[3]		526[3]		571[3]		272[3]		9,432[3]		9,704[3]		**0.01**[2]	0.63[2]
4–6	0	0.0	7	1.3	7	1.2	6	2.2	53	0.6	59	0.6		
7–8	44	97.8	484	92.0	528	92.5	248	91.2	8,569	90.9	8,817	90.9		
9–10	1	2.2	35	6.7	36	6.3	18	6.6	810	8.6	828	8.5		
Mean grade of theoretical school subjects in 1982	45[3]		526[3]		571[3]		272[3]		9,433[3]		9,705[3]		**0.01**	0.26[2]
4–6	7	15.6	66	12.5	73	12.8	48	17.6	1,124	11.9	1,172	12.1		
7–8	37	82.2	411	78.1	448	78.5	202	74.3	7,441	78.9	7,643	78.8		
9–10	1	2.2	49	9.3	50	8.8	22	8.1	868	9.2	890	9.2		
Variables considering physical activity at the age of 14														
Type of sport hobby	42[3]		491[3]		533[3]		228[3]		8,714[3]		8,942[3]		**0.05**	0.65
Does not have sport hobby	8	19.0	70	14.3	78	14.6	38	16.7	1,147	13.2	1,185	13.3		
Individual sport	23	54.8	299	60.9	322	60.4	144	63.2	5,225	60.0	5,369	60.0		
Team sport	11	26.2	122	24.8	133	25.0	46	20.2	2,342	26.9	2,388	26.7		

[1]P-value from Pearson's chi-square or [2]Fisher's exact test, bolded results are statistically significant. [3]Number of subjects with data on variable.

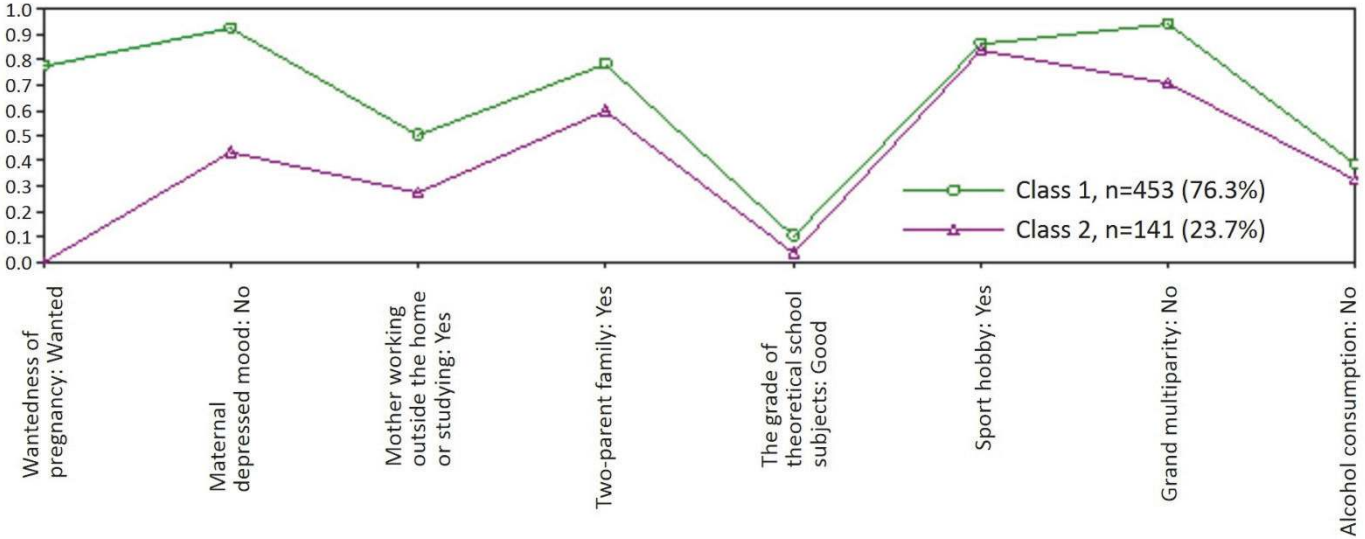

Fig. 8. Frequency of possible protective factors in two latent classes. The figure shows that the probability of having all the protective factors was higher in Class 1 (Study III, Figure 2).

7 Discussion

7.1 Main findings

Study I revealed that factors increasing the risk for psychosis were different between individuals with and without parental psychosis. Many risk factors during pregnancy and birth increased the risk for schizophrenia only among those with parental psychosis. Those risk factors were high birth weight, high birth length, high birth weight in relation to gestational age, advanced maternal age and grand multiparity. In the parental psychosis group, biological risk factors had a stronger association with schizophrenia than psychosocial factors, whereas in the group without parental psychosis, psychosocial risk factors particularly increased the risk for schizophrenia. Parental psychosis had significant interactions with factors relating to baby's large size at birth, advanced maternal age, mother's depressed mood during pregnancy and any biological risk factor giving some evidence of parental psychosis acting as an effect modifier, as it was hypothesized. Risk factors for other psychosis were different from schizophrenia and also differed between those with and without parental psychosis. Biological risk factors increased the risk for other psychosis only in the parental psychosis group similar to schizophrenia risk. Mother's smoking during pregnancy had significant interaction with parental psychosis in the risk for other psychosis.

In *Study II*, among those with parental psychosis, the delayed motor milestones were those appearing the earliest in the child's life in the schizophrenia risk, i.e. holding the head up and touching the thumb with the index finger. None of the delayed motor milestones increased the risk for other psychosis in the parental psychosis group. In the group without parental psychosis, the delayed motor milestones increasing the risk for schizophrenia and other psychosis were those appearing later in the first year of child's life, i.e. standing and walking without support. Interaction between parental psychosis and fine motor skills was found in respect of risk for schizophrenia and other psychosis. The principal component analysis showed that motor development was the slowest among those who developed schizophrenia and had parental psychosis. These results are in line with the hypothesis that delayed motor milestones would increase the risk for psychosis differently among those with and without parental psychosis, though significant interaction was found only regarding one motor milestone.

In Study III, several favourable factors in prenatal, childhood and youth periods and factors relating to school and family indicating health and stability were associated with an unaffected status in the total sample. These results are in line with the hypothesis that protective factors would have been found. However, factors associating with remaining unaffected among those with parental psychosis were surprisingly few. These factors related to the mother's non-depressed mood during pregnancy and the mother's work outside home or studies.

7.2 Comparison to earlier studies

7.2.1 Early risk factors for schizophrenia (I)

Early risk factors for schizophrenia among those with parental psychosis

An association between high birth weight, high birth weight in relation to gestational age, high birth length and schizophrenia was found among those with parental psychosis. Earlier studies support the finding of high birth weight increasing the risk for schizophrenia (Hultman *et al.* 1997, Bersani *et al.* 2007, Moilanen *et al.* 2010, Wegelius *et al.* 2011). However, opposite findings also exist (Dalman *et al.* 1999, Abel *et al.* 2010) and also low birth weight has been found to increase the risk for schizophrenia (Wahlbeck *et al.* 2001, Cannon *et al.* 2002, Abel *et al.* 2010, Matheson *et al.* 2011). A reverse J-shaped relationship between schizophrenia and birth weight, where both; low and high birth weight, increases the risk for schizophrenia, has been found (Gunnell *et al.* 2003, Moilanen *et al.* 2010). High birth weight and length can lead to obstetric complications such as respiratory distress in the baby during prolonged labour, resulting in hypoxia or ischemic brain damage (Bersani *et al.* 2007) and increasing the risk for schizophrenia via premature cortical synaptic pruning (Rosso *et al.* 2000).

Maternal diabetes can lead to the large size of a new born (Egan *et al.* 2014) and both high birth weight and maternal diabetes associate with increased risk for schizophrenia (Wegelius *et al.* 2011). In addition, mothers with psychosis are at an increased risk for diabetes (Stubbs *et al.* 2015). However, maternal diabetes should not account for the large size of the new born in this study because none of the mothers with psychosis reported having diabetes. Though, keeping in mind that the

diagnosis of gestational diabetes was not in routine use in Finland in 1966 (Wegelius *et al.* 2011).

High maternal BMI (>30) is thought to increase the risk for schizophrenia in the offspring via an associated lack of important nutrients and changes to maternal glucose metabolism (Schaefer *et al.* 2000). Glucose has toxic effects in developing neurons (Van Lieshout & Voruganti 2008). Maternal nutrition is imperative to foetal nutrition, growth and brain development. However, in this dissertation study, the association between parental psychosis and high birth weight, as well as high birth length, remained significant when maternal BMI was taken into account. When controlling for maternal BMI, high birth weight in relation to gestational age lost its statistical significance.

Several studies have reported that an advanced paternal age increases the risk for schizophrenia by increased possibility of higher amount of de novo mutations in progenitor sperm cells as men age (Perrin *et al.* 2007, Torrey *et al.* 2009). In this study, advanced maternal age increased the risk for schizophrenia only among those with parental psychosis. Advanced maternal age has been shown to increase the risk for schizophrenia (Byrne *et al.* 2003b, Zammit *et al.* 2003, Ekeus *et al.* 2006) and a positive linear correlation between increasing maternal age and the risk for psychotic disorder has been found (Lopez-Castroman *et al.* 2010). Some studies suggest that advanced maternal age acts independently as risk factor (Ekeus *et al.* 2006), whereas some have found it to associate with advanced paternal age (Byrne *et al.* 2003b, Zammit *et al.* 2003).

Accumulating mutations and chromosomal anomalies in reproductive cells may account for the largest part of the advanced age risk (Malaspina *et al.* 2002, Zitzmann 2013) but also social characteristics (Saha *et al.* 2009) and personality traits of the older parent (Zammit *et al.* 2003) account for part of the association. Additionally, obstetrical complications, such as preeclampsia, emergency caesarean section and gestational diabetes, are more common among older mothers (Khalil *et al.* 2013, Schimmel *et al.* 2015) and have also been shown to increase the risk for schizophrenia (Preti *et al*. 2000, Cannon *et al.* 2002).

Grand multiparity, i.e. being born from the sixth or greater pregnancy has been found to increase the risk for schizophrenia (Hultman *et al.* 1999). In one study, this association was found only among female offspring (Lahti *et al.* 2014). One explanation could be the increased levels of pre- and perinatal complications associating with grand multiparous pregnancies and births (Roman *et al.* 2004, Yasmeen *et al.* 2005, Teguete *et al.* 2012), another explanation is psychosocial

including exposure to compromised parenting or to early socioeconomic adversity, which associate with grand multiparous parenting (Lawson & Mace 2009).

The results of this thesis supported previous findings regarding the large size of the new born, advanced maternal age and grand multiparity as risk factors for schizophrenia. A novel finding is that these factors increased the risk only among those with parental psychosis and, in particular, biological risk factors increased the risk for schizophrenia and other psychosis in the parental psychosis group. It is possible that the inherited risk genes of psychosis are especially vulnerable to biological risk factors and that the expression of inherited risk genes for psychosis is moderated by the mechanisms behind these biological exposures. Or it might be that subsequent schizophrenia and biological factors, e.g. large size of the new born, are just independent but different expressions of the same genes. This has still remained unrevealed, but no signs of gene-environment correlation was found in this study, since above mentioned risk factors for schizophrenia and other psychosis were not more common in parental psychosis group than in those without it.

Early risk factors for schizophrenia among those without parental psychosis

In this study, low birth length increased the risk for schizophrenia only in the group without parental psychosis. Supporting the evidence of small size of the new born as a risk for schizophrenia, since low birth weight has been shown to increase the risk (Wahlbeck *et al.* 2001, Cannon *et al.* 2002, Abel *et al.* 2010, Matheson *et al.* 2011). The small size of the new born may result from intrauterine growth retardation or prematurity increasing the risk for psychosis (Cannon *et al.* 2002, Nosarti *et al.* 2012). Low birth weight and length might also be a marker of other adversities on the developing foetus (Cannon *et al.* 2002), e.g. poor nutrition (Picker & Coyle 2005, Pedersen *et al.* 2012, Papadopoulou *et al.* 2014), placental pathology (Gaillard *et al*. 2013) or the mother's smoking (Horta *et al.* 1997, Steyn *et al.* 2006). Additionally, the premature brain is especially vulnerable to environmental exposures and neonatal brain injury (Volpe 2009).

A mother's high education increased the risk for schizophrenia, but only among those without parental psychosis. Low socioeconomic status increases the risk for schizophrenia (Wicks *et al.* 2005), but Byrne *et al.* (2004) discovered that high levels of parental education may also increase the risk. Earlier in the NFBC 1966, the father's high social class increased the risk for schizophrenia in females

(Mäkikyrö *et al.* 1997). One explanation for this association may be stress relating to social changes within the family. Educational progress was particularly rapid in Finland during the post-war decades; in the 1950's and 1960's, a time when the cohort members' parents attended higher education and became professionals. It is suggested that a remarkable amount of effort was required by those from a lower social class to achieve the qualifications and professions that raised their social class. This effort may have resulted in considerable stress for the whole family (Mäkikyrö *et al.* 1997).

This study brings novel findings regarding previously found risk factors, since the new born's low birth length and high maternal education increased the risk for schizophrenia only among those without parental psychosis. Psychosocial risk factors particularly increased the risk for schizophrenia among those without parental psychosis. It is possible that chromosomal copy number variants (CNVs), which are thought to mostly account for sporadic (i.e. not inherited from parents) schizophrenia (Rees *et al.* 2014, Kirov *et al.* 2015), might be the results of vulnerability towards psychosocial and stress-related environmental factors. However, this has still remained unrevealed. None of the risk factors were more common among those without parental psychosis.

The classification of risk factors into biological and psychosocial

Biological and psychosocial factors may overlap, leading to differences in approaches to classification. For example, maternal antenatal depression can be classified as both biological and psychosocial risk factor, since it may affect via stress hormones (Maccari *et al.* 2003) but may also be related to prenatal attachment and impact on mother–child bonding (Pearson *et al.* 2012). Nevertheless, classification used in this study may help to clarify and even reveal novel relationships and phenomena, which might otherwise have remained unnoticed. Thus, risk factors that may directly affect foetal development were considered as biological. Psychosocial risk factors may affect in several ways or they might also be proxies for parental mental illness. This method of classification of risk factors has been discussed in previous studies also (Mäki *et al.* 2005, Tandon *et al.* 2008).

7.2.2 Delayed motor development in the risk for schizophrenia (II)

The association between parental psychosis and delayed motor development in the risk for schizophrenia

The delayed holding of the head up, gripping on an object and walking without support were more often achieved later among those with parental psychosis. In the parental psychosis group, the delayed milestones that increased the risk for schizophrenia, were the milestones that appear earlier in a child's development (holding the head up, touching the thumb with the index finger) than those in the group without parental psychosis (standing and walking without support). To my knowledge, there have been no such results in previous studies. In the principal component analysis, motor development in general was the slowest among those with parental psychosis and subsequent schizophrenia. However, this difference would not have been considered as abnormal in child welfare clinics.

In several other studies, a delay in walking has been the most significant risk factor for schizophrenia compared to other motor milestones (Jones & Rodgers 1994, Sørensen *et al.* 2010, Clarke *et al.* 2011), but delays in crawling, holding the head up, learning to sit, standing (Sørensen *et al.* 2010) and standing up have also increased the risk (Clarke *et al.* 2011). However, these studies have not investigated motor development separately among those with and without parental psychosis.

Genetic factors and the brain's self-produced internal activity have been found to play a substantial role in the first phase of brain development, whereas environmental factors and epigenetic mechanisms have been shown to interact intensively in brain maturation later on in the brain's development (Cioni & Sgandurra 2013). This might explain why parental psychosis associates particularly with motor milestones that appear earlier in child's life when genetic factors play a key role in brain development.

7.2.3 Risk factors for other psychosis (I, II)

There are not as many studies on risk factors for other psychosis as for schizophrenia. Genes and risk processes have been reported to overlap between psychotic disorders (Kessler *et al.* 2010, McLaughlin *et al.* 2010) but there are also findings of differentiating risk factors between schizophrenia and affective psychoses (Mortensen *et al.* 2003, Kelly *et al.* 2010, Østergaard *et al.* 2013). In this

study, other psychosis included delusional disorder, brief/acute and transient psychosis, schizoaffective disorder, affective psychoses and not otherwise specified/unspecified psychosis. Some of the risk factor studies have focused on "broad schizophrenia", i.e. other schizophrenia spectrum disorders in addition to schizophrenia, as the measured outcome.

To my knowledge, this study was the first to examine the risk factors for other psychosis separately among those with and without parental psychosis. This study brought new information on risk factors during pregnancy, birth and childhood for other psychosis. Risk factors for schizophrenia and other psychosis differed from each other indicating possibly different aetiological mechanisms behind these disorders.

Risk factors for other psychosis among those with parental psychosis

Maternal smoking during pregnancy increased the risk for other psychosis only among those with parental psychosis. Previously, maternal smoking has been associated with schizophrenia risk (Stathopolou *et al.* 2013) and risk for bipolar disorder (Talati *et al.* 2013). Prenatal tobacco exposure may increase the risk for the offspring's psychosis by causing chronic foetal hypoxia, dysregulation of endocrine equilibrium and disruption of foetal neurodevelopment (Stathopolou *et al.* 2013). Mothers with psychosis smoke also more often during pregnancy than mothers without it (Stathopolou *et al.* 2013).

This study revealed that none of the motor milestones were associating with parental psychosis in the risk for other psychosis differing from the results regarding schizophrenia.

Risk factors for other psychosis among those without parental psychosis

Low birth weight increased the risk for other psychosis among those without parental psychosis. Factors relating to the small size of a new born have been discussed above. Previous studies have not found an association between low birth size and affective disorders (Bain *et al.* 2000, Eaton *et al.* 2000, Øgendahl *et al.* 2006).

Later achievement of standing and walking without support increased the risk for other psychosis among those without parental psychosis. To my knowledge, early motor development in those with other psychosis has not been studied before,

but similar findings regarding schizophrenia have been made without distinguishing the parental psychosis groups from each other.

7.2.4 Interaction between parental psychosis and risk factors (I, II)

Previously interaction between parental psychosis and the mother's antenatal depressed mood (Mäki *et al.* 2010), unwantedness of pregnancy (McNeil *et al.* 2009, mother's upper urinary tract infection during pregnancy (Clarke *et al.* 2009) and cannabis use (McGuire *et al.* 1995) in psychosis risk has been found. Also synergistic effects with genetic vulnerability and urbanicity (van Os *et al.* 2004) and traumatic brain injury (Malaspina *et al.* 2001) have been reported. This study extends the study field of interactions to perinatal factors and also to the offspring's motor development in respect of risk for schizophrenia and other psychosis. To my knowledge, there are no other studies that have investigated the interaction between parental psychosis and risk factors in respect of risk for other psychosis.

In this study and others also, parental psychosis has been considered to be an indirect sign of genetic vulnerability to schizophrenia and other psychosis. Interaction indicates genetic risk acting as an effect modifier in relation to risk and outcome or environment regulating the gene expression of risk genes (Tsuang *et al.* 2004). The risk associated with parental psychosis might be inherited within genes and/or result from environmental factors such as poor prenatal care, obstetric complications, impaired parenting or social adversities that have been found to associate with parental psychosis (Lin *et al.* 2009, Matevosyan *et al.* 2011, Preti *et al.* 2012). Both, genetic and environmental factors influence a child's development. Moreover, genetic effects interact with environmental risk factors by making genetically vulnerable individuals more sensitive to environmental stress effects (Rutter *et al.* 2001, Wan *et al.* 2008a) supporting the vulnerability-stress model of mental health.

Interaction between parental psychosis and risk factors during pregnancy and birth in risk for schizophrenia and other psychosis (I)

Interaction between parental psychosis and high birth weight, high birth weight in relation to gestational age, advanced maternal age and mother's antenatal depressed mood was found regarding schizophrenia risk. Also interaction between parental

psychosis and maternal smoking during pregnancy regarding the risk for other psychosis was found.

Altogether, any biological risk had a significant interaction with parental psychosis in schizophrenia risk. The effect of these biological risk factors may even be confined exclusively to the parental psychosis group, since the risk acted only among those with parental psychosis. This might relate to inherited genes that are particularly vulnerable to biological exposures or that parental psychosis somehow favours these kinds of exposures.

Genes associating with schizophrenia and other psychosis are related to neuronal plasticity, immune system (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) and neurotransmission (Pocklington *et al.* 2015) and over half of the genes associating with schizophrenia are regulated by hypoxia-ischemia (Schmidt-Kastner *et al.* 2012). The effect of many of the found risk factors might be partly explained by hypoxia, e.g. prolonged labour and respiratory distress caused by the large size of the baby and maternal smoking during pregnancy. On the other hand, many of the observed risk factors have been shown to be more common among parents with psychosis, e.g. smoking during pregnancy (Stathopolou *et al.* 2013), older age (Nilsson *et al.* 2002), pre-and perinatal complications (Nilsson *et al*. 2002, Preti *et al.* 2012, Walder *et al*. 2014). However, it has been reported that the associations cannot fully be explained by parental features (Nilsson *et al.* 2002). In this study, large size at birth, advanced maternal age and mother's smoking were not more common among those with parental psychosis indicating gene-environment interaction instead of gene-environment correlation (rGE). However, mother's antenatal depression was more common among those with parental psychosis referring to gene-environment correlation.

Interaction between parental psychosis and delayed motor development in risk for schizophrenia and other psychosis (II)

To my knowledge, there are no other studies that have investigated the interaction between parental psychosis and delayed motor development in the first year of life in respect of risk for subsequent schizophrenia and other psychosis. Touching the thumb with the index finger had a significant interaction with parental psychosis in the risk for schizophrenia and other psychosis. Regarding other psychosis, reaching the touching the thumb with the index finger was later among those without parental psychosis than among those with parental psychosis. This might mean that

parental psychosis has an effect in particular on fine motor skills but needs to be replicated. Delayed touching the thumb with the index finger was not more common among those with parental psychosis supporting the interaction effect instead of gene-environment correlation effect. The association between parental psychosis and fine motor skills has been shown before considering children at school-age (Marcus 1974, Erlenmeyer-Kimling *et al.* 1984). However, some of the studies have found that gross motor skills particularly associate with parental psychosis (Erlenmeyer-Kimling *et al.* 2000).

How might parental psychosis interact with delayed development to increase the risk for later psychosis? One possibility is delayed motor development being a marker of how genetic risk for psychosis acts. As parental psychosis is a risk factor for delayed motor development, some of the same genes that lead to delayed brain development also appear to confer the risk for schizophrenia (operating via effects on neurodevelopment). Thus, observing delayed development in infancy can indicate that risk genes have been inherited and are taking an effect at an early age. It is shown that unaffected siblings of individuals with schizophrenia have more neuromotor deficits in childhood, especially with motor coordination, than healthy controls reflecting the effect of genetic factors (Rosso *et al.* 2000).

A further possibility is that delayed motor development may be a marker of other risk factors that interact with genetic risks, such as obstetric and perinatal factors. However, as the interaction between touching the thumb with the index finger and parental psychosis persisted despite adjusting for perinatal risk factors, this is unlikely to be the case.

7.2.5 Protective factors (III)

Antonovsky was the first to create the salutogenic model of health, which focused on the resources of health and promoting health in contrast to taking a pathogenic perspective. He showed that there are competing factors that drive each individual either towards health or disease (Antonovsky 1987). Those factors favouring health can be thought of as protective. Examples of protective factors include a healthy and positive family environment (Tienari *et al.* 2004, Gonzáles-Pinto *et al.* 2010), physical activity (Tao *et al.* 2007), individual social and emotional competence (Antonovsky *et al.* 1987) and resilience (Marulanda & Addington 2014).

There seems to be a lack of consensus on how to define a protective factor. It might be that there is a linear association in risk factors, where the other end of the

spectrum acts as a risk and the other as protective. There may also be factors that act directly as protective factors. Previous studies have not focused on the positive-end of environmental factors and only a few studies have focused on the distinct protective factors, therefore the discussion below is presented as a comparison of the results to risk factors.

This study was one of the very few to study protective factors and brought new information on the protective factors of psychosis in foetal life, childhood and youth and opened a new study path in the NFBC 1966. Understanding which factors confer protection is important as it can give a focus for positive psychological interventions.

Factors associating with unaffected status in the total sample

Those who remained unaffected in the total sample were more often wanted babies at the time of pregnancy and had no grand multiparity in the family, their mothers' worked outside the home or studied, family type was a two-parent family, the BMI of the cohort member was on or above the highest quartile, the grade in physical education and mean grade of non-theoretical and theoretical school grades were good, the school level was more often normal or upper compared to those who developed psychosis later and the child had more often a team sport hobby.

Previously, it has been shown that unwanted pregnancy increases the risk for schizophrenia spectrum disorders (Myhrman *et al.* 1996) and the interaction between parental psychosis and unwanted pregnancy has been found (McNeil *et al.* 2009). Not wanting the baby might reflect the socio-economical problems of the parents, or problems in the relationship between the mother and father, or problems in the psychiatric or physical health of the parents resulting in maternal distress that can cause hormonal changes in the placenta and foetus and therefore increase the risk for an offspring's psychosis (Myhrman *et al.* 1996, Herman *et al.* 2006, McNeil *et al.* 2009).

The mother's antenatal depressed mood increased the risk for schizophrenia in the NFBC 1966, even after adjusting for perinatal complications (Mäki *et al.* 2010). Grand multiparity as a risk factor for schizophrenia has been found in the NFBC 1966 earlier (Kemppainen *et al.* 2000) and also in other study samples for other severe mental disorders particularly among females (Lahti *et al.* 2014). In this study, the opposite or positive end of wantedness of the pregnancy, mother's antenatal mood and parity associated with the unaffected status in the total sample. This could relate to better mother-child bonding and family function, and better health of the

parents protecting from later psychosis since problems in these associate with later psychosis of the offspring (Helgeland & Torgersen 1997).

A study of Swedish adoptees showed that individuals adopted by single-parent households or by unemployed parents increased the risk for non-affective psychosis (Wicks *et al.* 2010). In the NFBC 1966, having a single-parent family increased the risk for other psychiatric disorder but not psychosis (Mäkikyrö *et al.* 1998). Financial problems in the family during adolescence may increase the risk for psychosis particularly (Bratlien *et al.* 2014). In this study, mother's working outside the home or studying and having two-parent family associated with the unaffected status in the total sample. The ability to work may relate to the better health of the parents and also to the better social class of the family. Having a two-parent family as a protective factor is supported by the finding that separation from either of the parents increases the risk for psychosis (Paksarian *et al.* 2015a).

Individuals with subsequent schizophrenia and other psychosis are found to be smaller at the time of birth and in childhood (between 7–15 years) also (Wahlbeck *et al.* 2001). This supports the finding that cohort members who remained unaffected had a BMI less often on or below the lowest quartile and more often on or above the highest quartile in adolescence possibly reflecting good socioeconomic status of the family. Since earlier the thinness of the child have reflected lower socioeconomic status of the family in Finland (Wahlbeck *et al.* 2001).

Good school grade in physical education and a good mean grade of theoretical and non-theoretical school subjects were associated with remaining unaffected among the cohort members. Also, the cohort members who remained unaffected were more often in the normal or even in the upper school class at the age of 14 than those who developed psychosis subsequently. Poor school performance at the age of 16 has been reported to associate with an elevated risk for psychosis (MacCabe *et al.* 2008, MacCabe *et al.* 2010) and the association remained significant after adjusting for pregnancy and birth complications, advanced parental age, parental educational level, socio-economic status, season of birth and migration (MacCabe *et al.* 2008). On the other hand, good school performance seemed to protect against schizophrenia (MacCabe *et al.* 2008), but increased the risk of bipolar disorder (MacCabe *et al.* 2010).

One study found that poor school grades, particularly in sports and handicrafts, were risk factors for schizophrenia (Cannon *et al.* 1999). This finding could relate to difficulties in motor functions found in children with subsequent schizophrenia

(Dickson *et al.* 2012). There are several abnormalities in cognitive functions, IQ, social behaviour and motor functions preceding years or even decades the onset of the psychosis (Reichenberg *et al.* 2002, Niemi *et al.* 2003, Zammit *et al.* 2004, Khandaker *et al.* 2011, Bora & Murray 2014). These findings could explain the poor school performance and also lower physical activity in individuals with subsequent psychosis and better results among those who remain unaffected.

There are findings that individuals with schizophrenia and other mental illnesses are less active physically compared to non-psychotic individuals (Daumit *et al.* 2005). The literature considering physical activity in childhood before the onset of illness is scarce. In the Northern Finland Birth Cohort 1986, those who developed psychosis subsequently were more likely to be physically inactive in childhood compared to those who remained non-psychotic (Koivukangas *et al.* 2010). Physical activity of low to moderate intensity has been found to be protective against psychotic symptoms (Tao *et al.* 2007). These previous studies support the finding that good grades in physical education and having a sport hobby were associating with the unaffected status of the cohort members. Part of the association might be explained also by better social skills, attention, memory and motivation (MacCabe *et al.* 2010), since problems in these have been associated with subsequent schizophrenia (Bora *et al.* 2014).

Factors associating with unaffected status among those with parental psychosis

Surprisingly few variables differed between unaffected and affected individuals with parental psychosis and were related to mother's antenatal non-depressed mood and mother's work outside the home or studies.

Wicks *et al.* (2010) found in the Swedish adoption study, that the risk for non-affective psychosis was higher in individuals with genetic vulnerability if they were reared in single-parent households or if the parents were unemployed. These factors relate closely to low socio-economic status, which has been found to associate with later psychosis (Wicks *et al.* 2005, Corcoran *et al.* 2009). Among those with parental psychosis, unaffected status was associated with mothers working outside the home or studying. This could relate to a better social class and also to the better health and functioning of the mother. The LCA supported this finding: mothers were working or studying outside the home, and also the family type was a two-parent family in the class with the highest amount of unaffected individuals. The mother's non-depressed mood during pregnancy also associated with the remaining

unaffected despite parental psychosis, which may also reflect the better health of the mother, better mother-child bonding and family function, the latter being found to protect from psychosis (Tienari *et al.* 2004, Gonzáles-Pinto *et al.* 2010).

The latent class analysis supported the results of mother's non-depressed mood and working outside home and also revealed that in the parental psychosis group a higher probability of the child being wanted at the time of pregnancy, having a two-parent family and having no grand multiparity in the family were associated with remaining unaffected when compared to the other class with higher proportion of affected cohort members.

7.2.6 Prevention of psychosis

The intriguing research on early intervention strategies has shown that preventive strategies are effective and indicated approach seems to be the most appropriate prevention strategy at the moment (Schultze-Lutter *et al.* 2015). For example, the risk for psychosis onset among people at clinical high-risk was reduced by 56% with the number needed to treat (NNT, i.e. number of individuals needed to treat with specific treatment in order to get one individual cured) of 10 after 12 months, 59% with the NNT of 13 in the 18 month follow-up (Schmidt *et al.* 2015) and 37% with the NNT of 12 in the 24–48 month follow-up (van der Gaag *et al.* 2012). These strategies have included low doses of antipsychotics, antidepressants, omega 3-fatty acids and psychosocial treatments (Yung *et al.* 2007, van der Gaag *et al.* 2012, Stafford *et al.* 2013, Schmidt *et al.* 2015).

Indicated preventions and early interventions are targeted at people already having observable impairments in function or incipient psychotic disorder. The transition rate from high-risk state to full-blown psychosis is relatively high, as subjects that have met the ultrahigh-risk or basic symptoms criteria had a transition rate to psychosis of 18% after 6 months, 22% after one year, 29% after two years and 36% after three years (Fusar-Poli *et al.* 2012). Practically, indicated prevention strategies can rather be considered as "early secondary prevention" than primary prevention, where the aim is to eliminate the aetiological risk factors or to strengthen an individual's resilience to the morbid risk (Häfner *et al.* 2004).

Existing impairments in function and attenuated psychotic symptoms may mark already occurring irreversible disturbances in neurobiology and the late state of developing the psychotic disorder, therefore primary prevention strategies may be more reasonable in psychosis prevention (Liu *et al.* 2015). There are already

many universal public health approaches decreasing exposure to the several environmental risk factors of many disorders including psychosis, such as influenza vaccination, folic acid and iron supplementation during pregnancy, improvements in perinatal care, efforts to reduce racial discriminations (Brown 2011a), mental health promoting and mental illness preventing programs in schools (Wells *et al.* 2003), major public health campaigns and effective community awareness campaigns (WHO 2004). However, these universal prevention strategies have not yet been very effective in psychosis prevention (Yung *et al.* 2007, Kirkbride & Jones 2011), since there is lack of sufficient aetiological knowledge of psychosis (Schultze-Lutter *et al.* 2015).

Selective primary prevention strategies for individuals at heightened risk for psychosis, for example for those with parental psychosis, may be effective, since 10% of them will go on to develop psychosis themselves (Liu *et al.* 2015). Primary prevention studies of high-risk individuals are underway and have included, e.g. targeted family-centred care, enhancing parental health, parenting skills and prenatal care for parents with psychosis (Liu *et al.* 2015). Previous meta-analysis of randomized controlled trials revealed that 40% of mental illnesses of the offspring of parents with mental disorders could be prevented with family-based or individual therapy with NNT of 17 (Siegenthaler *et al.* 2012).

Population attributable risk (or population attributable fraction) is an estimate of the magnitude of the risk. It is defined as the number or proportion of the cases of a disorder among a population that would have been prevented if the exposure to the certain environmental risk could be eliminated. Its calculation takes population prevalence and effect size of risk into account so that prevalent risk, even if with a low effect size, can be more effective than rare risk with higher risk ratio. For example, the effect size for cannabis use is modest (pooled odds ratio 1.4) but the exposure is prevalent. Therefore, PAR to cannabis use is calculated to be 14% (Moore *et al.* 2007). In other words, according to this study, 14% of individuals with psychosis could be prevented if cannabis use could be eliminated (Moore *et al.* 2007). In the NFBC 1966, the highest PAR of 33% was for late achievement of walking with a modest 1.9 Odds Ratio (OR) but high prevalence, whereas very rare perinatal brain damage had OR of 5.7 but PAR of 5% (Isohanni *et al.* 2006). According to this, it may be the most effective to focus on the most prevalent risk factors that are modifiable in the prevention of psychosis.

7.3 Theoretical discussion

The core features of all disease models of psychosis and especially schizophrenia are the same: a) none of the known risk factors are either sufficient or necessary to cause the disorder on their own and multiple events are required, b) both genes and the environment are involved and c) vulnerability arises during the foetal period of life.

According to both, two hit hypothesis and vulnerability-stress model, genetic or prenatal environmental risk factors interrupt some aspect of brain development and establish an increased vulnerability to later risk factors (Maynard *et al.* 2001). The progressive neurodevelopmental model of schizophrenia's aetiology proposes that the early impairments in brain development start already in utero, where genes and perinatal risk factors disrupt the neuronal development and the impaired developmental processes continue throughout life (Andreasen 2010). Studies have found several observable signs of impaired neurodevelopment in infancy, childhood and adolescence among those who later develop psychotic disorder (Niemi *et al.* 2003, Welham *et al.* 2008) supporting the neurodevelopmental model of schizophrenia. 50–70% of those with a family history of psychosis exhibit also impairments in neuromotor, cognitive and social functions (Liu *et al.* 2015). This study showed that motor development was slower among those with parental psychosis and particularly delayed motor milestones, which appear earliest in a child's life, increase the risk for schizophrenia among those with parental psychosis.

Later attainment of standing without support in childhood has been found to interact with cognitive decline in adulthood among those who developed schizophrenia (Kobayashi *et al.* 2014) advocating the neurodevelopmental model. However, the cognitive decline was greater among people with schizophrenia when compared to controls arguing for the neurodegenerative model of schizophrenia (Kobayashi *et al.* 2014). The progressive neurodevelopmental model links these two models together by suggesting that the onset of schizophrenia is preceded by an alteration in neurodevelopment that is affected by maturational processes in a way that is different from healthy aging (de Haan & Bakker 2004, Selemon 2004).

The genetic regulation of brain development is very complicated, with a wide number of genes regulating neuronal proliferation and differentiation, as well as signalling pathways and receptor function (Stolp *et al.* 2012). In the last trimester of gestation, functional networks and networks between brain regions develop and, through to the end of adolescence, these connections mature, i.e. myelinate,

providing the effective transfer of information (Dubois *et al.* 2014). Once the neuron has migrated to its final destination, it develops connections at both ends, having an overproduction of neuronal and synaptic processes, following apoptosis, axonal retraction and synaptic pruning. The overproduction/elimination process provides the functional network's plasticity. This synaptic pruning is dramatically sensitive to environmental factors (Huttenlocher & Bonnier 1991) and happens from the last weeks of gestation and the first two postnatal months through childhood and adolescence (Andreasen 2010). The different patterns of damage have been associated with selective sensitivities of developing cells at the time of insult (Stolp *et al.* 2012).

Schizophrenia and other psychosis are highly heritable and genes have an important role in the development of the disorder (Sullivan *et al.* 2003, Cardno & Owen 2014). The genes associated with schizophrenia are, e.g. involved in the brain's signalling pathways and neuronal synaptic plasticity (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). But genes are insufficient of causing the disorder on their own and are likely to impact mostly indirectly by increasing or decreasing the vulnerability to psychosis rather than as a direct cause of the disorder per se (Van Os *et al.* 2008).

Several perinatal risk factors have been found and many risk factors in childhood and adolescence have been revealed also. In addition to inherited genes, many of the risk factors found are more common among those with parental psychosis (Wan *et al.* 2007, Lin *et al.* 2009, Matevosyan *et al.* 2011), hence may increase the already heightened risk for an offspring's psychosis even more. This study revealed that especially biological risk factors act among those with parental psychosis to increase the risk for psychosis, but those factors were not more common among those with parental psychosis indicating that the association should not be confounded with gene-environment correlation.

Interaction between genes and environmental risk factors has been proposed and supported by many studies (Tsuang *et al.* 2004, van Os *et al.* 2008, Maric & Svrakic 2012). Genetically vulnerable people are shown to be more sensitive to environmental risk factors (Maynard *et al.* 2001, Rutter *et al.* 2001, Tsuang *et al.* 2004, Wan *et al.* 2008a, van Os *et al.* 2008) supporting the vulnerability-stress model and two hit hypothesis. This study supports the gene-environment interaction model by showing that parental psychosis had interactions with the new born's large size at birth, advanced maternal age, mother's antenatal depressed mood and mother's smoking during pregnancy, as well as with delayed fine motor skills.

Environmental risk factors may affect a child's genes leading to mutations and epigenetic alterations in gene expression subsequently affecting brain development (Dubois *et al.* 2014, Schmitt *et al.* 2014). The plausible mechanisms of several perinatal risk factors may be, e.g. hypoxia, stress altering the function of hypothalamus-pituitary-adrenal (HPA)-axis and inflammatory mechanisms.

Over half of the genes associating with schizophrenia are regulated by hypoxia (Schmidt-Kastner *et al.* 2012). Many prenatal and obstetric complications, maternal smoking during pregnancy and other adversities may cause hypoxia to foetus resulting in neuronal death, white matter damage with impaired myelination (Rees *et al.* 2008), premature synaptic pruning (Rosso *et al.* 2000, Bersani *et al.* 2007) and the expression of the risk genes for schizophrenia (Schmidt-Kastner *et al.* 2012).

Many psychosocial risk factors, e.g. social disadvantages, unwanted pregnancy and maternal depressed mood during pregnancy, could cause perinatal stress and parental psychosis could be considered also as a source of chronic stress on the developing foetus and child. Such could result in long-term neurobiological and architectural changes in the brain (Arnsten 2009), for example via oxidative stress altering the function of HPA-axis (Schiavone *et al.* 2013). Stressful experiences during the prenatal and postnatal periods may lead to subsequent dopamine dysfunction (Jahng *et al.* 2010, Huppertz-Kessler *et al.* 2012, Peña *et al.* 2014): a potential mechanism of raising the risk for later psychosis (Howes & Kapur 2009).

Also, immunological mechanisms, such as pro-inflammatory cytokine release, and the direct insult of neuronal cells by infectious agents have been proposed to be behind disrupted neurodevelopment (Potvin *et al.* 2008, Khandaker & Dantzer 2015) and altered systemic levels of immune modulating molecules are often reported in people with schizophrenia (Potvin *et al.* 2008).

Primary prevention strategies aim to reduce the exposure to those risk factors that can be modified, e.g. maternal smoking, prenatal infections and nutritional factors, as well as to strengthen the protective factors for psychosis. However, the prevention strategies targeted at the general population have not yet been very effective in psychosis prevention (Yung *et al.* 2007, Kirkbride & Jones 2011) and it might be more effective to focus especially on those with an increased risk, for example, those with a family history of psychosis or those with accumulating environmental risk factors.

Protective factors can mitigate or provide a buffer against the effects of risk factors. Only a few protective factors of psychosis have been identified, since the study field has been relatively intact to date. This study revealed several factors

relating to school performance and family indicating health and stability that were acting as protective against psychosis in the total sample.

Impairments in functioning and/or attenuated psychotic symptoms precede the full-blown psychosis by months or even years (van der Gaag *et al.* 2013). Several preventive strategies have been generated to prevent the onset of diagnostic criteria meeting psychosis (Yung *et al.* 2007, van der Gaag *et al.* 2012, Schmidt *et al.* 2015). The transition rate from clinical high-risk state to full-blown psychosis is relatively high and, at the end, the psychosis may turn out to be schizophrenia with a very individual course of illness. 73% of those developing a first psychotic episode developed a schizophrenia spectrum disorder and 11% affective psychosis (Fusar-Poli *et al.* 2013). Schizophrenia has devastating, life-long consequences on affected individuals and their families and also remarkable costs to society. It is estimated that schizophrenia causes more loss of lives than do most cancers and physical illnesses and is the costliest mental disorder in terms of human suffering and societal expenditure (van os & Kapur 2009).

Therefore, investigating the risk factors for psychosis in order to decrease their exposure, searching for protective factors and promoting preventive strategies is essential in order to lighten the burden of the disease in the individual as well as at the population level.

7.4 Strengths and limitations

Strengths

The NFBC 1966 is an unselected, general population-based birth cohort with very high coverage and reliable sources of information. The Finnish national registries cover the whole country and a unique identification number of every Finnish citizen secure the data linkages. The Finnish national registries have proven to be very reliable sources for case detection in schizophrenia (Miettunen *et al.* 2011). The Care Register for Health Care (CRCH) covers all public and private hospitals and welfare clinics in Finland. Aside from inpatient data, outpatient data was also available for 1998– 2012. Cohort members with psychosis were also detected from the registries of the Finnish Social Insurance Institute and the Finnish Centre for Pensions. Therefore, it was possible to identify also individuals with psychosis but who have not needed hospital treatment.

The data analysed in this study is collected from many sources: questionnaire data and clinical examination were also utilised along with patient record data and register data. Some of the questionnaire data, e.g. parental age and school level, could be completed with register data resulting in a very low amount of missing data regarding these variables. The missing data regarding separate variables was not dependent on parental psychosis or the subsequent psychosis of the cohort members, except regarding the postal questionnaire data at 14 years, which missed data more among those with subsequent psychosis. Those excluded from the study, i.e. those who had moved abroad or died before 16, twins and those with intellectual disability, formed only a small proportion (14.5%) of the original sample.

The exclusion of those with intellectual disability prevented their possible effect on the results of analyses regarding the risk factors during pregnancy and birth, and also analyses regarding motor development in childhood. It was possible to use several potential covariates in the analyses due to the large amount of data in the NFBC 1966.

Data collection beginning from the mid-pregnancy of the mothers and extending to offspring up to the age of 46 allowed investigation of the effects of early risk factors for psychosis with an adequate long-term follow-up in a population with the highest onset age of psychosis already passed. Prospective information of mothers' pregnancy and children´s development has been possible to collect due to the high coverage of Finnish antenatal clinics and child welfare clinics. The prospectively collected data minimises recall bias and makes it possible to study the temporal relations of risks and the onset of the illness, and directions of causality. Since this study is based on the general population, selection biases are minimised and the comparison of parental psychosis groups within the general population is possible.

Limitations

The CRCH covers events only since 1972, so there is a lack of information on hospital-treated parental psychoses at the time of, and before, childbirth. This is a limitation primarily in those cases whose parents had schizophrenia but did not need hospital treatment later, did not have disability pension because of psychosis, moved abroad or died before 1972 and were, therefore, not detected in this study. However, the information on disability pensions from the year 1964 should include most of the parents with psychosis.

All parental psychoses that were detected until year 2005 were included in this study, not only those with parental psychosis starting before or during pregnancy and birth. Because the CRCH started in 1972, the parental age of psychosis onset cannot be reliably studied in the NFBC 1966. However, since parental psychosis is considered to be an indirect measure of genetic vulnerability towards psychosis, it is not a limitation in this study. Parental psychosis can contain biological and psychosocial environmental aspects in addition to genetic effects. However, an advantage of this kind of design is the ability to model the net, albeit nonspecific, genetic load (van Os *et al.* 2008).

The detected psychosis diagnoses of the cohort members were validated until 1997 (Moilanen *et al.* 2003), while more recent (1998–2012) diagnoses and the diagnoses of parents were based on the clinical registers. The discordance rates between clinical and research diagnoses has been shown in 43% of cases, particularly among those with late-onset psychosis, marginal symptomatology, minimal contacts with treatment systems and good outcomes (Isohanni *et al.* 1997).

The number of cohort members with psychosis in the NFBC 1966 is relatively high (n=327) but the amount of those cohort members with psychosis in the parental psychosis group is very limited (n=48, 23 with schizophrenia). Therefore, some of the subgroup analyses lack statistical power, increasing the risk for type 2 errors. The lack of statistical power resulted in expanding the outcome focus to all non-organic psychoses instead of schizophrenia in Study III.

The risk factors used in this study were gathered from different sources from which all are not founded for scientific purposes. Therefore, some of the variables are proxy measures of the risk factors. It was not possible to investigate all known risk factors for psychosis in this study due to a rare variable in the cohort, e.g. infections during pregnancy and in childhood (Brown *et al.* 2004, Khandaker *et al.* 2012, Blomström *et al.* 2014, Blomström *et al.* 2015) and cannabis use (Arseneault *et al.* 2002, Zammit *et al.* 2002, Moore *et al.* 2007) or a lack of information on some of the known risk factors, e.g. communication deviance in family (Wahlberg *et al.* 2004), adverse rearing (Tienari *et al.* 2004) and adverse life events (Beards *et al.* 2013).

Information on some of the protective factors identified in earlier studies have not been collected in the NFBC 1966, e.g. family environment, relationships with friends and social support, or positive personality characteristics at childhood and adolescence (e.g. coping, sense of coherence, optimism, resilience) (Antonovsky 1987, Tienari *et al.* 2004, Gonzáles-Pinto *et al*. 2010, Marulanda & Addington 2014, Suvisaari *et al.* 2014).

All the milestones correlate to each other strongly and are therefore not independent risk factors, therefore the principal component analysis was performed to measure the motor development as a whole. Multiple analyses were performed, which may increase the possibility of type 1 errors. Therefore, further studies are needed to confirm these findings.

Some of the risk factors are based on self-reports and are not clinically assessed. For example, the mother's antenatal depressed mood may vary in gravity. However, subjectively assessed well-being has been found to relate strongly to depressiveness and has proven to predict clinically diagnosed depression (Rissanen *et al.* 2011).

The group of other psychosis is very heterogeneous and was used in this thesis as a comparison group for schizophrenia. In the future, it would be interesting to analyse the risk factors for different diagnostic groups separately, e.g. affective psychoses.

8 Conclusions

8.1 Main conclusions

The purpose of this study was to investigate whether risk factors during pregnancy, birth and childhood for schizophrenia and other psychosis are different among those with and without parental psychosis, and also to find interactions between risk factors and parental psychosis. Protective factors for psychosis were also investigated.

This study showed that many factors during pregnancy, birth and in childhood increased the risk for schizophrenia and other psychosis only among those with parental psychosis. There were also significant interactions between parental psychosis and risk factors. Hence, parental psychosis might even explain part of the association of several risk factors for schizophrenia and other psychosis. Genes, biological and psychosocial factors act in complex interplay together and this study revealed some of the biological risk factors especially associating with familial psychotic disorders. Delayed motor milestones in childhood, which associated with parental psychosis in respect of risk for schizophrenia, were those appearing early in child's life when genetic factors also play a key role in brain development. None of the milestones increased the risk for other psychosis among those with parental psychosis. It is possible that there are different aetiological mechanisms of psychoses between the groups with and without parental psychosis. Risk factors differed also between schizophrenia and other psychosis, indicating different aetiological mechanisms underlying between diagnostic groups. The mechanisms behind these associations remain undetected in this study.

This study revealed several favourable factors in prenatal, childhood and youth periods associating with the unaffected status in the total study sample. Factors associated with unaffected status among those with parental psychosis were surprisingly few and were related to the mother's non-depressed mood during pregnancy and the mother's work outside the home or studies. These factors may associate with the better health of the mother, better socioeconomic status and better mother-child bonding and on the other hand, to milder disorder or optimal treatment of the mother.

This study is one of the few examining risk factors separately among people with and without parental psychosis and investigating their interactions and novel findings regarding interactions were found. Also, the comparison of risk factors

between schizophrenia and other psychosis have not been performed commonly. This study is also one of the very few studying factors that associate with the remaining unaffected in the total sample and also among those with parental psychosis and brought new information on the protective factors for psychosis.

8.2 Clinical implications

Although the treatment and rehabilitation methods of schizophrenia have developed considerably, their effectiveness is still limited. Therefore, all measures that can prevent an individual from developing psychosis are very important. (Salokangas *et al.* 2004). The early screening of individuals with a high risk for developing schizophrenia and other psychosis and targeting interventions towards them could be effective. There are already several attempts to create reliable early screening methods for individuals who are in a high risk of developing psychosis. In order to recognize them, risk factor studies are crucial.

One approach to preventive strategies may be Bronfenbrenner's bioecological model (Bronfenbrenner 1994). According to this model, the preventive strategies could be developed into different levels of environmental systems including the child, child's family, day-care centres, schools and health organisations.

Health and wellbeing among families with a history of psychosis is important, since it has an influence on the offspring's vulnerability towards psychosis. Given that pregnancy and birth related risk factors and social adversities are more prevalent among those with parental psychosis, special monitoring and health promoting, social support and the treatment of symptoms in pregnant women with psychosis could help to reduce the risk for complications and hence protect offspring from exposure to the risk factors for psychosis. Special attention should be paid to the psychoeducation of pregnant women with psychosis to address the importance from abstaining of smoking, taking vaccinations, treating infections effectively and care for healthy nutrition during pregnancy. The effective treatment of diabetes among pregnant women could offer many beneficial results in offspring's health not only on psychosis prevention. Therefore, the antenatal clinics and children welfare clinics play a key role in the primary prevention of psychosis.

Special attention should be paid towards children with developmental delays, since developmental delays have been found to indicate heightened risk for psychosis. Day-care centres and play clubs could support the social, cognitive and motor development of children with a family history of psychosis by special health

promoting programmes. School nursing and mental health promotion programmes in day care centres and schools are also very important, since in the light of this study, and others, many factors in childhood and adolescence have an influence on psychosis risk either increasing or decreasing it.

Increasing people's knowledge of psychoses is important, so that individuals at high risk are able to seek help. By finding and strengthening the protective factors and reducing the exposure to risk factors, the onset of psychosis might be prevented or the severity of the illness might be reduced. This study revealed only a few factors that associated with the remaining unaffected despite of parental psychosis, but several regarding the total sample. By supporting, for example children's studying, physical activity and the working of the mother, there could be beneficial effects on many physical and psychiatric disorders at the population level.

8.3 Future research

The identification of environmental risk factors offers the opportunity for early detection of individuals at risk for a subsequent psychosis, which in turn may enable targeted interventions to prevent it, delay its onset or reduce its severity. Separate risk factors for schizophrenia are largely studied but risk pathways, where genes and two or more risk factors are cumulating in effect and interacting, are not studied in their full extremity, not to mention studies on the protective factors for psychosis. In addition to reducing or eliminating certain risk factors, by finding and strengthening the protective factors for psychosis, it might be possible to prevent psychosis in people at high-risk of developing psychosis. Also interactions between parental psychosis and protective factors for psychosis have not yet been studied. Interaction studies may especially be valuable in psychosis prevention, since it has been stated that the largest reduction in absolute risk for a disorder will always be obtained from interventions targeted at those exposed to both factors which interact in greater than additive model (Zammit *et al.* 2010c).

Prevention studies have concentrated on studying people at clinical high risk for psychosis and there are already promising results of early intervention. In the future, prevention studies concentrating on primary prevention targeted to those at genetic risk, with accumulating risk factors or having developmental delays in childhood, and therefore having increased risk for psychosis, are needed.

Important goals have already been accomplished in the genetic study field. However, researchers have not been able to replicate many of the found genes and the effect sizes of the risk genes have been small. One reason for these obstacles

might be that environmental factors may be necessary for the expression of susceptibility genes. Therefore, gene studies under certain environmental exposure may be needed in order to clarify the complex genetics of psychosis. Studies in this field have already been started.

This study revealed that risk factors differ among those with and without parental psychosis. Therefore, it may be important to distinguish these groups from each other and study their aetiology and outcomes separately.

The risk factors for other psychosis have not been studied as extensively as schizophrenia. Although, overlap between risk factors and genes have been established, this study revealed that the risk factors differ between schizophrenia and other psychosis possibly due to different aetiological mechanisms. In the future, it would be worthwhile to study the risk factors for other psychosis separately.

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Appendix 1

The welfare card used for recording the age (in months) of achievement of the motor milestones in the child welfare clinics.

Developmental Milestone (months)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Walking without support														
Standing without support														
Walking with support														
Standing up														
Touching the thumb with the index finger														
Sitting without support														
First tooth eruption														
Turning from back to tummy														
Gripping on object														
Holding head up														
Making sounds														

Appendix 2

A comparison between variables within parental psychosis groups and individuals with and without psychosis (Study III, Table 3).

Variable	Parental psychosis						No parental psychosis						Statistical comparisons[1]	
	Any psychosis						Any psychosis							
	Yes (A)		No (B)		Total (A+B)		Yes (C)		No (D)		Total (C+D)		A+C vs. B+D	A vs. B
	n	%	n	%	n	%	n	%	n	%	n	%	p-value	p-value
Variables considering pregnancy, birth and the first year of life														
Mother's antenatal depressed mood	47[3]		537[3]		584[3]		269[3]		9,344[3]		9,613[3]		0.19	**0.04**
Yes	15	31.9	105	19.6	120	20.5	36	13.4	1233	13.2	1269	13.2		
No	32	68.1	432	80.4	464	79.5	233	86.6	8111	86.8	8344	86.8		
Wantedness of the pregnancy	46[3]		538[3]		584[3]		268[3]		9,337[3]		9,605[3]		**0.02**	0.34
wanted at the time of pregnancy	23	50.0	308	57.2	331	56.7	159	59.3	6,048	64.8	6,207	64.6		
unwanted or mistimed	23	50.0	230	42.8	253	43.3	109	40.7	3,289	35.2	3,398	35.4		
Grand multiparity (≥6 siblings)	48[3]		544[3]		592[3]		278[3]		9,571[3]		9,849[3]		**0.04**	0.06
Yes	10	20.8	62	11.4	72	12.2	40	14.4	1108	11.6	8701	88.3		
No	38	79.2	482	88.6	520	87.8	238	85.6	8463	88.4	1148	11.7		
Mother's Body Mass Index in 1966	39[3]		491[3]		530[3]		259[3]		8,727[3]		8,986[3]		0.06	0.35[2]
<25 kg/m^2	28	71.8	394	80.2	422	79.6	207	79.9	6805	78.0	7012	78.0		
25–30 kg/m^2	9	23.1	80	16.3	89	16.8	36	13.9	1598	18.3	1634	18.2		
>30 kg/m^2	2	5.1	17	3.5	19	3.6	16	6.2	324	3.7	340	3.8		

Variable	Parental psychosis						No parental psychosis						Statistical comparisons[1]	
	Any psychosis						Any psychosis							
	Yes (A)		No (B)		Total (A+B)		Yes (C)		No (D)		Total (C+D)		A+C vs. B+D	A vs. B
	n	%	n	%	n	%	n	%	n	%	n	%	p-value	p-value
Mother has breastfed the child	18[3]		270[3]		288[3]		115[3]		4,714[3]		4,829[3]		0.63	0.77[2]
No	3	16.7	32	11.9	35	12.2	11	9.6	634	13.4	645	13.4		
1–3 months	13	72.2	206	76.3	219	76.0	88	76.5	3,436	72.9	3,524	73.0		
≥ 3 months	2	11.1	32	11.9	34	11.8	16	13.9	644	13.7	660	13.7		
Variables considering family and childhood														
Mother working outside the home in 1980	42[3]		500[3]		542[3]		241[3]		8,894[3]		9,135[3]		**0.006**	**0.005**
Yes (working full-time or part-time, or studying)	10	23.8	230	46.0	240	44.3	127	52.7	5093	57.3	5220	57.1		
No (housewife, unemployed, on sick leave, pensioned)	32	76.2	270	54.0	302	55.7	114	47.3	3801	42.7	3915	42.9		
Father working outside the home in 1980	37[3]		473[3]		510[3]		228[3]		8,421[3]		8,649[3]		0.26	0.56
No (farmer, unemployed, on sick leave, pensioned)	17	45.9	194	41.0	211	41.4	64	28.1	2248	26.7	2312	26.7		
Yes (working full-time or part-time, or studying)	20	54.1	279	59.0	299	58.6	164	71.9	6173	73.3	6337	73.3		
Social class in 1980	48[3]		546[3]		594[3]		279[3]		9,579[3]		9,858[3]		0.67	0.46
High (I–II)	9	18.8	140	25.6	149	25.1	85	30.5	2968	31.0	3053	31.0		
Low (III–IV)	31	64.6	340	62.3	371	62.5	165	59.1	5476	57.2	5641	57.2		
Other (V=farmers)	8	16.7	66	12.1	74	12.5	29	10.4	1135	11.8	1164	11.8		

Variable	Parental psychosis						No parental psychosis						Statistical comparisons[1]	
	Any psychosis						Any psychosis							
	Yes (A)		No (B)		Total (A+B)		Yes (C)		No (D)		Total (C+D)		A+C vs. B+D	A vs. B
	n	%	n	%	n	%	n	%	n	%	n	%	p-value	p-value
Moving home town in 1966–1982	47[3]		544[3]		591[3]		278[3]		9,562[3]		9,840[3]		0.67	0.27
No	41	87.2	501	92.1	542	91.7	237	85.3	8227	86.0	8464	86.0		
1–2 times	6	12.8	43	7.9	49	8.3	41	14.7	1335	14.0	1376	14.0		
Family type in 1980	48[3]		546[3]		594[3]		279[3]		9,585[3]		9,864[3]		**0.04**	0.27
Single-parent family	16	33.3	142	26.0	158	26.6	60	21.5	1744	18.2	1804	18.3		
Two-parent family	32	66.7	404	74.0	436	73.4	219	78.5	7841	81.8	8060	81.7		
Mother's somatic illness (need for hospitalisation ≥ 30 days) until 1982	48[3]		546[3]		594[3]		279[3]		9,585[3]		9,864[3]		0.23	0.24[2]
Yes	1	2.1	43	7.9	44	7.4	21	7.5	485	5.1	506	5.1		
No	47	97.9	503	92.1	550	92.6	258	92.5	9100	94.9	9358	94.9		
Father's somatic illness (need for hospitalisation ≥ 30 days) until 1982	48[3]		546[3]		594[3]		279[3]		9,585[3]		9,864[3]		0.65	0.11[2]
Yes	1	2.1	50	9.2	51	8.6	18	6.5	602	6.3	620	6.3		
No	47	97.9	496	90.8	543	91.4	261	93.5	8983	93.7	9244	93.7		
Variables considering health and habits at the age of 14														
Alcohol use	42[3]		511[3]		553[3]		242[3]		9,044[3]		9,286[3]		0.95	0.06[2]
Had never drunk alcohol	12	28.6	193	37.8	205	37.1	103	42.6	3675	40.6	3778	40.7		
Had drunk alcohol 1–2 times	26	61.9	303	59.3	329	59.5	135	55.8	5144	56.9	5279	56.8		
Occasional or regular use of alcohol	4	9.5	15	2.9	19	3.4	4	1.7	225	2.5	229	2.5		

Variable	Parental psychosis						No parental psychosis						Statistical comparisons[1]	
	Any psychosis						Any psychosis							
	Yes (A)		No (B)		Total (A+B)		Yes (C)		No (D)		Total (C+D)		A+C vs. B+D	A vs. B
	n	%	n	%	n	%	n	%	n	%	n	%	p-value	p-value
Smoking	34[3]		474[3]		508[3]		228[3]		8,485[3]		8,713[3]		0.48	0.64[2]
Had never smoked	8	23.5	143	30.2	151	29.7	81	35.5	2931	34.5	3012	34.6		
Had smoked 1–2 times	20	58.8	265	55.9	285	56.1	116	50.9	4570	53.9	4686	53.8		
Occasional or regular smoking	6	17.6	66	13.9	72	14.2	31	13.6	984	11.6	1015	11.6		
Body Mass Index	39[3]		474[3]		513[3]		230[3]		8,446[3]		8,676[3]		**0.04**	0.20
≤17.7 kg/m^2 (lowest 25th percentile)	5	12.8	122	25.7	127	24.8	75	32.6	2078	24.6	2153	24.8		
17.8–20.49 kg/m^2	23	59.0	244	51.5	267	52.0	115	50.0	4248	50.3	4363	50.3		
≥20.5 kg/m^2 (highest 25th percentile)	11	28.2	108	22.8	119	23.2	40	17.4	2120	25.1	2160	24.9		
Variables considering school performance														
School level in 1980	48[3]		546[3]		94[3]		279[3]		9,585[3]		9,864[3]		**0.03**	0.75[2]
Normal or upper class	45	93.8	515	94.3	560	94.3	262	93.9	9234	96.3	9496	96.3		
Below normal class or customised school	3	6.3	31	5.7	34	5.7	17	6.1	351	3.7	368	3.7		
Grade of physical activity	45[3]		524[3]		569[3]		270[3]		9,403[3]		9,673[3]		**0.004**	0.46[2]
4–6	4	8.9	57	10.9	61	10.7	31	11.5	704	7.5	735	7.6		
7–8	33	73.3	332	63.4	365	64.1	179	66.3	5954	63.3	6133	63.4		
9–10	8	17.8	135	25.8	143	25.1	60	22.2	2745	29.2	2805	29.0		

Variable	Parental psychosis						No parental psychosis						Statistical comparisons[1]	
	Any psychosis						Any psychosis							
	Yes (A)		No (B)		Total (A+B)		Yes (C)		No (D)		Total (C+D)		A+C vs. B+D	A vs. B
	n	%	n	%	n	%	n	%	n	%	n	%	p-value	p-value
Mean grade of non-theoretical school subjects	45[3]		526[3]		571[3]		272[3]		9,432[3]		9,704[3]		**0.01[2]**	0.63[2]
4–6	0	0.0	7	1.3	7	1.2	6	2.2	53	0.6	59	0.6		
7–8	44	97.8	484	92.0	528	92.5	248	91.2	8569	90.9	8817	90.9		
9–10	1	2.2	35	6.7	36	6.3	18	6.6	810	8.6	828	8.5		
The mean of theoretical school subjects	45[3]		526[3]		571[3]		272[3]		9,433[3]		9,705[3]		**0.01**	0.26[2]
4–6	7	15.6	66	12.5	73	12.8	48	17.6	1124	11.9	1172	12.1		
7–8	37	82.2	411	78.1	448	78.5	202	74.3	7441	78.9	7643	78.8		
9–10	1	2.2	49	9.3	50	8.8	22	8.1	868	9.2	890	9.2		
Variables considering physical activity at the age of 14														
Frequency of sport hobbies	43[3]		510[3]		553[3]		240[3]		8,929[3]		9,169[3]		0.17	0.48
At least every second day	17	39.5	203	39.8	220	39.8	83	34.6	3426	38.4	3509	38.3		
At least once a week	12	27.9	179	35.1	191	34.5	90	37.5	3383	37.9	3473	37.9		
At most once a fortnight	14	32.6	128	25.1	142	25.7	67	27.9	2120	23.7	2187	23.9		
Type of sport hobby	42[3]		491[3]		533[3]		228[3]		8,714[3]		8,942[3]		**0.05**	0.65
Does not have sport hobby	8	19.0	70	14.3	78	14.6	38	16.7	1147	13.2	1185	13.3		
Individual sport	23	54.8	299	60.9	322	60.4	144	63.2	5225	60.0	5369	60.0		
Team sport	11	26.2	122	24.8	133	25.0	46	20.2	2342	26.9	2388	26.7		

[1]P-value from Pearson's chi-square or [2]Fisher's exact test, bolded results are statistically significant. [3]Number of subjects with data on variable.

List of original publications

I Keskinen E, Miettunen J, Koivumaa-Honkanen H, Mäki P, Isohanni M & Jääskeläinen E (2013) Interaction between parental psychosis and risk factors during pregnancy and birth for schizophrenia–the Northern Finland 1966 Birth Cohort study. Schizophr Res 145(1–3): 56–62.

II Keskinen E, Marttila A, Marttila R, Jones P, Murray G, Moilanen K, Koivumaa-Honkanen H, Mäki P, Isohanni M, Jääskeläinen E & Miettunen J (2015) Interaction between parental psychosis and early motor development and risk of schizophrenia in the general population birth cohort. Eur Psychiatry 30(6): 719–727.

III Keskinen E, Marttila R, Koivumaa-Honkanen H, Moilanen K, Keinänen-Kiukaanniemi S, Timonen M, Isohanni M, McGrath J, Miettunen J & Jääskeläinen E (2015). Search for protective factors for psychosis–A population based sample with special interest in unaffected individuals with parental psychosis. Manuscript.

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

1318. Hannula, Virva (2015) The prevalence of diabetic retinopathy and its effect on social well-being and health related quality of life in children and young adults with type 1 diabetes

1319. Leppänen, Virpi (2015) Epävakaan persoonallisuuden hoitomallitutkimus Oulun mielenterveyspalveluissa

1320. Piira, Olli-Pekka (2015) Effects of emotional excitement on cardiovascular regulation

1321. Sonkajärvi, Eila (2015) The brain's electrical activity in deep anaesthesia : with special reference to EEG burst-suppression

1322. Tirkkonen, Tiina (2015) Early attachment, mental well-being and development of Finnish children at preschool age : twinship – risk or opportunity?

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