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OFFSPRING OF MOTHERS WITH PSYCHOTIC DISORDER: CHILDHOOD DEVELOPMENT AND ADULTHOOD PSYCHIATRIC MORBIDITY

Laura Niemi

Academic Dissertation

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CONTENTS

ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
DSM-IV-TR	Diagnostic and Statistical Manual of Mental disorders, Fourth Edition, Text Revision
HR	High-Risk
ICD	International Classification of Diseases
MMPI	Minnesota Multiphasic Personality Inventory
MSSS	Major Symptoms of Schizophrenia Scale
OCCPI	Operational Criteria Checklist for Psychotic Illness
OR	Odds Ratio
PDM	Pandysmaturation
RR	Relative Risk
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SD	Standard Deviation
UHR	Ultra High-Risk

1. ABSTRACT

The High-Risk (HR) method attempts to study the effects of genetic and environmental risk factors on the development of psychosis, as well as indicators of emerging psychotic disorder, by using repeated assessments through childhood and adolescence among individuals who are at increased risk for psychotic disorder, typically offspring of an affected parent(s). The Helsinki High-Risk Study follows up all women born between 1916 and 1948 who were treated for schizophrenia spectrum disorders in mental hospitals in Helsinki, and their offspring and controls. The present study forms part of the Helsinki HR Study, and follows the HR offspring born between 1960 and 1964.

The aims of this thesis were:

- to comprehensively review the findings of previous HR studies and to compare them with those obtained from cohort and family studies

- to determine the cumulative incidence of adulthood DSM-IV-TR disorders based on hospital case notes among HR offspring grouped according to maternal DSM-IV-TR diagnosis

- to determine if maternal symptomatology has an effect on offspring's morbidity from psychotic disorders

- to compare the development of HR and control children based on information obtained from childhood and school health cards, and to investigate which developmental factors predict future psychiatric disorders

- to compare childhood growth among HR and control children, and to investigate whether factors related to childhood growth predict later development of psychotic disorders.

The cumulative incidences of any psychotic disorder were 13.5, 10.0, 10.0, 4.0, and 1.1 % among offspring of mothers with schizophrenia, schizoaffective disorder, other schizophrenia spectrum disorders, affective disorders, and controls, respectively. The corresponding figures for schizophrenia were 6.7, 5.0, 6.7, 0, and 0.6 %, and for any

mental disorder 23.1, 20.0, 20.0, 12.0, and 6.9 %. In the factor analysis of maternal psychotic or affective symptomatology, a four-factor solution was found (negative, positive, catatonic, and affective symptom factors). High maternal positive symptom factor score predicted decreased morbidity from schizophrenia among HR offspring.

During childhood and adolescence, HR children had more behavioural and neurological symptoms compared to controls. Among HR offspring, social adjustment problems at pre-school age and severe neurological symptoms predicted future schizophrenia spectrum disorder. The high-risk girls were shorter and lighter at birth, while HR boys were shorter at age 10 compared with controls. Among HR children, the combination of being in the lowest tertile for ponderal index at birth but having BMI in the highest tertile at seven years predicted future schizophrenia spectrum disorder.

Several factors were associated with an increased or decreased risk for mental disorders. Maternal positive symptoms seem to be less harmful to the child than other maternal psychotic symptoms. Pre-school problems in social adjustment and severe neurological symptoms predicted future schizophrenia spectrum disorders, while school-age problems - emotional symptoms and problems in social adjustment -predicted non-psychotic psychiatric morbidity. Catch-up growth seems to be especially harmful for offspring of mothers with psychotic disorder. Whether these factors are independent risk factors, reflections of some other risk factors for psychotic disorders, or merely indicators of an ongoing process, needs further research.

2. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications.

I. Niemi, LT, Suvisaari, JM, Tuulio-Henriksson, A, Lönnqvist, JK. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. Schizophrenia Research 2003;60:239-258.

II. Niemi, LT, Suvisaari, JM, Haukka, JK, Wrede, G, Lönnqvist, JK. Cumulative incidence of mental disorders among offspring of mothers with psychotic disorder. Results from the Helsinki High-Risk Study. British Journal of Psychiatry 2004;185:11-17.

III. Niemi, LT, Suvisaari, JM, Haukka, JK, Lönnqvist, JK. Do maternal psychotic symptoms predict offspring's psychotic disorder? Findings from the Helsinki High-Risk Study. Psychiatry Research 2004;125:105-115.

IV. Niemi, LT, Suvisaari, JM, Haukka, JK, Lönnqvist, JK. Childhood predictors of future psychiatric morbidity in offspring of mother with psychotic disorder. Results from the Helsinki High-Risk Study. British Journal of Psychiatry, in press.

V. Niemi, LT, Suvisaari, JM, Haukka, JK, Lönnqvist, JK. Childhood growth and later development of psychotic disorder among Helsinki high-risk children. Schizophrenia Research, in press.

3. INTRODUCTION

Psychotic disorders are severe psychiatric disorders. They are described as conditions where there has been some loss of contact with reality and where abnormal inner experiences are mistakenly taken as real (Bogenschutz & Nurnberg, 2000). They are usually divided into disorders with predominantly affective (mood-related) symptoms or disorders without prominent affective symptoms (so called schizophrenia spectrum or nonaffective psychoses), the latter being traditionally considered the more severe. Schizophrenia, the most prevalent nonaffective psychotic disorder (Gottesman, 1994), is one of the most severe of all psychiatric disorders. It is a clinical syndrome that causes enormous personal and economic costs worldwide. In Finland, the Mini Finland Health Survey Study found a prevalence of all psychotic disorders of 2.2%, and of schizophrenia 1.3% (Lehtinen et al., 1990). Schizophrenia is the most common reason for disability pension: it is the cause of 8% of all disability pensions in Finland (ETK & KELA, 2004). Many of the individuals who develop schizophrenia are not able to return to work or school, and are usually able to manage only limited social relationships. About 10% of patients with schizophrenia commit suicide (Siris, 2001). On this basis, the World Health Organisation considers schizophrenia to be one of the ten most disabling disorders.

It seems that schizophrenia is a complex disorder, whose onset and course are influenced by both genes and environmental risk factors. One of the goals of psychiatric epidemiological research is to search for risk factors in the physical and social environment and early antecedents that are associated with the disorder. The High-Risk method is one method to study the effects of genetic and environmental risk factors and indicators of emerging schizophrenia by using repeated assessments through childhood and adolescence among individuals who are at increased risk for schizophrenia, typically offspring of an affected parent(s).

3.1. Schizophrenia

3.1.1. History of the concept ’schizophrenia’

Descriptions of psychotic symptoms have been found as early as the 15th century BC (Colp, 2000). In 100-200 AD, Greek physicians described a pathological behaviour of patients with delusions of grandeur and paranoia, and that the same patients had a deterioration in cognitive functions and personality (Colp, 2000). However, according to a recent review,

there were no descriptions of individuals that would meet DSM-IV criteria for schizophrenia in ancient Greek and Roman literature (Evans et al., 2003). In the 19th century clinical descriptions of the behaviour of patients contained many descriptive categories, but they were not divided into specific groups (Colp, 2000).

Emil Kraepelin (1856-1926) was first to suggest that major psychoses could be divided into three groups: dementia praecox, which deteriorated to dementia; manic-depressive psychosis, which did not deteriorate; and paraphrenias. Paraphrenias were characterised by delusions and hallucinations and lack of symptoms of emotion and volition. The symptoms of dementia preacox were hallucinations, delusions, incoherence of thought and speech, catatonic symptoms, disordered attention, disordered judgement, emotional dullness, avolition, and autism. However, he considered no symptom as pathognomonic for dementia preacox. He divided dementia preacox into three clinical subtypes: hebephrenic, catatonic, and paranoid. (Kraepelin et al., 1919)

Eugen Bleuler (1857-1939) introduced the name "schizophrenia" and described its symptoms. The term came into persistent use because it described the fragmentation of mental functioning characteristic of the disorder. Bleuler divided symptoms of schizophrenia into two groups: fundamental symptoms and accessory symptoms. Fundamental symptoms were present in every schizophrenia patient throughout the entire illness period, while accessory symptoms were not necessarily present throughout the whole illness period and only some patients had them (Bleuler, 1911). He considered hallucinations and delusions to be accessory symptoms. Fundamental symptoms were disturbances in association, affect and attention, and symptoms of ambivalence and autism. He suggested that a person with schizophrenia does not necessary have delusions or hallucinations, and that patients without accessory symptoms are more common in community and that they (those with "simple schizophrenia") often remain unrecognised and untreated (Bleuler, 1911). This historical distribution into broad and narrow concepts of schizophrenia still exerts an important impact on epidemiological studies.

Kurt Schneider (1887-1967) described characteristic symptoms for schizophrenia and divided them into "first rank" and "second rank symptoms". First rank symptoms were a group of hallucinations and delusions which he regarded as pathognomonic for schizophrenia (Carpenter et al., 1973). They were: audible thoughts, voices arguing or discussing, or both, commenting voices, somatic passivity experiences, thought withdrawal and other experiences of influenced thought, thought broadcasting, delusional perception, made impulses, thoughts, or volitional acts. The concept of first rank symptoms is still used in psychiatry.

3.1.2. Symptoms of schizophrenia

Schizophrenia is clinically heterogeneous. The criteria of symptomatology for the disorder have changed over time. There still are no objective, measurable criteria for assigning the diagnosis of schizophrenia, which is based on symptomatology. (Ratakonda et al., 1998)

3.1.3. Current diagnostic classifications of schizophrenia

The essential features of schizophrenia are the presence of characteristic psychotic symptoms (hallucinations, delusions, thought disorder) during the active phase of the disorder, a decline in social or occupational functioning below the level prior to the disorder, and a certain duration of the disorder. These symptoms must not be caused by organic brain disease, by alcohol or drugs, or by mood disorder. (WHO, 1993; APA, 2000)

The current diagnostic criteria according to the main diagnostic classifications DSM-IV-TR and ICD-10 are listed in Tables 1 and 2.

The principal differences between DSM-IV-TR and ICD-10 classifications are the duration of illness (in ICD-10 one month, in DSM-IV-TR six months) and premorbid deterioration. DSM-IV-TR requires deterioration from a premorbid level of functioning. The criterion for the schizoaffective and mood disorder distinction is different in ICD-10 and DSM-IV-TR: for diagnosing schizophrenia, ICD-10 requires that psychotic symptoms precede the onset of mood symptoms, while DSM-IV-TR allows affective symptoms only if the duration of those symptoms is brief relative to the total duration of active and residual symptoms. (WHO, 1993; APA, 2000)

Table 1. Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision, published in 2000

A. Characteristic symptoms: Two or more of the following, each present for a significant portion of time during a one-month period (or less if successfully treated):

1. Delusions
2. Hallucinations
3. Disorganized speech
4. Grossly disorganized or catatonic behaviour
5. Negative symptoms

Only one Criterion A symptom is required if delusions are bizarre, or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices are conversing with each other.

B. Social/occupational dysfunction: for a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations or self-care are markedly below the level achieved prior to the onset (or, when the onset is in childhood or adolescence, failure to achieve the expected level).

C. Duration: Continuous signs of the disturbance persist for at least six months, of which at least one month should be of symptoms that meet Criterion A. The six months may include periods of prodromal and residual symptoms.

D. Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms, or if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance or a general medical condition.

F. Relationship to a pervasive developmental disorder: if there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

(APA, 2000)

Table 2. International Classification of Diseases, Tenth Edition, published in 1993

I. Either at least one of the syndromes, symptoms and signs listed under 1. below, or at least two of the symptoms and signs listed under 2. should be present for most of the time during an episode of psychotic illness lasting for at least 1 month (or at some time during most of the days):

1. At least one of the following must be present:

a) Thought echo, thought insertion or withdrawal, or 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 giving a running commentary on the patient's behaviour, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body
d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible

2. Or at least two of the following:

a) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions without clear affective content, or by persistent over-valued ideas
b) Neologisms, breaks, or interpolations in the train of thought, resulting in incoherence or irrelevant speech
c) Catatonic behaviour, such as excitement, posturing, or waxy flexibility, negativism, mutism or stupor
d) "Negative" symptoms, such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses

II. Exclusion clauses:

1. If the patient also meets criteria for manic episode or depressive episode, the criteria listed under I(1.) and I(2.) above must have been met before the disturbance of mood developed

2. The disorder is not attributable to organic brain disease, or to alcohol- or drug-related intoxication, dependence or withdrawal

(WHO, 1993)

3.1.4. History of the theories of schizophrenia

Throughout history, insanity has affected and interested humankind. There have been various attempts to explain divergent behaviour.

Hippocrates of Cos (ca 460 BC-370 BC) was perhaps the first to create a theory of mental disorders. He suggested that abnormal human behaviour was caused by imbalance in four humors (blood, phlegm, yellow bile, and black bile), for example melancholia was due to excess of black bile, and that the disorders were treatable by specific diets. Plato (427 BC-347 BC) instead divided soul into three parts: rational, appetitive (lusts and greed), and affective. He suggested that insanity is either inspired by the divine, or caused by the lost of the influence of the appetitive soul on the rational soul, and that insanity could be treated with a verbal dialectic between the patient and a philosopher or physician. Plato's pupil Aristotle (384 BC-322 BC) suggested that mental disorders are caused by changes of temperature, black bile, or the emotions in the soul. (Colp, 2000)

In the middle ages, 400-1400 AD, the causes of mental disorders were thought to be evil astrological influences or demons affecting the soul. Treatment (including driving out demons with magical techniques, folk remedies and medical treatments) was applied by physicians or lay persons who were thought to have special powers. (Colp, 2000)

During the renaissance, fear of witchcraft influenced the understanding and treatment of psychiatric disorders. Women (or rarely men) who showed psychotic or hysterical symptoms were thought to be witches, and this led to the execution of many thousands. (Colp, 2000)

Nevertheless, mental disorders did not emerge as a medical condition worthy of study and treatment in common until the 18th century, when the power of rational thinking replaced older beliefs. This century gave birth to many hypotheses for mental illnesses. William Cullen (1710-1790) thought that mental disorders were caused when parts of the brain were simultaneously in unequal states of excitement and collapse, whereas Franz Joseph Gall (1758-1828) suggested that the brain can be divided into specific areas which shape the personality. During this century, most individuals with mental diseases were thought to be incurable. Philippe Pinel (1745-1826), however, stated that mental disorders were mainly caused by heredity and influences from the environment, and that most psychiatric symptoms could be relieved. (Colp, 2000)

In the early 19th century, psychiatry became a specialty apart from medicine, and most psychiatrists were guided by the principles of Philippe Pinel in their work with patients. During this century, the first drug-induced psychoses were described (Colp, 2000).

Kraepelin (1856-1926) noted at the turn of the 20th century that "dementia praecox is without doubt one of the most frequent of all forms of insanity", and that "the causes of

dementia praecox are at the present time still wrapped in impenetrable darkness" (Kraepelin et al., 1919). He also noted that the abnormal development in some cases began in early childhood, and that most individuals who developed schizophrenia had symptoms before the onset of the illness.

Sigmund Freud (1856-1939) discovered the effect of the unconscious on psychiatric symptomatology and started to use it in treating psychiatric patients (Freud, 1900; Freud, 1905). Although he created an aetiological model of schizophrenia, he did not suggest treating patients with schizophrenia with psychoanalytic techniques.

Franz Kallman (1897-1965) indicated that familiality is relevant in schizophrenia and established the first full-time genetic department in a psychiatric institution in America (Colp, 2000).

3.1.5. Current theories of schizophrenia

Twin, family and adoption studies have shown that schizophrenia is at least partly a *genetic disorder*. However, there seem not to be single genes that cause schizophrenia. The mode of transmission is complex, oligogenic or polygenic, and non-Mendelian. One possible mechanism of the effect of genes is that certain genes make an individual more vulnerable to environmental factors, and that schizophrenia develops at a critical threshold. (Gottesman & Shields, 1967; McGue & Gottesman, 1989) See also section 3.3.1.

The *viral hypothesis* of schizophrenia is not new. Already a hundred years ago there were investigators who suggested that infections are involved in schizophrenia (Colp, 2000). There are now many studies which have investigated the association between certain viruses and schizophrenia (Yolken & Torrey, 1995; Brown & Susser, 2002), especially virus exposure *in utero*. The association between virus exposure and schizophrenia appears equivocal (Brown & Susser, 2002), but virus exposure is nowadays more likely to be seen as a risk factor for schizophrenia among others, not as an independent hypothesis. The association between virus exposure and schizophrenia in described in detail in section 3.3.2.3.

The *neuroanatomical theories* of schizophrenia are based on structural findings associated with schizophrenia. The most replicated structural findings are enlargement of the lateral and third ventricle(s) (McCarley et al., 1999; Shenton et al., 2001), and reduced volume of the hippocampus or hippocampal-amygdala complex (Lawrie & Abukmeil, 1998; Wright et al., 2000; Shenton et al., 2001), which have also been found among individuals prior to their first psychosis (McCarley et al., 1999), in unaffected relatives of a patient with schizophrenia (O'Driscoll et al., 2001; Seidman et al., 2002; van Erp et al., 2002), and in young adults at high risk for developing schizophrenia (Lawrie et al., 1999; Schreiber et al., 1999; Lawrie et al., 2001). This suggests that these abnormalities are not caused by medication or untreated psychosis. The enlargement of the lateral or third ventricle (McDonald et al., 2002) and abnormalities in the superior temporal region (Rajarethinam et

al., 2004) are associated with a familial risk for schizophrenia. A history of obstetric complications seem to further increase the volume of the ventricles in subjects who are at genetic risk for schizophrenia (McDonald et al., 2002), and the amount of the reduction in temporal lobe size is greater among those with psychotic symptoms than in those without (Johnstone et al., 2002). However, individuals with ultra high-risk (UHR) for developing psychosis have been found to have smaller hippocampal volume compared to controls if they did not develop psychosis within 12 months, while larger left hippocampal volume was associated with a higher risk of psychosis within that time (Velakoulis et al., 2000). However, some brain changes observed in imaginary studies have been found to be reversible, suggesting that at least some of them could be neuroplastic adaptations to environmental factors (such as unstimulating environment, long-standing chronic disease, substance abuse, or long-term medication) (Weinberger & McClure, 2002).

The dopamine hypothesis is perhaps the most promising *biochemical hypothesis* of schizophrenia. It is based largely on the efficacy of neuroleptic medication, and suggests that patients with schizophrenia have abnormal dopamine activity (Davis et al., 1991; Abi-Dargham, 2004). Decreased levels of dopamine in the cortical regions (especially prefrontal) have been reported in patients with schizophrenia with poor prognosis and severe social impairment, while increased levels in the subcortical (especially striatal) regions have been found among patients with prominent positive psychotic symptoms (Davis et al., 1985; Davis et al., 1991; Laruelle et al., 2003; Abi-Dargham, 2004). Some studies have shown that the regions with low dopamine receptor binding are situated in the thalamic subregions, which is suggested to be the mechanism underlying positive symptoms in schizophrenia (Yasuno et al., 2004). It has been shown that individuals with schizotypal personality disorder also have temporal lobe reductions, but that they have greater frontal capacity and reduced striatal dopaminergic activity compared to individuals with schizophrenia, which might contribute to sparing individuals with schizotypal personality disorder from psychosis and severe deterioration of chronic schizophrenia (Siever & Davis, 2004). Glutamatergic neurons are the major excitatory pathways linking the cortex, limbic system, and thalamus. Postmortem studies have shown alterations in pre- and postsynaptic markers for glutamatergic neurons among patients with schizophrenia. Thus, dysfunction of glutamatergic neurotransmission may also play an important role in the pathophysiology of schizophrenia (Goff & Coyle, 2001). A study comparing 20 adolescents with a high genetic risk for schizophrenia with those without genetic risk found that the HR offspring more often had glutamate/glutamine abnormalities in the brain than controls (Tibbo et al., 2004).

The *psychoanalytic theories* still have much to contribute to overall understanding of the causes and especially pathogenesis of severe mental disorders. The clinical treatment of mental disorders is influenced by a psychoanalytically based understanding of the personality factors that contribute to the illness. The classical psychoanalytic model was initiated by Freud (Freud, 1900; Freud, 1905), who thought that individuals with psychotic disorders were not suited for psychoanalytic treatment. However, he suggested an aetiological hypothesis of schizophrenia, which stated that the precondition for

schizophrenia is the withdrawal of object cathexis (i.e. individuals with schizophrenia loose themselves from any libidinal or emotional connection to external objects or their intrapsychic representations). He originally considered schizophrenia as a regression from object love to an autoerotic stage of human development in which one does not have to deal with the frustrations and conflicts associated in interpersonal relationships. Thus, he suggested that patients with schizophrenia cannot form transference attachments to those treating them. He regarded psychosis as a conflict between the internal and the external world; reality is remodelled to conform to the patient's internal distortions. However, recent psychoanalytic papers have demonstrated that at least some schizophrenic patients do develop transference, although it is qualitatively different from that seen among neurotic patients. After Freud's time came many other psychoanalytic theories of schizophrenia. The British object relation theorist Melanie Klein (Klein, 1980), for example, described a child prone to schizophrenia who had strong sadistic and envious impulses leading to paranoid anxieties, which in turn progressed to withdrawal, splitting and projective identification. Another approach came from D.W. Winnicott (Winnicott, 1951), who actually never presented a hypothesis of schizophrenia, but from his theories it has been interpreted that schizophrenia can be seen as a failure in the development of the spontaneous and competent true self out of its relational matrix. Psychoanalytic theories are difficult to evaluate scientifically, although life events have been demonstrated to have an effect on the onset and symptomatology of schizophrenia (Lukoff et al., 1984; Norman & Malla, 1993).

In the 1980s, the hypothesis that schizophrenia is a *neurodevelopmental disorder* became popular (Murray & Lewis, 1987; Weinberger, 1987). This suggests that interaction between early pathology or insult and normal processes of structural and functional brain development makes the central nervous system prone to psychosis (McGrath et al., 2003). This hypothesis is supported by several lines of evidence (Weinberger, 1995; McGrath et al., 2003). It is based on the results of follow-up, cohort and conscript studies that have found delays or abnormalities in childhood or adolescent cognitive (Crow et al., 1995; David et al., 1997; Kremen et al., 1998; Davidson et al., 1999; Cannon et al., 2000), motor (Fish et al., 1992; Jones et al., 1994; Crow et al., 1995; Cannon et al., 1999; Walker et al., 1999; Rosso et al., 2000; van Erp et al., 2002), speech (DeLisi et al., 1991; Jones et al., 1994; Bearden et al., 2000), and/or social (Walker et al., 1993; Crow et al., 1995; Malmberg et al., 1998; Davidson et al., 1999; Bearden et al., 2000) development among children who later develop schizophrenia. The presence of minor physical anomalies (Murphy & Owen, 1996; Ismail et al., 1998) that are thought to be caused by some injury during the first or second trimester of foetal life, obstetric complications (Geddes & Lawrie, 1995; Zornberg et al., 2000; Cannon et al., 2002b), and infections or malnutrition during pregnancy (Mednick et al., 1988; Barr et al., 1990; Susser et al., 1996; Brown et al., 2000a) among children who later develop schizophrenia are seen as further support for the neurodevelopmental aspect. Neuropathological findings suggest abnormalities in brain development among patients with schizophrenia; absence of gliosis suggests, although does not prove, that they may be of foetal origin (Dwork, 1997; Heckers, 1997).

There are several more recent theories of the neurodevelopmental mechanism underlying schizophrenia. The *progressive neurodevelopmental mechanism of schizophrenia* suggests that the process begins prenatally, progresses until it reaches a critical threshold (typically in the second or third decade), and causes progressive brain volume loss at a rate that is maximal in the first two decades, slows with age, and does not cause persistent gliosis (Woods, 1998). This hypothesis is supported by results from imaging studies, which have shown that excessive brain volume loss occurs after maximum brain volume expansion, and that it continues after the onset of the illness (Woods, 1998). Another hypothesis is that schizophrenia is a *disorder of developmentally reduced synaptic connectivity* (McGlashan & Hoffman, 2000). It suggest that changes in brain structure in schizophrenia are caused by a reduction of neuritic processes rather than loss of neuronal or glial cell bodies. The reduced synaptic connectivity arises from disturbances of brain development during prenatal and adolescent periods (McGlashan & Hoffman, 2000). There is some evidence for reduced connectedness in schizophrenia from postmortem and neuroimaging studies (McGlashan & Hoffman, 2000). A *neo-Bleulerian unitary model of schizophrenia* suggests that an abnormality in the circuitry between cortical regions and the cerebellum mediated through the thalamus leads to misconnection in many aspects of mental activity (Andreasen, 1999).

There has been increased interest in the role of psychosocial factors in the development or precipitation of schizophrenia. The *stress-vulnerability model* (also known as diathesis-stress, gene-environment, developmental risk factor, or descriptive life-span model) suggests that schizophrenia is caused by an underlying psychobiological vulnerability, determined early in life by genetic and environmental effects (Mueser & McGurk, 2004). The onset and course of the disorder is then determined by the dynamic interplay of biological (e.g. medication, substance misuse) and psychosocial (stress, coping skills, social support) factors (Mueser & McGurk, 2004). In other words, according to this model, persons have different levels of sensitivity to environmental circumstances (Isohanni et al., 2000). It has been found that stress worsens the symptoms of schizophrenia, and that individuals prone to schizophrenia are hypersensitive to stress (Walker & Diforio, 1997). A clinical example could be an anxious schizotypal personality (which is probably genetically determined) who has cognitive deficits probably due to an underlying abnormality of neural networks and which lead already during childhood to increasing social isolation and academic difficulties, which then further leads to increasing isolation from friendships (that perhaps could normalize his ideas and behaviour) (Murray & Fearon, 1999). This suggests a cascade that propels a child to more and more extreme situations, and perhaps to cannabis abuse and social adversity, for example, which are possible risk factors for schizophrenia (Murray & Fearon, 1999). The stress-vulnerability hypothesis is consistent with findings on prenatal factors, and with biochemical and neuroanatomical abnormalities. It is supported by findings from the Copenhagen HR Study, for example, where obstetric complications increased the ventricle-brain ratio, especially among offspring of mothers with psychotic disorder (Cannon et al., 1993). Again, in the Finnish Adoptive Family Study, the risk for

schizophreniform thought disorder and schizophrenia spectrum disorder was highest among adoptees of parents with schizophrenia who were living in an adoption family with a dysfunctional rearing environment (communication deviance, i.e. a pattern of confusing, indirect, and unclear communication that is similar to, but milder than, overt thought disorder) (Tienari et al., 1994; Tienari et al., 2004). However, it is also possible that people with a certain genotype would select an environment that increases the risk for schizophrenia. Still, the stress-vulnerability model provides a framework for explaining some key features of the developmental course and clinical presentation (Walker & Diforio, 1997).

3.1.6. Prevalence and incidence of schizophrenia

The prevalence or prevalence rate refers to the proportion of a population who have a particular health condition at a point or period in time. A point prevalence rate is the number of cases of a disorder present at a particular point in time (for example the persons fulfilling the diagnostic criteria of major depression at a stated point in time divided by the number of persons in the community). A period prevalence rate uses the same denominator as a point prevalence rate, but expands the numerator to include all cases present during a selected time period (week(s), month(s), year, or lifetime). The period prevalence is often used in psychiatry because it allows individuals with chronic psychiatric conditions who are temporarily in remission to be included in prevalence rates. (Zahner et al., 1995)

The prevalence of schizophrenia has been assessed in several studies around the world. A recent review compared the prevalence between 18 studies and found a pooled rate of 0.55 per 100 for lifetime prevalence (Goldner et al., 2002). Prevalence variations were found across geographical regions of between two- and five-fold. The US National Comorbidity Survey, one of the largest cohort studies, found a lifetime prevalence rate of 0.15 per 100 for schizophrenia (the male/female ratio was 1.4), and 0.7 per 100 for all nonaffective psychotic disorders (Kendler et al., 1996). In Finland, the incidence for schizophrenia has found to be 1.3 per 100 in a interview-based study (Lehtinen et al., 1990), and 1.2 per 100 in a register-based study (Hovatta et al., 1997).

Incidence refers to new outcomes occurring over time among a population with candidates for such outcome. Incidence density refers to a number of outcomes occurring per unit of population per unit of time. In estimating incidence density, the population under study should exclude all individuals with the health outcome at the start of the period of observation. This candidate population is often referred to as the population at risk. Cumulative incidence is an estimate of the probability of the occurrence of an outcome over a specified period of time. It is usually used to describe the probability of outcome occurrence among a group or population. Risk is usually used to predict an individual's chance of such an event. Risk can also be expressed by its mathematical complement, the probability of surviving (survival rate). (Zahner et al., 1995)

Incidence rates are epidemiologically more informative than prevalence (Campbell & Machin, 1993), because prevalence rates are influenced by death rates and migration, and are therefore not stable.

A recent review found that the incidence density of schizophrenia from studies around the world varied between 7.7 and 43 per 100 000 person years. Older studies reported higher rates. The rates were higher among males than females (the male/female ratio was 1.4) and among migrants compared to native-born persons (the migrant/native ratio was 4.6). (McGrath et al., 2004b)

In Finland, the incidence density of schizophrenia and schizophreniform disorder has been found to be 36 per 100 000 person years (Salokangas, 1993), which is in the range of broadly defined schizophrenia in the WHO Ten Country Study (Jablensky et al., 1992). A study based on the Finnish Hospital Discharge Register found that the incidence density of all nonaffective psychotic disorders was 69 per 100 000 person years (Korkeila et al., 1998). The incidence of schizophrenia has declined among individuals born between 1954 and 1965, which may suggest that the intensity or frequency of some risk factors has decreased (Suvisaari et al., 1999b).

3.2. Methods to studying the effects of environmental and genetic factors associated with schizophrenia

3.2.1. Family studies

It has long been known that psychotic disorders run in families. Family studies traditionally calculate the morbid risk for a disorder among relatives of a proband with the disorder. The risk is usually calculated separately for parents, siblings and offspring, since the expected genetic covariance between parents and offspring differs from that between siblings. The morbid risk for the disorder is compared to that of control probands or the general population. Several family studies have found that relatives of probands with schizophrenia have an increased risk for schizophrenia, and that the risk decreases from close to distant relatives (Gottesman, 1994). The risk for schizophrenia among first degree relatives of an individual with schizophrenia is approximately 10% (Kendler & Diehl, 1993), and the risk for other schizophrenia spectrum disorders is also increased (Kendler & Diehl, 1993). The most recent epidemiological family study found a morbid risk of 6.5 for schizophrenia, 6.7 for schizoaffective disorder, 6.9 for schizotypal personality disorder, 5.1 for other nonaffective psychosis, 2.8 for psychotic affective illness, and 0.6 for nonpsychotic affective illness among first-degree relatives of probands with schizophrenia (Kendler et al., 1993a). The risk of schizophrenia was also higher among relatives of probands with psychotic affective illness. Among relatives, the risk of schizophrenia was significantly higher in siblings than in parents (Kendler et al., 1993a).

3.2.2. Adoption studies

There are three types of adoption studies: *a) adoptee studies* (Tienari et al., 2004), where the biological parent of an adoptee is the proband. Parents have the diagnosis of schizophrenia and have had a child adopted away soon after birth. The risk of schizophrenia is compared between adoptees whose biological parent(s) has schizophrenia and adoptees whose biological parent(s) does not have schizophrenia; *b) adoptee's family studies* (Kety et al., 1994; Cardno et al., 2002), where the adoptee is a proband. The adoptee has the diagnosis of schizophrenia, and the risk for schizophrenia is compared in their biological parents, their adoptive parents, and in the biological and adoptive parents of unaffected control adoptees; *c) cross-fostering design studies* (Gottesmann & Shields, 1982), where the risk for schizophrenia is compared between adoptees with unaffected adoptive parents but affected biological parents and adoptees with affected adoptive parent(s) but unaffected biological parents.

Adoptee studies can be regarded as part of HR studies. However, the adoptees are not exposed to the same environmental risk factors as HR offspring, and therefore the two study methods are kept separately.

Several adoption studies have shown a higher rate (about 4 to 9-fold) of schizophrenia among biological relatives of probands than controls (Tienari et al., 2000; Owen et al., 2002; Tienari et al., 2003). A gene-environment interaction has also been found in the Finnish Adoption Study; offspring who had a biological risk for schizophrenia also had the highest risk for schizophrenia (Tienari et al., 2004) or for schizophreniform thought disorder (Tienari et al., 1994) if their adoptive family had a communication deviance. Thought disorder predicted later development of schizophrenia in both low and high-risk groups (Metsanen et al., 2004). The relatives of an adoptee with schizophrenia also had more frequent other schizophrenia spectrum psychotic disorders and schizotypal personality disorder (Kendler et al., 1994a; Tienari & Wynne, 1994; Tienari et al., 2003).

3.2.3. Twin studies

The twin study method is feasible for comparing the effects of genetic and environmental risk factors for disorders. Monozygotic twins have almost identical genomes, and dizygotic twins share approximately half of their genes. In straightforward terms, if environmental factors were to entirely explain the familiar clustering, there would be no differences in the concordances (i.e. the proportion of twin pairs who are similarly affected) between monozygotic and dizygotic twins. Conversely, if genetic factors were to entirely explain the familiar clustering, there would be 100% concordance among monozygotic twins and 50% concordance among dizygotic twins. In the twin study design, monozygotic and dizygotic twins are proposed to share environmental risk factors to the same degree. However, monozygotic twins may share the environmental risk factors to a larger degree, because they tend to socialise together more and their parents tend to emphasise their

similarities more (Kendler & Gardner, 1998). Further, about 65% of monozygotic twins share the same chorion, while dizygotic twins always have two chorions. Sharing the same chorion could make the monozygotic twins either more or less similar (Martin et al., 1997). Sharing the same chorion could make the environment more similar, because the foetuses share the same blood supply and are therefore equally likely to be exposed to viral infections, for example. On the other hand, sharing the same chorion can lead to competition for nutrition and thereby to different growth rates. The concordance rate of schizophrenia for monozygotic twins in some studies has been approximately 40-46%, while the comparable rate for dizygotic twins has been about 5-10% (Cannon et al., 1998; Cardno et al., 1999; Sullivan et al., 2003). However, heritability estimates of schizophrenia from twin studies are as high as 83% (Cannon et al., 1998; Cardno et al., 1999). The results of twin studies suggest that genetic factors are important risk factors for schizophrenia, but that environmental factors also play a role in its aetiology.

3.2.4 High-Risk studies

As the morbidity from schizophrenia in the general population is quite low, a study method has been developed to enrich the sample with individuals who are more likely to later develop schizophrenia. This method is called the High-Risk (HR) method.

High-Risk (HR) research refers to a method of studying genetic and environmental risk factors and their interaction in the aetiology of schizophrenia and its early antecedents by investigating individuals who have an increased risk for developing it (Cornblatt & Obuchowski, 1997). HR studies of schizophrenia have typically followed up offspring of an affected parent(s), because the risk of developing schizophrenia among such individuals is approximately 10%, increasing to almost 50% if both parents are affected, compared to a 1% risk in the general population (Gottesman, 1994). In essence, the approximate contribution of genetic or other family related risk can be studied by comparing HR offspring with control children, and the approximate contribution of environmental factors by comparing HR offspring who develop schizophrenia with those who remain unaffected. Indicators of emerging schizophrenia can be studied by repeated examinations through childhood and adolescence, and then in adulthood by comparing offspring who developed schizophrenia with those who did not. The HR method is suitable for studying such indicators, for example neuropsychological deficits, because the functioning of persons who already have schizophrenia may simply reflect epiphenomena related to the disorder (Mednick & McNeil, 1968).

HR research for schizophrenia started in the 1920s with small studies of children of psychiatrically ill mothers. The New York Infant Study, begun in 1952, was the first to add longitudinal follow-up to the study design (Fish et al., 1992). Since then there have been several long-term HR studies. Recently, the concept of Ultra High-Risk (UHR) studies has been emerged, whereby the high-risk status is based on clinical risk estimation. The criteria for UHR individuals differ between studies, but the risk is generally defined as having a genetic risk and some prodromal symptoms of schizophrenia.

The advantage of the HR method is that the information is prospectively collected and can be quite detailed (Cornblatt & Obuchowski, 1997). When adulthood psychiatric morbidity and its determinants among HR children are investigated, an ideal control group exists already: those HR children who remained unaffected. These benefits of HR research outweigh the disadvantages of the method, the most important of these being that HR children who develop schizophrenia represent a highly familial form of schizophrenia, and the findings may not be generalizable to less familial forms of the disorder.

3.2.4.1 General characteristics of High-Risk studies

In this chapter, the most important HR studies are introduced. Studies which have included 20 or fewer schizophrenia HR offspring are not reported here, with the exception of the first genuine HR study, the New York Infant Study. Only studies with longitudinal follow-ups have been included here.

The following 14 HR studies were included here: the New York Infant Study, the HR Studies of the National Collaborative Perinatal Project (NCPP), the Copenhagen HR Study, the St. Louis Risk Research Project, the Minnesota HR Study, the Israeli HR Study, the Rochester Longitudinal Study, the New York HR Study, the Stony Brook HR Study, the University of Rochester Child and Family Study, the Jerusalem Infant Development Study, the Swedish HR Study, the Emory University Project, and the Edinburgh HR Study. Table 3 summarizes their general characteristics (and additionally the Helsinki HR Study). There may be small inaccuracies concerning sample sizes, birth years and ages at follow-ups, because there was some variation in these between different publications from the same study. The reported sample size in the Minnesota HR Study includes only the first phase of the study conducted by Rolf during 1968-69, because the sample size of the subsequent study by Marcus (conducted in 1972) was not available (Garmezy et al., 1984). The reported sample sizes in the New York HR Study and the Jerusalem Infant Development Study include siblings who were recruited into the studies later.

Table 3. General characteristics of HR studies for schizophrenia

Study	Start year	Location	Inclusion criteria	Offspring's year of birth	Sample size	Follow-ups (age)
The New York Infant Study (Fish, 1987)	1952	New York, NY, USA	Mother DSM-I sch	1952-53, 1959-60	HR=12 C=12	0, 9-10, 15-16, 18-19, 20-21, 27-34 years
The Boston NCPP HR Study (Rieder et al., 1977)	1959	Boston, MA, USA	Parent sch (criteria described in (Rieder et al., 1975))	1959-66	HR=93, C=*	0, 4, 8 months, 1, 4, 7 years
The Boston and Providence NCPP HR Study (Goldstein et al., 2000)	1959	Boston, MA, USA; Providence, RI USA	Parent DSM-IV sch or aff	1959-66	HRsch=118, HRaff=126, C=165	0, 4, 8 months, 1, 4, 7 years
The Copenhagen HR Study (Mednick et al., 1987)	1962	Denmark	Mother sch (project criteria, later DSM III)	1942-52	HR=207 C=104	10-20, 15-25, 20-30, 28-38, 34-48 years
The Israeli HR Study (Marcus et al., 1987; Mirsky et al., 1995a)	1964	Israel	Parent sch (hospital records, later DSM-III-R)	1952-59	HR=50 C=50	8-15, 14-21, 23-30, 31-40 years
St. Louis Risk Research Project (Worland et al., 1984)	1966	St. Louis, MO USA	Parent DSM-II sch or aff	1955-61	HRsch=100 HRaff=60 C=130 Cphys=78	7, 10, 13, 16, 19, 22, >25years
The Minnesota HR Study (Rolf, 1972; Garmezy et al., 1984)	1968	Minnesota, MN, USA	Mother DSM-II sch (case records, later project criteria described in (Nuechterlein, 1984))	1952-59	HRsch=28 Csch=56 HRint=26 Cint(HR)=52 Int=27 Cint=54 Ext=26 Cext=52	13-23 years
The Rochester Longitudinal Study (Sameroff et al., 1984; Sameroff et al., 1987)	1970	Rochester, NY, USA	Mother DSM-II sch, de, or pd	1970-73	HRsch=29 HRde=58 HRpd=40 C=57	0, 4 months, 1, 2.5, 4 years

Study	Start year	Location	Inclusion criteria	Offspring's year of birth	Sample size	Follow-ups (age)
The New York HR Study (Erlenmeyer-Kimling & Cornblatt, 1987; Erlenmeyer-Kimling et al., 1997; Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling et al., 2000)	A: 1971 B: 1977	NY, USA	A: Parent sch or aff (DSM II, later RDC) B: Parent RDC sch or aff	A:1959-65 B:1965-72	A:HRsch=84 HRaff=67 C=136 B:HRsch=46 HRaff=39 C=65	6 assessments, first 9 years, latest 30 years
The Stony Brook HR Project (Weintraub & Neale, 1984; Weintraub, 1987)	1971	Stony Brook, NY, USA	Parent sch, bd, or mdd (DSM-II, later DSM III)	1956-64	HRsch=80 HRmdd=154 HRbp=134 C=176	7-15, 10-18, >18 years
The University of Rochester Child and Family Study (Wynne et al., 1987)	1972	Rochester, NY, USA	Parent sch, aff, op, or other (DSM-II, later DSM III)	1963-72	HRsch=20 HRaff=38 HRop=10 other=77	4, 7, 10, 13 years
The Jerusalem Infant Development Study (Marcus et al., 1981; Marcus et al., 1993)	1973	Israel	Parent sch, pd, neu or affective disorder (DSM-II, later RDC)	1973-77	HRsch=29 other=30 C=27	0, 3, 14 days, 4, 8, 12 months, 7-14, 14-21 years
The Swedish HR Study (McNeil et al., 1987)	1973	Southwest Sweden	Mother RDC psychosis	1973-77	HRsch=23 HRaff=22 HRop=8 HRschaff=11 C=103	0, 3 days, 3, 6 weeks, 3.5, 6 months, 1, 2, 6 years
The Helsinki HR Study (Wrede et al., 1980)	1974	Helsinki, Finland	Mother ICD-8 sch	1960-64	HRsch=204 C=204	15 years
The Emory University Project (Goodman, 1987; Goodman & Emory, 1992)	1981	Atlanta, GA, USA	Mother DSM-III sch, mdd	1976-81	HRsch=61 HRmdd=33 C=33	0-5, 1-6, 2-7, studied 3 times one year apart
The Edinburgh HR Study (Hodges et al., 1999; Lawrie et al., 1999; Johnstone et al., 2000)	1994	Scotland	2 or more first or second degree relatives sch (DSM III-R)	1969-	HRsch=162 C=36	16-25, follow-ups at 18-month intervals for 5 years

Key: aff affective psychosis, bd bipolar disorder, C control group, de depression, ext externalizer, HR high risk group, int internalizer, mdd major depressive disorder, mo mother, neu neuroses, op other psychosis, other other mental disorder, pd personality disorder, phys physical problem, sch schizophrenia, schaff schizoaffective disorder, * cohort study

The Rochester Longitudinal Study, the Jerusalem Infant Development Study and the Swedish HR Study began when the mothers were pregnant. Data collection in both NCPP HR studies also began when the mothers were pregnant, although the follow-ups as HR studies began only later. All the other studies began when the offspring were children or adolescents. The offspring have been followed-up until adulthood only in the New York Infant Study, the Copenhagen HR Study, the Israeli HR Study, the New York HR Study, and the Swedish HR Study. The first reports from the ongoing follow-up of the Edinburgh HR Study have also been published (Johnstone et al., 2000; Miller et al., 2002b; Miller et al., 2002c; Byrne et al., 2003).

The New York Infant Study (Fish et al., 1992) was the first HR Study. It was initiated in 1952 to test the pandysmaturation hypothesis, which postulated that the inherited part in schizophrenia was a neurointegrative defect. Although the children underwent a comprehensive and systematic examination, the sample size was small, only 12 HR children and 12 controls (Fish, 1987).

The Copenhagen HR Study (Mednick & Schulsinger, 1968; Carter et al., 1999), the first statistically notable HR study, has a special focus on psychophysiological measurements and brain imaging, although it has also collected a wealth of obstetric and developmental data. Besides having one of the largest study samples, it also has the longest follow-up time. The National Collaborative Perinatal Project has collected information on pregnancy, delivery, and neonatal period, and assessed children's mental, motor, sensory and physical development at several points during the first seven years of life (Goldstein et al., 2000). The Boston NCPP HR Study initially consisted of offspring of parents with schizophrenia from the Boston NCPP sample (Rieder et al., 1977). The Boston and Providence NCPP HR Study extended the Boston NCPP HR Study sample to include offspring of parents with DSM-IV psychotic disorder from both sites, and is currently conducting a follow-up study on the sample (Goldstein et al., 2000).

Both the New York and Israeli HR Studies have concentrated primarily on neuropsychological assessments, the main emphasis in the former being attention dysfunction (Erlenmeyer-Kimling & Cornblatt, 1992), and in the latter attention deficit disorder-like neurointegrative deficits in HR offspring (Marcus et al., 1987). The third study with the primary focus on assessing attention functioning was the Minnesota HR Study (Garmezy et al., 1984), which chose four high-risk groups: children having a mother with schizophrenia, children having a mother with psychopathology manifesting as internalizing symptoms, and children without genetic predisposition but considered vulnerable because of internalizing or externalizing behaviour pathology (Rolf, 1972). The Israeli HR Study has also studied the influence of the rearing environment: half of the index and control-children were raised on a kibbutz and the other half with their biological parents. The Stony Brook HR Project emphasised investigation of the family environment (Weintraub, 1987).

The St. Louis Risk Research Project was more psychodynamically oriented than the others and also included offspring of parents with severe physical disorders (Worland et al., 1984). The University of Rochester Child and Family Study concentrated on developmental relationships, parental and child's psychopathology and health, and family system functioning (Wynne et al., 1987). The focus of the Swedish HR Study (McNeil et al., 1983) has been on intensive assessment of pre- and perinatal complications and early childhood development, which have also been the main interest in the Jerusalem Infant Development Study (Marcus et al., 1981). The Emory University Project assessed neuropsychiatric, social and intellectual functioning of preschool-aged HR children (Goodman, 1987). The Edinburgh HR Study (Hodges et al., 1999) is the most recent HR study to begin, and uses a slightly different methodology from the others mentioned. The HR group, aged between 16 and 25 years at entry, has at least two first- or second-degree relatives suffering from schizophrenia. The individuals are being followed up for five years, and are regularly monitored by neuropsychological assessment and magnetic resonance imaging (Hodges et al., 1999).

3.2.4.2. Differences between high-risk and control children in HR studies

The findings of HR children in childhood and adolescence are presented in Table 4.

Children at high risk for schizophrenia have more developmental problems than controls. They have abnormalities in neurological and motor development from infancy on, which continue through school age and adolescence. Most HR studies that have addressed this issue have found that schizophrenia HR children have more problems in neurological and motor development than controls (Rieder & Nicholas, 1979; Fish, 1984; Marcus et al., 1985; Marcus et al., 1987; Marcus et al., 1993; McNeil et al., 1993a; McNeil et al., 1993b; Hans et al., 1999; Rund & Borg, 1999; Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling et al., 2000). The Swedish HR Study found more neurological deviations among schizophrenia HR offspring than among controls already in the third to fourth day of life (Blennow & McNeil, 1991). However, these abnormalities found during infancy seem not to persist until adulthood, while neurological abnormalities during school-age were predictive of the presence of neurological soft signs in adulthood (Schubert & McNeil, 2004). Nevertheless, the Emory University Project failed to find any relationship between mother's diagnosis and the presence of neurological signs in her offspring (Goodman, 1987).

Table 4. Findings of HR children in childhood and adolescence

Age (years)	Neuromotor development	Cognitive functioning	Behaviour and social adjustment	Psychiatric symptoms
0-2	• pandysmaturation (NYIS) (Fish et al., 1992) • passivity (CHR, NYIS) (Parnas et al., 1982; Fish, 1987) • poorer psychomotor development during 1st year (RLS, JIDS) (Marcus et al., 1981; Sameroff et al., 1984) • neuromotor deviations neonatally (SHR) (McNeil et al., 1993b)	• low IQ (EUP) (Goodman, 1987) • abnormal use of language (SHR) (Walker & Aylward, 1984)	• absence of fear of strangers (SHR) (Näslund et al., 1984a) • low communicative competence (EUP) (Goodman, 1987) • quietness (NYIS)(Fish, 1987) • lower reactivity to the examiner (RLS) (Sameroff et al., 1984)	
2-7	• neurological deviation, e.g. clumsiness, poor coordination, choreatic involuntary movements, poor balance, difficulty in crossing the body midline (SHR, BNCPP) (Rieder et al., 1979; McNeil et al., 1993b)	• low IQ (BNCPP, BPNCPP) (Rieder et al., 1979)	• less expression of affection, anxiety, and hostility (EUP) (Goodman, 1987) • isolation and loneliness (BNCPP, RLS) (Rieder & Nicholas, 1979; Sameroff et al., 1984) • disturbed behaviour (NYIS, EUP) (Fish, 1987; Goodman, 1987)	• depressivity (RLS) (Sameroff et al., 1984), hyperactivity (BNCPP) (Rieder & Nicholas, 1979) • immaturation (BNCPP) (Rieder & Nicholas, 1979) • increased activity, impulsivity, distractibility, and emotional lability (BNCPP) (Rieder & Nicholas, 1979)
8-12	• poor coordination, balance, and motor overflow (IHR) (Marcus et al., 1985) • poor neurobehavioural functioning (JIDS) (Marcus et al., 1993; (Hans et al., 1999) • dyslexia, poor neurological maturation (NYIS) (Fish, 1987) • poorer gross motor skills (NYHR) (Erlenmeyer-Kimling et al., 2000)	• lower IQ (CHR, IHR, NYHR, SB) (Mednick & Schulsinger, 1968; Neale et al., 1984; Sohlberg & Yaniv, 1985; Mednick et al., 1987; Dworkin et al., 1993) • attention dysfunction (NYHR, SB, MHR) (Garmezy et al., 1984; Weintraub, 1987; Erlenmeyer-Kimling & Cornblatt, 1992; Erlenmeyer-Kimling et al., 2000) • poor concentration (IHR) (Lifshitz et al., 1985; Sohlberg, 1985) • formal thought disorder (SB, NYHR) (Weintraub, 1987; Bolinskey et al., 2001) • poorer memory (NYHR) (Erlenmeyer-Kimling et al.,2000)	• disturbing and aggressive school behaviour (CHR, SB) (Mednick & Schulsinger, 1968; Weintraub et al., 1984) • lower cognitive and social competence in school (SB, IHR) (Marcus et al., 1987; Weintraube & Neale, 1984) • problems in interpersonal relations, social isolation (IHS, NYIS, EHR, MHR) (Garmezy et al., 1984; Nagler & Glueck 1985; Fish, 1987; Hodges et al., 1999; Johnstone et al., 2000) • low self-esteem (IHS) (Nagler & Glueck 1985) • early offending behaviour (EHR) (Hodges et al., 1999) (Johnstone et al., 2000) • poor affective control (NYIS, IHS) (Nagler & Glueck 1985; Fish, 1987)	• more psychopathology (StL) (Worland et al., 1979; Worland et al., 1984) • more clinical involvement (e.g. need for residential treatment, special school for emotional problems, externalizing and/or internalizing) (SB) (Weintraub, 1987) • tendency to anhedonia or euphoria, depression, and aggression (IHR) (Nagler & Glueck, 1985)

Age (years)	Neuromotor development	Cognitive functioning	Behaviour and social adjustment	Psychiatric symptoms
13-19	• poorer coordination and balance, lower perceptual-motor and visual motor functioning (IHR) (Lifshitz et al., 1985; Marcus et al.,1985; Sohlberg, 1985) • poorer neurobehavioural functioning (JIDS) (Hans et al., 1999)	• low IQ (CHR, SB, EHR) (Mednick & Schulsinger, 1968; Neale et al., 1984; Weintraub et al., 1984; Weintraub, 1987; Byrne et al., 1999) • greater decrease in IQ scores between 7 and 16 years of age (StL) (Worland et al., 1982) • worse in arithmetic tests and spelling (IHR) (Ayalon & Merom, 1985; Lifshitz et al., 1985; Sohlberg & Yaniv, 1985) • evidence of formal thought disorder (CHR, SB) (Weintraub, 1987) • attention dysfunction (NYHR, SB, IHR) (Lifshitz et al., 1985; Sohlberg, 1985; Weintraub, 1987; Erlenmeyer-Kimling & Cornblatt, 1992) • poor executive functioning (EHR) (Byrne et al., 1999) • neuropsychological differences in many areas (EHR) (Byrne et al., 2003) • deficient ability to ignore irrelevant input (SB) (Weintraub, 1987) • problems in learning and memory (EHR) (Byrne et al., 1999)	• disturbed (aggressive or withdrawn) behaviour (SB, CHR, IHR) (Mednick & Schulsinger 1968; Weintraub et al., 1984; Nagler & Glueck, 1985; Marcus et al., 1987) • poor peer relations (IHR) (Ayalon & Merom, 1985) • problems in school adjustment (IHR, StL) (James & Worland, 1983; Ayalon & Merom, 1985) • poor social competence (SB, NYHR) (Weintraub et al., 1984; Dworkin et al., 1993)	• greater affective flattening, reduced smiling (NYHR) (Dworkin et al., 1993) • more anxious (IHR) (Kugelmass et al., 1995) • more clinical involvement (e.g. need for residential treatment, special school for emotional problems, externalizing and/or internalizing) (SB) (Weintraub, 1987) • poorly adjusted (CHR) (Mednick & Schulsinger, 1968)

BNCPP Boston NCPP HR Study, BPNCPP Boston and Providence NCPP Study, BSID Bayley Scales of Infant Development (Bayley, 1969), CHR Copenhagen HR Study, EHR Edinburgh HR Study, EUP Emory University Project, HHR Helsinki HR Study, IHR Israel HR Study, JIDS Jerusalem Infant Development Study, MHR Minnesota HR Study, NYHR New York HR Study, NYIS New York Infant Study, RLS Rochester Longitudinal Study, SB Stony Brook HR Study, SHR Swedish HR Study, StL St. Louis Risk Research Project

Several (Mednick & Schulsinger, 1968; Rieder et al., 1977; Neale et al., 1984; Goodman, 1987; Dworkin et al., 1993; Byrne et al., 1999; Goldstein et al., 2000) HR studies, although not all (Klein & Salzman, 1984; Sameroff et al., 1984; Worland et al., 1984; Sohlberg & Yaniv, 1985; Sameroff et al., 1987), found a lower IQ among schizophrenia HR children than controls. In some studies, the difference between HR and control children diminished with age (Goodman, 1987; Dworkin et al., 1993), while the opposite trend was found in the St. Louis Risk Research Project (Worland et al., 1982). The Edinburgh HR Study found differences in many areas of neuropsychological functioning among both HR offspring who later developed schizophrenia and those who did not, suggesting that the disorder itself is not inherited but rather a state of vulnerability which is manifested by neuropsychological impairment (Byrne et al., 2003). However, the Rochester Longitudinal Study (Sameroff et al., 1993) found in the early childhood assessments that low social status and severity of maternal illness were stronger predictors of low IQ than specific maternal diagnosis (Sameroff et al., 1993).

Several HR studies have investigated positive formal thought disorder-like symptoms. HR children in the Copenhagen HR Study tended to give more idiosyncratic and fragmented associations in the single-word association test (Mednick & Schulsinger, 1968). Children of the Stony Brook HR Study were found to have cognitive slippage, i.e. poor control of thoughts and verbal expression, at school-age and adolescence (Weintraub, 1987). The New York HR Study assessed the occurrence of thought disorder among HR children retrospectively from videotaped interviews conducted at age nine, and found that positive thought disorder could be observed already at that age and was predictive of adulthood schizophrenia spectrum disorders (Ott et al., 2001). Other abnormalities in cognitive functioning among HR children include poor concentration (Lifshitz et al., 1985; Sohlberg, 1985), decreased ability to ignore irrelevant input (Weintraub, 1987), poor performance in mathematics and spelling (Ayalon & Merom, 1985), poor executive function, poor mental coding/encoding and learning, and poor memory (Byrne et al., 1999). The most consistently found neurocognitive deficit among schizophrenia HR children was attention deficit (Garmezy et al., 1984; Lifshitz et al., 1985; Sohlberg & Yaniv, 1985; Weintraub, 1987; Erlenmeyer-Kimling & Cornblatt, 1992).

The Rochester Longitudinal Study (Sameroff et al., 1984) investigated social adjustment during the first four years, and found more abnormalities in social adjustment among offspring of mothers with depressive disorder than among schizophrenia HR offspring (Sameroff et al., 1984). Severity and chronicity of maternal illness and low social status were more powerful predictors of poor social adjustment than maternal diagnosis (Sameroff et al., 1984; Sameroff et al., 1987). Several HR studies have found more problems in social adjustment among school-aged (Nagler & Glueck, 1985; Hodges et al., 1999; Johnstone et al., 2000) and adolescent HR offspring (Rolf, 1972; James & Worland, 1983; Ayalon & Merom, 1985; Nagler & Glueck, 1985; Marcus et al., 1987; Dworkin et al., 1993; Hodges et al., 1999; Johnstone et al., 2000). Teachers (James & Worland, 1983; Worland et al., 1984;

Olin et al., 1995) or peers (Ayalon & Merom, 1985) rated them as being more aggressive, disruptive or withdrawn, or having poorer concentration and less participation in class (Ayalon & Merom, 1985), and as being susceptible to future emotional or psychotic problems (Olin et al., 1995). They also had problems in peer relations as judged by both teachers (Rolf, 1972; Ayalon & Merom, 1985) and peers themselves (Rolf, 1972; Garmezy et al., 1984; Worland et al., 1984; Ayalon & Merom, 1985). At the outset of the Copenhagen HR Study (Mednick & Schulsinger, 1968), children already mentally ill at the initial assessment were excluded. However, the psychiatric interview rated 24% of the HR children as poorly or relatively poorly adjusted, as opposed to only 1% of the low risk children (Mednick & Schulsinger, 1968). Several other HR studies also found more non-specific psychopathology among HR offspring at their initial assessment (Worland et al., 1984; Weintraub, 1987; Kugelmass et al., 1995).

The mother-infant interaction has been found to be different in HR families in some of the HR studies. The Rochester Longitudinal Study found that when the children were four months of age, both depressed mothers and those with schizophrenia were less spontaneous and less in proximity to their children than controls, but the effect of maternal diagnosis had disappeared by the 12-month assessment. However, the severity and chronicity of maternal disorder were associated with problems in the mother-infant interaction at both assessments (Sameroff et al., 1984). In the Emory University Project, mothers with schizophrenia showed less affectional involvement and responsiveness to their children than control mothers, and this was significantly associated with the child's IQ (Goodman & Brumley, 1990). The child rearing environment of mothers with schizophrenia was significantly poorer, while mother's education or severity of illness had no effect (Goodman & Brumley, 1990). The mother-infant interaction was evaluated regularly during the first two years of the Swedish HR Study (Persson-Blennow et al., 1988). Interaction was consistently more negative among the schizophrenia HR group than controls (McNeil et al., 1985; Näslund et al., 1985; Persson-Blennow et al., 1986), and anxious attachment at one year of age was more common among schizophrenia HR children (Näslund et al., 1984b). Compared with controls, schizophrenia HR offspring also more often showed a total absence of fear of strangers during the first year of life (Näslund et al., 1984b). Mental disturbance at six years, measured by the Children's Global Assessment Score, was related in the HR group to maternal psychotic episodes during the offspring's early childhood (six months to two years) (McNeil & Kaij, 1987). None of the studies assessing mother-infant interaction has completed an adulthood follow-up.

The Edinburgh HR Study (Lawrie et al., 1999) was the first to include repeated brain imaging as a part of the longitudinal follow-up. In the initial magnetic resonance imaging assessment, HR adolescents were compared with matched controls and patients having their first episode of schizophrenia. The general pattern was that the findings of high-risk individuals were midway between those of controls and first episode patients. Significant difference emerged in the volume of the left amygdala-hippocampal complex, which was significantly smaller in the first episode patients than in the other two groups, and significantly smaller among HR individuals than among controls. HR individuals

also had a significantly smaller thalamus than the control group. Within the high-risk group, individuals with at least one affected first-degree relative had smaller regional brain volumes and greater ventricular volumes than individuals with only second-degree relatives with schizophrenia, suggesting that structural brain abnormalities are largely genetically mediated (Lawrie et al., 1999).

3.3. Risk factors for schizophrenia

The term risk refers to the likelihood of a person who does not currently have schizophrenia developing the disorder after exposure to certain factors (risk factors). A risk factor is a characteristic or an external condition associated with increased probability of developing schizophrenia. Current understanding of causal mechanisms supports the view that there is no single causal factor for any complex disorder, and the current view is that there are multiple risk factors for schizophrenia. (Mueser & McGurk, 2004)

3.3.1. Genetic factors

3.3.1.1. Familiality of schizophrenia

Numerous family studies have found a morbid risk for schizophrenia among the first-degree relatives ranging from 1.4% to 6.5% (Kendler & Diehl, 1993). The risk for schizophrenia has been found higher among siblings than parents of a patient with schizophrenia (Kendler et al., 1993a; Gottesman, 1994). The risk for schizophrenia is about 6% among half-siblings, 4% among nephews or nieces, and 2% among first cousins of a patient with schizophrenia (Gottesman, 1994).

The prevalence of schizophrenia among adoptees having a biological mother with schizophrenia was 5.1% in the Finnish (Tienari et al., 2003) and 5.7% in the Danish Adoption Study (Kendler & Gruenberg, 1984). A Danish population-based cohort found that having a mother with schizophrenia was associated with 9-fold risk wheareas having a father with schizophrenia was associated with 7-fold risk of developing schizophrenia compared to controls (Mortensen et al., 1999). In previous HR studies, the risk for schizophrenia among offspring of a parent with schizophrenia has varied between 3.6% in the Swedish HR Study (Schubert & McNeil, 2003) and 16.2% in the Copenhagen HR Study (Parnas et al., 1993). For this estimation, the offspring of the Swedish HR Study had been followed up only until 22 years of age, which explains the lower prevalence. The Copenhagen HR Study includes several families in which both parents have schizophrenia (Parnas, 1985). It is also possible that the high prevalence observed in the Copenhagen HR study was partly caused by the case selection method (they included only families where the mother was hospitalized by the beginning of the study), or diagnostic criteria (self made criteria for the project, DSM-III criteria in later publications) used in the study.

The relatives of probands with schizophrenia also have an increased risk of other schizophrenia spectrum disorders: schizotypal and paranoid personality disorder (about 8-fold), and other nonaffective psychotic disorders (about 1.2-fold) (Kendler & Diehl, 1993). Some studies have also shown that the risk for non-schizophrenic disorders is increased among first-degree relatives of schizophrenia as well. The New York HR Study found that schizophrenia-related psychotic disorders, schizoaffective disorders, and non-psychotic and psychotic affective disorders were all increased among the schizophrenia HR offspring compared with controls (Erlenmeyer-Kimling et al., 1997). Swedish (Schubert & McNeil, 2003) and Israeli (Ingraham et al., 1995) HR Studies found an increased rate of non-psychotic mood disorders among HR offspring. In the Copenhagen (Parnas et al., 1993) and Swedish (Schubert & McNeil, 2003) HR studies, alcohol or other substance abuse was more common among the HR than control offspring, whereas there was no significant difference between the HR and control groups in the New York HR Study (Erlenmeyer-Kimling et al., 1997).

Some studies have shown that there is an approximately equal morbid risk for schizophrenia among relatives of probands with any of the schizophrenia spectrum disorders. The Irish Roscommon Family Study found that the risk of schizophrenia and schizophrenia spectrum disorders was approximately equal among the relatives of probands with schizophrenia, schizotypal personality disorder, schizoaffective disorder, or other non-affective psychotic disorders (Kendler et al., 1993a; Kendler et al., 1993b; Kendler et al., 1993c). In the Roscommon Family Study, the risk of schizophrenia was also higher among relatives of probands with psychotic affective illness (Kendler et al., 1993a). The Iowa Study found an increased risk for schizophrenia among relatives of probands with schizophrenia, schizophrenia spectrum disorders or psychotic affective illness (Kendler et al., 1985; Kendler et al., 1986).

3.3.1.2. Gene findings associated with schizophrenia

The high heritability of schizophrenia has stimulated much research to locate the susceptibility genes for it. However, in a recent meta-analysis of genetic research on schizophrenia, only the region 2p11.1-q21.1 in chromosome 2 met the criteria for genome-wide significance (Lewis et al., 2003), although many other regions almost reached significance.

Most recent studies implicate the Neuregulin 1 (NRG1) and Dysbindin (DTNBP1) genes as schizophrenia susceptibility genes (Harrison & Owen, 2003), and other genes, such as G72, Catechol-O-methyltransferase (COMT) or proline dehydrogenase (PRODH) (both situated in 22q11), AKT1, DISC-1, and GSK-3β have also been of great interest (O'Donovan et al., 2003; Ozeki et al., 2003; Emamian et al., 2004).

Neuregulin is a component of the dystrophin protein complex, which modulates synaptic function in the brain, e.g. of the glutaminergic NMDA-receptors (Suvisaari, 2004). The association between Neuregulin 1 and schizophrenia was first found in Iceland (Stefansson et al., 2002), and this association has been replicated in six independent studies (Suvisaari, 2004). *Dysbindin* was first found in an Irish Study (Straub et al., 2002), and the association with schizophrenia has been replicated in four independent studies (Suvisaari, 2004). It probably participates in synaptic regulation, particularly in the same regions as GABA-A receptors are located.

G72 activates D-amino acid oxidase (DAAO), which oxidizes the D-serine and which in turn is an activator of the NMDA receptor. It has been found to be associated with both schizophrenia and bipolar disorder (Suvisaari, 2004). Thus, it has been suggested that there is an overlap in genetic susceptibility to schizophrenia and bipolar disorder that can be thought as predisposing to psychosis, and other genes and environmental effects might then have specific effects leading to schizophrenia or bipolar disorder (Walker et al., 2002).

A microdeletion of 22q11 causes velo-cardio-facial syndrome (VCFS), and about 25% of patients with this syndrome develop schizophrenia. *COMT* and proline dehydrogenase *(PRODH)* lie in this area, and are therefore of interest. COMT inactivates dopamine molecules in the synaptic cleft. The association between COMT and schizophrenia has been found in two studies, but has not been replicated (Suvisaari, 2004). PRODH has been associated especially with childhood onset schizophrenia in one study, but this result has yet to be confirmed (Suvisaari, 2004). *AKT1* and *GSK-3*β were also associated with schizophrenia in a recent study, but again the result awaits confirmation (Emamian et al., 2004).

The *DISC-1* gene located on Chromosome 1 has been associated with schizophrenia in Finnish (Ekelund et al., 2001; Hennah et al., 2003; Ekelund et al., 2004) and Scottish (Millar et al., 2000) studies. Expression of DISC-1 displays pronounced developmental regulation in late embryonic life when the cerebral cortex develops. It interacts with a variety of cytoskeletal proteins that are important in neurodevelopment (Ozeki et al., 2003).

Epigenetic factors have also been suggested to play a major role in the development of schizophrenia. This would mean that genomic functions are regulated by heritable and potentially reversible changes in DNS methylation and/or chromatin structure. Epigenetic factors may not be completely erased during meiosis and could therefore be transmitted from one generation to another. Epigenetic regulation is only partially stable, and therefore the daughter chromosomes do not necessarily carry the same epigenetic patterns as parental chromosomes. Accordingly, schizophrenia can be seen as a result of a pre-mutation that increases the risk for schizophrenia, but does not necessarily indicate that the disorder is unavoidable. Pre-mutations may undergo further changes during tissue differentiation in the foetal period, childhood or adolescence, as well as due to sporadic factors and probably some external environmental factors. (Petronis, 2004)

Showing that a disorder runs in families does not conclusively mean that genes cause the disorder. All mechanism that could lead to a familial clustering of disease should be considered. It may also include a threshold effect. Nevertheless, if the genetic research can clarify the genes that are underlying schizophrenia, it may help us to understand the basic pathophysiology, to develop new drugs or to help to select proper drugs for a certain genotype, to identify genetic vulnerable HR individuals for early intervention, and to improve classification of psychiatric disorders.

3.3.2. Environmental risk factors

3.3.2.1 Birth and pregnancy complications

The suggestion that perinatal hypoxia may be aetiologically relevant to hippocampal dysfunction in schizophrenia, at least among individuals who are at high genetic risk for it, was firstly suggested by Mednick in the 1970s (Mednick, 1970). However, findings pointing to pregnancy and delivery complications are somewhat contradictory: other studies show that low birth weight and premature birth increase the risk of schizophrenia (Jones et al., 1998), and some that obstetric complications, particularly hypoxic-ischemia-related complications, increase the risk for later development of schizophrenia (Geddes & Lawrie, 1995; Zornberg et al., 2000), while some case-control studies have shown that these factors have only minor (Byrne et al., 2000) or no influence at all (Kendell et al., 2000).

However, a meta-analysis of the association of obstetric complications and schizophrenia found that three groups were significantly associated with schizophrenia: pregnancy complications, abnormal foetal growth and development, and delivery complications (Cannon et al., 2002b). A recent study revealed a dose-response relationship between number of obstetric complications and decreasing age of onset of schizophrenia (Kelly et al., 2004).

Some cohort studies have found an association between maternal-foetal Rh incompatibility and schizophrenia (Hollister et al., 1996; Cannon et al., 2002b). It has been confirmed that the cause of this phenomenon is not genetic, because in the proximity of the RhD-locus there was no genetic relationship with schizophrenia (Palmer et al., 2002). It has therefore been suggested that the relationship is caused by foetal hypoxia resulting from haemolysis caused by maternal-foetal incompatibility, or by hyperbilirubinaemia in the infant (Hollister et al., 1996). Since most of the children with obstetric complications do not develop schizophrenia, such complications may interact with genetic vulnerability to increase the risk of the disorder (Mueser & McGurk, 2004).

Nevertheless, it remains unclear whether the increased number of obstetric complications among individuals who later develop schizophrenia is at least partly a result of maternal characteristics, since studies have shown that women with a psychotic disorder are more prone to obstetric complications (Wrede et al., 1980; Bennedsen et al., 1999; Bennedsen et al., 2001).

3.3.2.2. Malnutrition

Mother's nutritional status during pregnancy seems to influence the child's later metabolism and adulthood morbidity from several disorders, such as hypertension and coronary heart disease (Barker, 1994; Barker, 1998; Parizkova, 1998). Whether maternal nutritional state might have an effect on later psychiatric disorders is not known, although individuals who were exposed to severe malnutrition *in utero* during a famine in the Netherlands during the Second World War had an increased incidence of schizophrenia (Susser et al., 1996). However, the association between the famine and later schizophrenia may have been caused by some other factor related to the time point, since in developing countries, where poor nutrition is common, the prevalence of schizophrenia is not increased (Jablensky et al., 1992). A Finnish cohort study found an association between low BMI during childhood and later development of schizophrenia (Wahlbeck et al., 2001).

3.3.2.3. Infections

Infections during pregnancy may also increase the risk for later developing schizophrenia among the offspring. Many studies (Mednick et al., 1988; Barr et al., 1990; Susser et al., 1996; Brown et al., 2000a) have found an association between second-trimester influenza epidemics and later development of schizophrenia, but not all (Torrey et al., 1988; Susser et al., 1994). However, these studies were based on dates of influenza epidemics or on maternal recall to define influenza exposure. A recent serological study found an association between influenza exposure during the first trimester and later schizophrenia (Brown et al., 2004). Another recent cohort study found that increased maternal plasma concentration of immunoglobulins G and M, and especially of Herpes Simplex type 2, before delivery were associated with increased risk for schizophrenia among offspring (Buka et al., 2001). Enteroviruses, especially poliovirus, have also been suggested to be associated with schizophrenia, but only a few studies have investigated this association. Some studies have found an association between poliomyelitis-infection during pregnancy and later development of schizophrenia (Torrey et al., 1988; Suvisaari et al., 1999a), while some have not (Watson et al., 1984; O'Callaghan et al., 1994; Cahill et al., 2002). *In utero* exposure to rubella infection has been studied with serological tests and found to be associated with later development of schizophrenia (Brown et al., 2000b; Brown et al., 2001). *In utero* exposure to respiratory infection has been similarly associated with

later schizophrenia (Brown et al., 2000a). A Finnish study found an association between childhood CNS infections and later development of schizophrenia (Rantakallio et al., 1997; Koponen et al., 2004), but another did not (Suvisaari et al., 2003). Despite the evidence of an association between influenza and schizophrenia, the link between virus exposure and schizophrenia appears equivocal (Brown & Susser, 2002).

3.3.2.4. Season of birth

Patients with schizophrenia have an excess of births during the winter and early spring compared with the general population (Torrey et al., 1997). In the northern hemisphere, children who later develop schizophrenia are more often born from January to April (Davies et al., 2003), whereas in the southern hemisphere they are more often born from July to September (McGrath et al., 1995). Interestingly, it has been shown that both patients and unaffected siblings have the same seasonal birth clustering, but that this seasonal clustering is wider among offspring who develop schizophrenia (Suvisaari et al., 2001). The cause of this phenomenon is unknown. It has been suggested that parents of individuals with schizophrenia have a seasonal conception pattern that differs slightly from that of the general population, possibly because of different or missing family planning, or some biological factor that has an effect on fertility (Suvisaari et al., 2001). Other suggested causes include meteorological factors (Tochigi et al., 2004), infections (Yolken & Torrey, 1995; Brown & Susser, 2002), nutritional factors (McGrath et al., 2004a), factors on the paternal side (Lam et al., 2002; Tochigi et al., 2004), and factors involving the infant after birth (Brown et al., 2000a; Xu et al., 2001; Tochigi et al., 2004). However, except for evidence of the effect of infections on subsequent schizophrenia, none of these hypotheses has been confirmed (Tochigi et al., 2004).

3.3.2.5. Urbanization

The prevalence of schizophrenia has been observed to be higher in urban than rural areas in most western countries (Tsuang, 2000; McGrath et al., 2004b), and the risk increased with rising levels of urbanization in a dose-response matter (Sundquist et al., 2004; van Os, 2004). The incidence of schizophrenia in Finland used to be higher in rural areas, but in younger birth cohorts the risk is higher in urban-born individuals (Haukka et al., 2001). The risk for schizophrenia increases with the number of years spent in an urban region during childhood (Pedersen & Mortensen, 2001b). Psychosis-like experiences are also more common in urban (23%) than rural (13%) areas (van Os et al., 2001). The reason for this association remains unknown, although there are several hypotheses to explain it, including a viral hypothesis (Tochigi et al., 2004), obstetric complications (Harrison et al., 2003), maternal educational level (Harrison et al., 2003), amount of substance misuse (van Os, 2004), selective migration (Tochigi et al., 2004), or socio-economic factors during childhood (Tochigi et al., 2004). However, none of these hypotheses have been confirmed by convincing evidence.

3.3.2.6. Social environment and family related factors

The association between urbanization and schizophrenia might be explained by influences in the wider social environment, such as community level of social fragmentation, social isolation and social inequality, all of which have been found associated with schizophrenia in small areas (van Os et al., 2000; van Os, 2004). Social adversity during early life or adolescence may be associated with schizophrenia (Howes et al., 2004). It has also been suggested that because stress induces dopamine release, genetically vulnerable individuals who may be neurodevelopmentally impaired might be susceptible to dysregulation of dopamine, which could act as a final pathway leading to the onset of a psychotic illness (Howes et al., 2004).

Some factors related to family structure have been found associated with schizophrenia, e.g. number of siblings, birth order, and age difference to older siblings. The Northern Finland 1966 Birth cohort found that multiparity (i.e. mother who has undergone six or more deliveries) was associated with psychoses other than schizophrenia, and with alcoholism and depressive disorder, but not with schizophrenia itself (Kemppainen et al., 2000). Nevertheless, the same study found that specific birth order status was associated with schizophrenia: the risk for schizophrenia was increased among male first-borns and female last-borns (Kemppainen et al., 2001). However, other studies have found a decreased incidence of schizophrenia among first-borns (Hare & Price, 1970; Sham et al., 1993), or no effect of birth order on schizophrenia (Westergaard et al., 1999). One study has suggested that having siblings three to four years older would be associated with later development of schizophrenia (Sham et al., 1993), while another study found that having less than two years age difference to the nearest older or younger sibling was associated with later development of schizophrenia (Westergaard et al., 1999). It has been suggested that some biological factors or psychological stressors linked with these positions may have an impact on the risk for schizophrenia (Kemppainen et al., 2001). Advanced paternal age has also been found to be associated with schizophrenia in several studies (Malaspina et al., 2001; Brown et al., 2002; Dalman & Allebeck, 2002).

The Copenhagen HR Study found that institutionalization (Walker et al., 1981) and severe instability of the early rearing environment (Parnas et al., 1985) predicted later development of schizophrenia among offspring of mothers with schizophrenia (Mednick & Schulsinger, 1968; Cannon et al., 1990). The HR children who were raised in children's homes had an increased risk for schizophrenia, while those who were raised by relatives had a more favourable outcome than their peers raised by mothers with schizophrenia (Carter et al., 2002). A poor relationship with both parents also predicted later development of schizophrenia (Schiffman et al., 2002). The Israeli HR Study found that Axis I disorders were more prevalent among the kibbutz-reared HR offspring than in those reared by their own parents, or in control offspring (Mirsky et al., 1995b).

However, a recent Finnish study found no association between maternal separation at birth and later development of psychotic disorders (Maki et al., 2003). This divergent finding might be explained by the relatively short duration of separation used in the study (from directly after birth for seven months, on average), or by the fact that these children were separated because of tuberculosis in the family, and not because of an otherwise suboptimal rearing environment (Maki et al., 2003).

Nevertheless, familial or parental dysfunction has been shown to predict schizophrenia in several studies (Wahlberg et al., 1997; Carter et al., 2002; Tienari et al., 2004). Other studies have shown an increased risk in children subjected to adverse physical conditions, such as overcrowded housing and deprived neighbourhoods (Carter et al., 2002). A recent study found that early psychological childhood trauma increased the risk for later positive symptoms (Janssen et al., 2004).

3.3.2.7. Cannabis

Cohort studies have shown that a dose-related association exists between schizophrenia and cannabis abuse (Arseneault et al., 2004): the risk for schizophrenia is greater when the abuse has started earlier and has been heavier (Arseneault et al., 2002; Zammit et al., 2002). There was no relationship between other drugs and psychotic disorders (Arseneault et al., 2002; Zammit et al., 2002). A recent review suggested that elimination of cannabis use would reduce the incidence of schizophrenia by about 8% (Arseneault et al., 2004).

3.4. Early indicators for schizophrenia

Kraepelin and Bleuler observed almost a century ago that many of the individuals who develop schizophrenia already differ from others during childhood and adolescence (Bleuler, 1911; Kraepelin et al., 1919). Clouston observed a syndrome of ’developmental insanity’, where developmental abnormalities predicted later psychosis (Colp, 2000). Indeed, the first schizophrenia HR study was initiated to test the hypothesis of developmental disorder (Fish et al., 1992).

3.4.1. Neurological and motor development

A large follow-up study of children with childhood-onset schizophrenia conducted in the 1940s observed deviations in neurological maturation among them (Fish et al., 1992). This led Barbara Fish to propose that "what was inherited in schizophrenia, at least in individuals with the earliest onset and most chronic course, was a neurointegrative defect" (Fish et al., 1992). Specifically, she suggested that a neurointegrative disorder in infancy termed pandysmaturation (PDM), consisting of concurrent transient retardation of motor and/or visual motor development, abnormal profile of function, and retarded skeletal growth, predicted later development of schizophrenia. She tested the hypothesis

in the New York Infant Study (Fish et al., 1992), in which seven out of 12 HR infants and one out of 12 controls were found to have had PDM. The seven HR subjects who received a diagnosis of schizophrenia or schizotypal or paranoid personality disorder in the adulthood follow-up had all had PDM in infancy. Several HR and cohort studies since then have investigated early childhood motor and neurological development.

Later attainment of motor milestones (Jones et al., 1994; Isohanni et al., 2001b) and deficits in motor coordination (Crow et al., 1995; Walker et al., 1999; Bearden et al., 2000; Cannon et al., 2000; Rosso et al., 2000) have been associated with schizophrenia in several cohort studies. The British 1958 Perinatal Mortality Survey (Crow et al., 1995) found that pre-schizophrenic children had poor coordination compared with controls (Crow et al., 1995). The Northern Finland 1966 Birth cohort found that severe perinatal brain damage is associated with increased risk for developing schizophrenia (Jones et al., 1998). HR studies have also found poor neurobehavioural functioning associated with later schizophrenia (Fish, 1984; Marcus et al., 1987; Hans et al., 1999; Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling et al., 2000; van Os, 2004). In the New York HR Study, neuromotor deviance predicted affective flattening among the schizophrenia HR group in adolescence and identified 75% of those who developed schizophrenia spectrum psychoses in adulthood (Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling et al., 2000). The Northern Finland 1966 Birth cohort found that children who learned to stand latest were more likely to perform poorly in school in motor and academic subjects, independent of genetic and perinatal factors (Isohanni et al., 2004). A population-based longitudinal study in Finland found that children who later developed schizophrenia performed worse in sports and handicrafts, suggesting problems in motor development (Cannon et al., 1999).

There seems to be a continuity between childhood developmental problems in neuromotor functioning and neurological signs in adult patients with schizophrenia. The Swedish HR Study found that neurological signs in young adulthood were associated with the presence of neurological signs during childhood, but not during infancy (Schubert & McNeil, 2004). A review concluded that the prevalence of most neurological signs is higher among patients with schizophrenia than among controls, and particularly impaired motor coordination seems to be specific to schizophrenia (Boks et al., 2000). Neurological soft signs are also more common among individuals with first episode psychosis (Dazzan & Murray, 2002).

However, a recent cohort study found that deviance in motor coordination in childhood predicted both adult schizophrenia and being an unaffected sibling of a patient with schizophrenia (Rosso et al., 2000). Interestingly, motor uncoordination has been the most common finding differentiating HR children from controls in many HR studies, too. This could suggest that deviance in motor coordination may be associated with the genetic risk for developing schizophrenia, or with some other family-related factors, but is not necessarily an indicator for its development. In a recent study, maltreatment but not parental psychopathology was found to affect children's neuromotor functioning (Bergman et al., 1997). The same study observed that maltreatment of children was quite common in families with a schizophrenic parent (Bergman et al., 1997). Thus, it is possible that

some of the observed differences in neuromotor development between schizophrenia HR and control children are related to family characteristics other than having a parent with schizophrenia.

3.4.2. Cognitive functioning

Bleuler regarded attention deficit as one of the fundamental symptoms of schizophrenia (Bleuler, 1911). Family studies have since found that attention deficits are evident in patients with schizophrenia as well as their unaffected first-degree relatives, although they are less severe among relatives (Michie et al., 2000). The deficit in patients is independent of clinical state, suggesting that the impairment is trait- rather than state-dependent (Michie et al., 2000). A deficit in sustained attention is regarded as one of the most promising phenotypic indicators of vulnerability to schizophrenia for genetic studies (Michie et al., 2000). It is also one of the key features of "schizotaxia", a term introduced by Meehl to describe the premorbid neurological substrate of schizophrenia which precedes but does not necessarily proceed to schizophrenia (Tsuang et al., 2000). Childhood attention deficit has been found to predict schizophrenia spectrum psychoses in adulthood in some HR studies (Marcus et al., 1987; Erlenmeyer-Kimling & Cornblatt, 1992; Mirsky et al., 1995a; Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling et al., 2000), although the Edinburgh HR Study failed to find any association between sustained attention deficit and genetic liability to schizophrenia, nor between sustained attention deficit and the occurrence of psychotic symptoms (Cosway et al., 2002).

The British 1958 Perinatal Mortality Survey (Crow et al., 1995) found in cognitive assessments conducted at the ages of 7, 11, and 16, that preschizophrenic subjects performed worse than controls in both oral and reading abilities as well as in tests of mathematical skills. Verbal short-term memory deficit predicted 83% of the HR offspring who developed schizophrenia-related psychosis in the New York HR Study (Erlenmeyer-Kimling & Cornblatt, 1992; Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling et al., 2000).

Many cohort and conscript studies have found that low IQ increases the risk of developing schizophrenia (Aylward et al., 1984; Davidson et al., 1999), one even finding a linear trend in risk regarding intellectual functioning and schizophrenia (Davidson et al., 1999). Adolescents who later developed schizophrenia showed significant premorbid deficits on all intellectual and reading measures (Reichenberg et al., 2002). It seems that low IQ is also associated with psychiatric disorders other than schizophrenia, but for non-schizophrenic disorders the effect is less marked and non-linear (David et al., 1997). The Edinburgh HR Study found a decline in IQ from the initial assessment among individuals who developed psychotic symptoms during the follow-up (Cosway et al., 2000). However, not all studies have been able to confirm this association. Adulthood schizophrenia was not related to IQ in the New York HR Study (Dworkin et al., 1993), and the Copenhagen HR Study even found that children who later developed schizophrenia had a slightly higher premorbid IQ than their unaffected HR peers (Carter et al., 2002). Two Finnish cohort studies found no difference in school marks in academic subjects between

children who later developed schizophrenia and other cohort members (Isohanni et al., 1998; Cannon et al., 1999), while another found that excellent school marks were more common among males who later developed schizophrenia than among males with no psychiatric disorders (Isohanni et al., 1999).

The Philadelphia NCPP cohort study found that subjects who later developed schizophrenia and their siblings both performed worse than controls in verbal and nonverbal cognitive tests at four and seven years (Cannon et al., 2000), suggesting that low IQ may be associated with the familial risk of developing schizophrenia but is not necessarily a risk factor for it. Low IQ could also reflect other risk factors that are more prevalent in these families, as suggested by the Rochester Longitudinal Study (Sameroff et al., 1998). However, a recent family study found that schizophrenic patients had significantly lower premorbid IQ than their relatives and controls (Gilvarry et al., 2000). One reason for these disparate findings could be the different ages at assessment. It is also possible that low IQ is associated with an environmental risk factor for schizophrenia, but is not a risk factor itself.

3.4.3. Behaviour and social adjustment

Several cohort, conscript and HR studies have found that problems in behaviour or antisocial competence from early childhood predict later development of schizophrenia (Jones et al., 1994; Mirsky et al., 1995a; Olin et al., 1995; David et al., 1997; Isohanni et al., 1998; Davidson et al., 1999; Bearden et al., 2000).

Walker et al. (Walker et al., 1993) compared the early childhood development of children who later developed schizophrenia and their unaffected siblings by investigating their behaviour in home movies made in early childhood. They found that children who later developed schizophrenia showed greater negative affect, and preschizophrenic girls also showed less joy responses. Other cohort studies have found that solitary play preference at the age of four and six years (Jones et al., 1994), or social maladjustment at seven years (Bearden et al., 2000) predicted later development of schizophrenia. The Philadelphia follow-up of the National Collaborative Perinatal Project found that children who developed schizophrenia, as well as their unaffected siblings, showed more focal deviant behaviour than controls (Bearden et al., 2000). It seems that problems in social adjustment continue into young adulthood: pre-schizophrenic conscripts have reported problems with interpersonal relationships more often (Malmberg et al., 1998).

Behavioural problems seem to differ between males and females. The British 1958 Perinatal Mortality Survey (Done et al., 1994; Crow et al., 1995) found that only boys at the age of seven who were more anxious and hostile towards adults and children and more often engaged in inconsequential behaviour had an increased risk for schizophrenia. At the age of 11, male pre-schizophrenic subjects were more depressed than controls. Female pre-schizophrenic subjects were more withdrawn and depressed and more likely to dismiss adult values. In the HR group of the Copenhagen HR Study, males who later developed

schizophrenia had disrupted class with inappropriate behaviour more often, were emotionally highly-strung, lonely, and judged by their teachers as susceptible to future emotional or psychotic problems (Olin et al., 1995). Females who later developed schizophrenia were more nervous, and again judged by their teachers as susceptible to future emotional or psychotic problems (Olin et al., 1995).

Disruptive school behaviour (Mirsky et al., 1995b; Olin et al., 1995) or delinquent, aggressive or withdrawn behaviour (Miller et al., 2002b) have been found to predict later development of schizophrenia in some other HR studies, too. In the Israeli HR Study, eight of the nine children who later received a schizophrenia spectrum diagnosis had behaved undesirably (Marcus et al., 1987), and in the Copenhagen HR Study, the HR adolescents who later developed schizophrenia also experienced more interpersonal difficulties and showed disruptive behaviour (Parnas et al., 1982). Cannon et al (Cannon et al., 1997) found that the risk of psychosis increased linearly with worsening premorbid social and school adjustment functioning.

It is not clear whether problems in social adjustment are early manifestations of emerging schizophrenia, or risk factors for it (Ellison et al., 1998). However, poor social and school adjustment seem to be among the most commonly found development abnormalities in pre-schizophrenic individuals.

3.4.4. Structural brain abnormalities

Many studies have shown that non-psychotic individuals who later develop schizophrenia have premorbid brain abnormalities, such as reduced volume of the hippocampus or hippocampal-amygdala complex (Lawrie & Abukmeil, 1998; McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001).

In one study, small left amygdala-hippocampal complex was associated with familial risk for schizophrenia, while increased volume of this complex predicted the onset of psychosis within one year (Velakoulis et al., 2000). A recent study of a Finnish twin cohort found that hippocampal volumes of individuals with schizophrenia were smaller than those of their healthy co-twins and healthy twins, while the hippocampal volume of their co-twins was smaller than that of healthy twins (van Erp et al., 2004). The hippocampal volume of MZ or DZ healthy co-twins of an individual with schizophrenia were similar, which suggests that although the hippocampal volume is largely mediated by genetic factors, there seems to be a greater modulation by environmental factors in individuals with schizophrenia and their relatives (van Erp et al., 2004). However, a recent study of adolescent offspring of a patient with schizophrenia found that they had superior temporal gyrus abnormalities more often, possibly suggesting that this developmental deviance is associated with a genetic risk for schizophrenia (Rajarethinam et al., 2004). The Edinburgh HR Study found a greater reduction in temporal lobe size among HR individuals who had psychotic symptoms than among HR individuals who did not (Johnstone et al., 2002).

In the Copenhagen HR Study, HR and control offspring underwent a computed tomographic scan of the brain in adulthood. As in the Edinburgh HR Study, cortical and ventricular cerebrospinal fluid-brain ratios increased linearly with increasing genetic risk (Cannon et al., 1993). Genetic risk interacted with birth complications in predicting enlargement of the ventricular system (Cannon et al., 1993). In comparing HR individuals with schizophrenia, schizotypal personality disorders and unaffected HR individuals, an equal degree of sulcal enlargement was found among both HR individuals with schizophrenia and schizotypal personality disorder, while ventricular enlargement was evident only among HR individuals who developed schizophrenia (Cannon et al., 1994).

However, at least some of these brain changes could be neuroplastic adaptations to environmental factors, since some of the brain changes found among individuals with schizophrenia have been found to be reversible (Weinberger & McClure, 2002).

3.4.5. Psychiatric symptoms

The findings of predictive factors associated with schizophrenia in cohort studies are presented in Table 5, and the predictive factors associated with schizophrenia in HR studies are presented in Table 6.

Children who later develop schizophrenia have been found to have emotional symptoms already before school-age (Study I).

A cohort study found that childhood possible or definite psychotic symptoms in childhood predict the development of schizophreniform disorder in adulthood (Poulton et al., 2000). Moreover, the Finnish Adoption Study found that thought disorder predicted later development of schizophrenia in both low risk and high risk groups (Metsanen et al., 2004). Both the New York and Copenhagen HR Studies found that schizophrenia HR children who later developed schizophrenia scored higher on several psychosis-related MMPI-scales (Carter et al., 1999; Bolinskey et al., 2001). Scales of the MMPI measuring unusual beliefs and antisocial traits have also been predictive of schizophrenia among individuals who are not at high genetic risk for schizophrenia (Carter et al., 2002). The New York HR Study investigated physical anhedonia among HR children, as measured with the Physical Anhedonia Scale (PAS) (Freedman et al., 1998). PAS scores were directly related to lack of empathy in adulthood and to suspicious solitude. Male schizophrenia HR children had higher PAS scores than their female counterparts, and high scores were associated with poor social outcome in adulthood (Freedman et al., 1998). They found also that global, positive or negative thought disorder, or negative symptoms at the age of nine, predicted later development of schizophrenia (Ott et al., 2002).

Table 5. Factors that have predicted later schizophrenia in cohort studies

Study	Country	Birth years	Factors that predicted later development of schizophrenia
The Northern Finland 1966 Birth cohort (Isohanni et al., 2001b)	Finland	1966	• later learning to stand (boys only) • abnormalities in neurological development • not attending age-appropriate class at the age of 14 • especially good performance in school (boys only)
British 1946 National Birth cohort (Jones et al., 1994)	UK	1964	• later learning to walk • problems in speech development • problems in social adjustment • worse performance in school
National Child Development Study (Crow et al., 1995)	UK	1958	• problems in speech development • problems in social adjustment • worse performance in school • attention problems • depression at the age of 11 years • problems in coordination • clumsiness
Dunedin Multidiscplinary Health and Development Study (Cannon et al., 2002a)	New Zealand	1972-73	• later learning to walk • abnormalities in neurological development • delayed motor development • problems in speech development • lower IQ • internalized symptoms • problems in social adjustment
National Collaborative Perinatal Project (Bearden et al., 2000; Cannon et al., 2000; Rosso et al., 2000)	USA	1959-66	• lower IQ • problems in coordination • abnormal movements

Table 6. Factors predicting schizophrenia among HR offspring

Study	Sample size	Factors that predicted schizophrenia
The New York Infant Study (Fish, 1987)	HR=12 C=12	• pandysmaturation (Fish et al., 1992)
The Copenhagen HR Study (Mednick & Schulsinger, 1968)	HR=207 C=104	• institutional care (Walker et al., 1981; Cannon et al., 1990) • severe instability of early rearing environment (Walker et al., 1981; Cannon et al., 1990) • passivity in infancy (rated by parents) (Parnas et al., 1982), inappropriate behaviour (Mednick & Schulsinger, 1968; Parnas et al., 1982; Olin et al., 1995) • being emotionally highly-strung (Mednick & Schulsinger, 1968; Parnas et al., 1982; Olin et al., 1995) • being lonely, susceptible (by teachers) to future emotional or psychotic symptoms (Olin et al., 1995) • poor affective control (Mednick & Schulsinger, 1968; Parnas et al., 1982; Olin et al., 1995) • higher scores on several scales of the MMPI (Carter et al., 1999)
Israeli HR Study (Marcus et al., 1987; Mirsky et al., 1995a)	HR=50 C=50	• poor neurobehavioural functioning (Marcus et al., 1987) • undesirable behaviour (Marcus et al., 1987) • higher anxiety ratings (Kugelmass et al., 1995)
The New York HR Study (Erlenmeyer-Kimling & Cornblatt, 1987; Erlenmeyer-Kimling et al., 1997; Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling et al., 2000)	A:HR=sch=84 HRaff=67 C=136 B:HRsch=46 HRaff=39 C=65	• deficits in verbal short-term memory (Erlenmeyer-Kimling et al., 2000) • attentional deficit (Erlenmeyer-Kimling et al., 2000) • deficit in gross motor skills (Erlenmeyer-Kimling et al., 2000) • behavioural problems (Amminger et al., 1999) • positive formal thought disorder (NYHR) (Ott et al., 2001) • high scores on Schizophrenia Proneness Scale (MMPI-derived) (NYHR) (Bolinskey et al., 2001)
The Jerusalem Infant Development Study (Hans et al., 1999)	HR=29 C=27	• poor neurobehavioural functioning (Hans et al., 1999)
The Edinburgh HR Study (Hodges et al., 1999; Miller et al., 2002b; Miller et al., 2002c)	HR=162 C=36	• delinquent-aggressive behaviour (Miller et al., 2002b) • withdrawn behaviour (Miller et al., 2002b) • high RISC (Rust Inventory of Schizotypal Cognitions) scores (Miller et al., 2002c) • reduction in temporal lobe size (Johnstone et al., 2002)
The Boston and Providence NCPP HR Study (Goldstein et al., 2000)	HRsch=118 HRaff=126 C=165	• problems in social adjustment (Goldstein et al., 2000)

Higher anxiety ratings at age 16 were predictive of future development of schizophrenia in the Israeli HR Study (Kugelmass et al., 1995). The Edinburgh HR Study found that high scores on the Rust Inventory of Schizotypal Cognitions (RISC) were associated with later development of schizophrenia, although less than half of those who developed schizophrenia had high RISC scores (Miller et al., 2002a). The Hillside Recognition and Prevention programme (RAP) studied adolescents at high clinical risk for schizophrenia and found that negative symptoms and other behavioural abnormalities (decline in school functioning, magical beliefs or delusions, anxiety, and paranoid or referential thoughts) characterized those adolescents who were at the prodromal phase for developing schizophrenia (Lencz et al., 2004).

3.5. Ultra High-Risk studies and prevention of psychotic disorders

The idea of preventing psychotic disorders among individuals with prodromal symptoms was originally initiated by Falloon (Falloon, 1992), who asked general practitioners in an English county to send patients with signs and symptoms suggestive of schizophrenic disorders to mental health services. The incidence of first episode schizophrenia subsequently declined, which was seen as a possible effect of early intervention (Yung, 2003). Enthusiasm for early intervention is based on several observations. Firstly, it has been shown that individuals with prolonged duration of untreated psychosis need a longer period of treatment to attain clinical remission (Mueser & McGurk, 2004). Secondly, clinical symptoms tend to worsen during the first years after the onset of the illness (Mueser & McGurk, 2004). Thirdly, the development of schizophrenia is associated with an arrest of both social development and attainment of usual social roles, which contributes to a worse clinical and social prognosis (Mueser & McGurk, 2004). Thus, is has been suggested that rapid intervention at the first psychosis could improve long-term outcome, relieve the burden on relatives and patient, and reduce the cost of treatment (Mueser & McGurk, 2004).

The first pre-psychosis clinical and research centre (PACE clinic) was established in Melbourne (Yung, 2003). Based on knowledge of the clinical symptoms of the prodrome prior to first episode psychosis, and on the high-risk literature, Yung and colleages developed criteria for identifying individuals at high risk of onset of psychosis within a brief follow-up time. These are: attenuated psychotic symptoms occurring several times a week, this change in mental state having been present at least one week, OR transient psychotic symptoms having resolved spontaneously within one week, OR family history of a first degree relative with any psychotic disorder, or schizotypal personality disorder in the individual and any change in mental state, and functioning which results in a loss of 30 points or more on the Global Assessment of Functioning scale for at least one month (Yung et al., 1998). Individuals fulfilling these criteria were named as Ultra High-Risk (UHR) individuals. The transition rate to psychosis over six months was 40% among UHR individuals. Poor functioning, long duration of symptoms, high levels of depression and reduced attention were the strongest predictors of psychosis (Yung et al., 2004). There are several prodromal studies ongoing. The only published clinical trial among the Ultra High-Risk population used antipsychotic medication combined with cognitive therapy compared with treatment as usual (supportive case management) (Yung, 2003). Significantly

fewer individuals in the prodromal treatment group developed psychosis during the six-month follow-up. However, this difference did not remain at the post-treatment six-month follow-up (Yung, 2003). The same clinic is now conducting a study where pharmacological and psychological treatments are analyzed separately, and a trial of psychological treatment alone is currently underway in Manchester. At this point in time the long-term benefits of early intervention are still unknown.

While the prodromal criteria are suitable for investigating factors immediately preceding the onset of psychosis which promote or prevent the development of psychosis, they are not helpful for investigating childhood developmental factors associated with schizophrenia or other psychotic disorders.

3.6. Summary of the review of the literature

According to family studies, first degree relatives of a proband with schizophrenia have an increased risk for schizophrenia spectrum disorders. Cohort studies have shown that individuals who develop psychotic disorder in adulthood show developmental abnormalities in childhood, including delays in attainment of speech and motor milestones, problems in social adjustment, and poorer academic and cognitive performance. HR studies have found that the development of children of a parent with schizophrenia differs from that of children without a family history of schizophrenia, but it is not clear which mechanisms are involved in addition to having a parent with schizophrenia. Factors which appear to predict schizophrenia among HR children include problems in motor and neurological development, deficits in attention and verbal short-term memory, poor social competence, positive formal thought disorder-like symptoms, higher scores on psychosis-related scales in the MMPI, and severe instability of early rearing environment.

As the morbidity of schizophrenia in the general population is quite low, very large numbers of children are needed to detect predictive factors for schizophrenia or other psychotic disorders. The HR method enriches the sample with individuals who will develop schizophrenia in adulthood. The study method offers the possibility of searching for factors that differentiate HR and control children and that predict later development of psychiatric disorders. Although previous HR studies have used various factors in assessing these children, none has assessed childhood growth patterns or compared maternal symptomatology and adulthood morbidity among HR offspring. Moreover, this is the first HR study to employ standard ratings of childhood development that are in use in general population health care systems and have been used in larger cohort studies. Therefore, the results of previous HR studies may not be applicable in the primary care setting. Neither is a comparison of developmental problems predictive of schizophrenia between HR children and those in the general population possible, since all previous HR studies have used different assessments from cohort studies. Compared to cohort studies, the HR method is more suitable for assessing factors related to parents and childhood family that predict future development of psychiatric disorders (parental diagnoses and symptomatology, other family or rearing environment related factors). Because of the increased risk of psychotic disorders in HR groups, this special group of children and adolescents form an important target group for preventive programmes.

4. AIMS OF THE STUDY

The present study forms part of the Helsinki High-Risk Study, and its aim was to determine which psychiatric disorders the HR offspring born between 1960 and 1964 are at increased risk of, what developmental factors distinguish the HR and control offspring, and what maternal or childhood developmental factors are associated with later psychiatric morbidity.

The specific aims of the study were (the roman numbers of each aim refer to the original publications):

I. to comprehensively review the findings of previous HR studies and to compare them with those obtained from cohort and family studies.

II. to assess the cumulative incidence of hospital-treated DSM-IV-TR Axis I disorders among HR and control mothers, fathers and offspring.

III. to analyse psychotic and affective symptoms among HR mothers and to compare them with those obtained from previous studies, and to examine whether maternal symptom patterns were able to predict offspring's morbidity from psychotic disorders.

IV. to compare the childhood development of high-risk offspring and controls, and to determine which behavioural or developmental factors predicted future emergence of mental disorders among the high-risk offspring.

V. to compare childhood growth of high-risk offspring and controls, and to determine if any patterns in childhood growth predicted future emergence of psychotic disorders among the high-risk offspring.

5. MATERIALS AND METHODS

5.1. Design

The Helsinki High-Risk Study was launched in the 1970s (Wrede et al., 1980; Wrede, 1984). Initially, mothers were rediagnosed on the basis of their hospital case notes as suffering from chronic (n=54) or "mild" (n=117) schizophrenia or other psychotic disorder (n=28). "Mild" schizophrenia was further divided into paranoid and non-paranoid. Studies performed in the 1970s were limited to the offspring of mothers with schizophrenia (Wrede, 1984). Two separate studies were conducted in the 1970s in this cohort (Wrede et al., 1980; Wrede, 1984). The first one compared the incidence of pre-, peri- and neonatal complications among the high-risk and control mothers and their offspring. The same-sex hospital delivery that took place in the same maternity hospital immediately before that of the high-risk child was taken as the control. Both pre- and perinatal complications were found to be more common among mothers with schizophrenia than among controls, and the neonatal condition was worse among the high-risk than control children (Wrede et al., 1980). The second study assessed social adjustment among the high-risk children when they were approximately 15 years old. While the children of mothers with chronic or non-paranoid schizophrenia did not differ significantly from their peers, children of mothers with paranoid schizophrenia were rated superior to controls in social adjustment, both by peers and teachers (Wrede, 1984).

Since the 1980s, this cohort of high-risk children has not been followed up until now. They have now passed the age of highest risk for developing schizophrenia. The Helsinki HR Study cohort has recently been extended to include all offspring born to these mothers, but this study investigates only the original study sample, children born between 1960 and 1964.

This follow-up has been approved by the Ethics Committees (Institutional Review Board) of the National Public Health Institute (25.8.1999) and of the Hospital Discrict of Helsinki and Uusimaa (30.10.2002), and by the Social Insurance Institution, the Statistics Finland, the National Research and Development Center for Health and Welfare, by the Legal Register Center, and by the Ministry of Social Affairs.

5.2. Subjects

In 1974, all women (n=3242) born between 1916 and 1948 who had been treated for schizophrenia, schizoaffective disorder, or schizophreniform disorder (named as acute schizophrenic episode in the ICD-8) up till 1974 in any mental hospital of the City of Helsinki were identified from the central archives of mental hospital care, Helsinki, Finland (Wrede, 1984). The original case selection was made according to ICD-8 diagnoses (Wrede et al., 1980), according to which criteria schizophrenia, schizoaffective disorder and acute schizophrenic episode (known today as schizophreniform disorder) were all under the schizophrenia diagnosis. Thereafter, those (n=192) who had given birth between 1960 and 1964 were identified from the Helsinki register office (central register of the Lutheran Church, register of the Greek Orthodox Church, and Population Register of non-church-members). Their offspring born from 1960 to 1964 (n=212) formed the high-risk group.

Because social security numbers were not used uniformly in the early 1960s when the offspring were born and most of the mothers had their hospital treatments, the first task in this follow-up was to identify social security numbers for the index and control mothers, fathers, and offspring. Of the original high-risk group (192 mothers), we were able to find the social security numbers of 183 (born between 1918 and 1946), who had produced 203 offspring between 1960 and 1964. The control group was then re-formed by locating for each HR offspring the previous same-sex birth at the same maternity hospital.

For the adulthood follow-up of the offspring we collected developmental, social, occupational and psychiatric outcome information. Information on mental disorders was obtained from two sources: data on hospital treatments from 1969 to 1999 (age of offspring 35-39 years, age of HR mothers 53-81 years), plus after 1995 all inpatient detoxification treatments in social welfare institutions, were derived from the Finnish Hospital Discharge Register kept by the National Research and Development Centre for Health and Welfare, while Statistics Finland provided data on causes of death and death certificates till 2000, and occupational information. Based on the Finnish Hospital Discharge Register information, all hospital records including any psychiatric diagnosis were collected. If any information on outpatient treatments was obtained from the hospital records, the outpatient records were collected as well. Lack of adequate information meant we were unable to assign a diagnosis for 22 mothers (with 24 offspring). For 20 of them we could not obtain the case records, either because all information on the patient had been destroyed (n=4), or the case records had been destroyed (n=16). For only two of them was the information in the hospital case notes too limited to assign a diagnosis (n=2). In contrast, for HR fathers as well as for their offspring and the control group, inadequate information leading to diagnostic deferral was often caused by a scarcity of data from a short treatment period for non-psychotic symptoms. The Hospital Discharge Register data for the mothers for whom we could not assign any diagnosis revealed the following diagnoses at discharge: 12 with schizophrenia, two with schizophreniform disorder, one with psychosis due to a general medical condition, two with psychotic disorder NOS, and

one with depressive disorder NOS. Of their 24 offspring, two had psychiatric hospitalisations. The consensus diagnosis for one of them was psychotic disorder NOS, while the case notes of the other were missing and the only relevant document found was a register diagnosis of schizophreniform disorder. (Studies II-V)

The final HR sample consisted of 161 mothers with 179 offspring. For 149 offspring, the father was identified (altogether 132 fathers), whereas for the remainder the father was unknown to the Population Register. The final control group consisted of 176 offspring, 176 mothers and 176 fathers. Three controls were missing because of problems in their identification. (Studies II-V)

5.3. Methods

5.3.1. Diagnostic assessment and demographic information

Based on the register information, all case records from hospital and outpatient treatments until 1999 were collected and assessed separately by two residents in psychiatry, Laura Niemi and Jaana Suvisaari, followed by consensus diagnoses based on the DSM-IV Text Revision criteria (APA, 2000). Based on the Finnish Hospital Discharge Register, all hospital records including any psychiatric diagnosis were collected. If any information on outpatient treatments was obtained from the hospital records, the outpatient records were collected as well. Diagnostic assessment was similar for HR and control mothers, fathers and offspring. It consisted of assigning DSM-IV-TR diagnosis and completing the Operational Criteria Checklist for Psychotic Illness (OCCPI checklist) (McGuffin, 1991), the Major Symptoms of Schizophrenia Scale (MSSS) (Kendler et al., 1993a), the global ratings of anhedonia-asociality and of avolition-apathy on the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1982), and the global rating of bizarre behaviour on the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). (Studies II-V)

OCCPI is a scale designed for the assessment of psychotic and affective symptoms. It includes 90 items assessing i.e. the onset and duration of symptoms, premorbid social and work adjustment, deteriation from premorbid level of functioning, family history, and several symptoms (i.e. catatonic, manic, and depressive symptoms, disorganized thought and behaviour, anhedonia, and several types of hallucinations and delusions) of psychotic and affective disorders. (McGuffin, 1991) (Studies II-V)

The Major Symptoms of Schizophrenia Scale (MSSS) was designed for use in a best-estimate procedure to code symptom and course features over the entire duration of illness. For each symptom, the rating was made according to the duration of symptom over the course of the illness, its effect of patients behaviour and functioning, and e.g. regarding

delusions, on the degree of conviction related to the particular delusion. All the other variables were coded on a five-point scale, but the variable 'chronicity of the course' was coded on a four-point scale. The scales had the following guidelines: 1=clearly not present, 2=possibly present but subthreshold, 3=clearly present but moderate, 4=clearly present and prominent, 5=clearly present and severe. (Kendler et al., 1993a) (Study III)

Because the OCCPI and the MSSS do not assess some symptoms in detail, we decided to add the global ratings of anhedonia-asociality and of avolition-apathy on the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1982), and the global rating of bizarre behaviour on the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) to the assessment battery. These variables were coded on a six-point scale with the following grades: 0=no evidence of the symptom, 1=questionable, 2=mild, 3=moderate, 4=marked, 5=severe. (Study III)

Besides the rating scales, we collected some additional information concerning symptomatology, medication, and childhood living circumstances (e.g. number of siblings, maltreatment, parental alcohol abuse, divorce, periods when living separately from the mother and/or father) where available. The author completed the whole assessment procedure for all case notes. Jaana Suvisaari assigned DSM-IV-TR diagnoses for all case notes but completed the whole procedure only for every 5th case note. In cases of disagreement, the case records were reassessed together and consensus ratings made. (Study II)

Age of onset of the disorder was recorded, using the OCCPI (McGuffin, 1991) definition, as the earliest age (nearest year) at which medical advice was sought for psychiatric reasons. The duration of treatment contact was calculated from the earliest to the latest date of medical contact for psychiatric reasons, obtained from the case records. (Study II)

Offspring were grouped according to the most severe maternal diagnosis, the four groups being schizophrenia (n=104), schizoaffective disorder (n=20), other schizophrenia spectrum disorders (n=30), affective disorders (n=25), and controls (n=176). Because the sample sizes of separate affective disorders were small, we formed one group for the analysis by combining bipolar I disorder with or without psychotic features, major depressive disorder with or without psychotic features, and mood disorder NOS (n=23). Similarly, mothers suffering from psychotic disorder NOS, schizophreniform disorder, schizotypal personality disorder, and brief psychotic disorder were combined to form the group of schizophrenia spectrum disorders (n=28). (Studies II-V)

5.3.2. Interrater reliability

Interrater reliabilities (between Laura Niemi and Jaana Suvisaari) concerning DSM-IV-TR-diagnoses were tested using kappa values. (Studies II and III) The interrater reliability for DSM-IV-TR diagnoses between the two raters was lowest for schizophrenia spectrum disorder (κ=0.42, 95% CI 0.25-0.60) and highest for schizophrenia (κ=0.79, 95% CI 0.61-0.79). The kappa values for schizoaffective disorder, bipolar disorder and major depressive disorder were 0.47 (95% CI 0.29-0.65), 0.57 (95% CI, 0.36-0.79) and 0.48 (95% CI 0.23-0.73), respectively. (Study II)

Interrater reliabilities (between Laura Niemi and Jaana Suvisaari) in the MSSS, SANS, and SAPS ratings were tested using intraclass correlations. Intraclass correlation between the two raters in assessing maternal symptomatology varied between 0.51 (negative thought disorder) and 0.81 (catatonic behaviour). The mean of intraclass correlations was 0.68. (Study III)

5.3.3. Information on childhood development and growth

Information on childhood development was obtained from childhood developmental records and school health care records that are kept in separate archives in each school district. Guidance relating to child health in Finland is provided by public health nurses and physicians in co-operation with other specialists in primary care. Child health guidance provided for newborn babies and their families is a continuation of prenatal and maternity guidance, and extends to all children under school age (seven years). Thereafter the children visit school health nurses and physicians in their school area. After the initial home visit from a public health nurse at eight to 14 days old, infants attend the child health centre at 1 month, and 2, 3, 5, 6, 10, 12 and 15 months of age; toddlers are taken when 2, 3, 4 and 5 years old. They see a doctor at 1.5, 4, 8 and 18 months, and at 3 and 6 years. Nurses and physicians complete a standard form with measurements (e.g. weight, height) and other standard observations (e.g. reaching motor milestones) at every visit. School children visit the school nurse once a year and are seen by the school doctor at 7, 12, 15 and 17 years. Using the information obtained from the Population Register Centre and maternal records, we located the municipal area where each child was living during pre-school and school ages. In most cases, the entire childhood health check information was collapsed in the last school health card. In some of the cases we located separately the area of living during pre-school and school ages. The health cards for each HR and control child were obtained from their home district. The card data cover childhood health checks for each visit from infancy to the end of school age. (Studies IV and V)

We found childhood and school health cards for 159 HR offspring of 143 HR mothers, and for 99 control offspring of 99 mothers. Childhood and school health cards were missing for 12 offspring of mothers with schizophrenia, for one offspring of a mother with

schizoaffective disorder, for three offspring of mothers with other schizophrenia spectrum disorder, and for four offspring of mothers with affective disorder. Because we had less information on the controls, we were able to trace the cards of only 99 of them. (Studies IV and V)

The following items were extracted from each card: information on child's growth (weight and height), nurse's rating on whether the child was walking at 12 months, and whether speaking words at two years; nurse's or doctor's ratings on whether the child had a speech problem during childhood (at 5 or 6 years) or during school-age (7-17 years), whether there were emotional symptoms during childhood (before 7 years) or during school age (7-17 years), problems in social adjustment (only at 5 and 6 years), problems in neurological development (coded as severe neurological symptoms in severe cases, e.g. with hemiplegia or spasticity, and as neurological soft signs in less severe cases, e.g. with tics or subthreshold hypotony) during childhood or adolescence; nurse's rating of failure to reach the age-appropriate level of mental development (coded as delayed mental development, assessed yearly between 1 and 6 years), and of need for extra follow-up in the school health system for any reason (assessed at school age); nurse's or doctor's rating during school age for being socially inhibited, and having conduct problems, attention problems or academic impairment indicated by repeating the same class; any examination by a psychologist or doctor because of severe problems in academic performance, or any transfer to a special school due to severe problems in academic performance. (Studies IV and V)

Information was often missing for variables assessing walking at 12 months (the information was missing of 30% of HR and of 46% of the control children) and speaking at two years (the information was missing of 53% of the HR and of 67% of the control children). Otherwise, missing information was minimal. (Study IV)

The needed information on growth and height (at least 9 height and weight measurements available from childhood and school health cards by age 15) was found for 114 HR and 53 control offspring (12 offspring of mothers with DSM-IV-TR diagnosis of affective disorder, 16 offspring of mothers with other nonaffective psychoses, 69 offspring of mothers with schizophrenia, and 17 offspring of mothers with schizoaffective disorder). (Study V)

5.3.4. Statistical methods

Differences in background demographic variables between the groups were tested for proportions with the likelihood ratio statistics using the χ^2-test. For comparing the means between groups we used the analysis of variance (ANOVA), and significance was tested using the F-test. These methods are commonly used to compare differences between multiple groups. Incidences were modelled using Poisson regression, with the group (schizophrenia, any psychotic disorder, non-psychotic mood disorders, hospital treated alcohol, other substance abuse or dependence) as the explanatory variable, and tested with likelihood

ratio statistics using the χ^2-distribution. Differences between the groups were reported as relative risks (RR). In the outcome analyses the odds for having mental disorder among HR and control fathers were compared using logistic regression, tested with likelihood ratio statistics using the χ^2-test, and reported as odds ratios (OR). (Study II)

Poisson regression is a commonly used model for investigating the incidence of a particular disorder when the study population is large and the probability small (Vogt, 1999). Likelihood is a measure of the support provided by data for a particular value of the parameter of a probability model (Clayton & Hills, 1993). Likelihood ratio is a ratio of two likelihoods. Likelihood ratio tests are widely used as test statistics in epidemiology to test the statistical significance of the observed parameter value (Clayton & Hills, 1993). They are usually based on log likelihood ratios (Clayton & Hills, 1993). Relative (or excess) risk is the ratio of the incidence of an outcome in those who are exposed to a certain risk factor compared with the incidence in an unexposed group. In other words, it is a measure of how much more prone those who have been exposed to a risk factor are to have a given effect, compared to those who have not been exposed. (Study II)

The effect of paternal alcohol or substance use disorder on offspring's risk of the same disorders was analysed using logistic regression with maternal and paternal alcohol or substance use disorders as explanatory variables. Because there were only a few mothers (n=16) with more than one offspring belonging to the selected birth year range, there was no need to take intrafamily correlation into account. (Study II)

All tests for Study II were two-tailed, with α level set at 0.05.

In the principal factor analysis, we used for all mothers ratings made by Laura Niemi. The following items from the MSSS were used in the factor analysis: Hallucinations, delusions, bizarreness of delusions, positive thought disorder, catatonic behaviour, affective deterioration, negative thought disorder, depressive symptoms, manic symptoms, course, outcome, precipitating factor. In addition, we used the global ratings of bizarre behaviour from SAPS, and the Global rating of avolition-apathy and of anhedonia-asociality from SANS. (Study III)

Factor analysis is a technique where a set of variables is presented in terms of a smaller number of hypothetical variables. We hypothesised that maternal symptoms could be collapsed into factors representing different aspects of maternal symptomatology, and that some symptoms might be more harmful to the offspring than others. Before conducting the principal factor analysis, we calculated the mean maternal symptom scores among affected and unaffected offspring for each individual symptom item. For the principal factor analysis, the offspring were classified into four diagnostic groups according to DSM-IV-TR diagnostic criteria: schizophrenia (n=9), schizoaffective disorder (n=3), affective psychoses (n=4), and any schizophrenia spectrum disorder (n=17) (including schizophrenia, schizoaffective disorder, schizotypal personality disorder, delusional disorder, and psychotic disorder NOS). (Study III)

To compare symptom profiles in each maternal diagnostic group we calculated the mean scores for each symptom and course item for each maternal diagnostic group. After that, the information on all mothers was combined, and a principal factor analysis with VARIMAX rotation was conducted. VARIMAX rotation is a orthogonal rotation method. The number of factors was determined using the likelihood ratio test. To examine whether the factor structure was similar in the combined group and among mothers with schizophrenia, the factor analysis was also conducted using information on mothers with schizophrenia only. We then examined whether the factor scores predicted offsprings' psychiatric morbidity. The relationship between factor scores of maternal symptoms and offspring's probability of developing schizophrenia, schizoaffective disorder, affective psychosis, or any schizophrenia spectrum disorder was first modelled using generalized additive models (GAM) (Hastie & Tibshirani, 1990). Further modelling was carried out using logistic regression analyses (McCullagh, 1994), and tested using likelihood ratio statistics. The explanatory variables in models were maternal factor score and offspring's sex. (Study III)

The occurrence of developmental problems was compared between HR and control offspring using the χ^2-test, or Fisher's exact test when the expected number in any cell was less than five. Fisher's test is a test statistic for measures of association that relate two nominal variables. It is used mainly in 2x2 tables when the expected frequency is too small to trust the use of the chi-square test (Vogt, 1999). (Study IV)

Developmental problems were compared between offspring in each maternal diagnostic group using the Likelihood ratio test. Examining the relationship between childhood developmental problems and psychiatric morbidity in adulthood was confined to the high-risk group, because the cumulative incidence of mental disorders in the control group was low (Study II). To investigate the relationship within the HR group we used logistic regression models in which the six dichotomised diagnostic outcomes were used as dependent variables. Logistic regression analysis is a regression analysis used when the dependent variable is dichotomous. It is usually used for predicting whether something will happen or not. Independent variables may be categorical or continuous (Vogt, 1999). Models were calculated for all combinations of dependent and explanatory variables; sex and social class were incorporated as covariates. Odds ratios with 95% confidence intervals and Wald test statistics with significance levels were calculated. (Study IV)

Differences in weight, height, ponderal index and BMI between HR and control groups at different ages were tested using two-tailed t-test; which is a test of statistical significance, often of the difference between two group means. A two-tailed t-test is used to test the significance of a non-directional hypothesis, i.e. a hypothesis that says there is a difference between two averages without indicating which of the two is bigger (Vogt, 1999). A one-tailed t-test is directional, because it tests the hypothesis that one of the two group averages is bigger (Vogt, 1999). (Study V)

The relationship between childhood growth and psychiatric morbidity in adulthood was investigated only within the high-risk group, because the cumulative incidence of mental disorders, particularly psychotic disorders, in the control group was low. To investigate the relationship between growth and adulthood psychiatric morbidity within the HR group, we used logistic regression models in which the three dichotomised outcomes (schizophrenia (n=7, 6 males), schizophrenia spectrum disorder (n=11, 9 males), and any psychotic disorder (n=14, 10 males)) were used as dependent variables. Models were calculated for all combinations of dependent and explanatory (weight, height, BMI and ponderal index) variables; sex and social class were incorporated in the models as covariates. Odds ratios with 95% confidence intervals as well as likelihood ratio statistics with significance tests were reported. We also investigated whether transition from being thin at birth to having high BMI later, or vice versa, had an effect on the risk of schizophrenia. For this analysis, the ponderal index at birth, and BMI at seven and 12 years, were divided into tertiles. Changes from the 1^{st} to 3^{rd} tertile, or vice versa, were coded and used as an explanatory, three-category variable (change from lowest to highest tertile, change from highest to lowest tertile, or other) in the logistic regression model. Sex and social class were used as background variables. Odds ratios with 95% confidence intervals as well as likelihood ratio statistics with significance tests were reported. (Study V)

Statistical analyses in Studies II and III were performed using S-PLUS statistical software (MathSoft, 1996). For the analysis of growth change (transition from being thin at birth to having high BMI later, or vice versa) of Study IV, we used the Computer software R (Ihaka & Gentleman, 1996). All the other analyses in Study IV, as well as the analyses of Study V were performed using using SPSS statistical software (SPSS, 2002).

6. RESULTS

6.1. Cumulative incidence of mental disorders among high-risk offspring (Study II)

6.1.1. Demographic information of the cohort

In most cases in all the groups the mother's first hospitalisation was after the birth but before the offspring's school age. The mean age of the child at the mother's first hospitalization was lowest in the schizophrenia HR group (3.9 years), and highest in the control group (13.3. years). Obviously, most of the mothers in the control group had never been hospitalized for psychiatric reasons.

The proportion of hospital-treated offspring was largest in the schizophrenia HR group (26.9%), followed by the schizoaffective HR (20.0%) and schizophrenia spectrum disorder HR (20.0%) groups, and lowest in the affective disorder HR (8.0%) and control groups (11.9%). The average duration of treatment contact was longest among the offspring of mothers with other schizophrenia spectrum disorders, since the group contained offspring already treated in child psychiatric hospitals. The duration of treatment was considerably shorter among the control offspring, reflecting the fact that they had been treated for less severe disorders. Two HR offspring had died before 16 years of age; one from the schizophrenia HR group, and the other from the schizophrenia spectrum disorder HR group.

Only a few mothers (n=16) had more than one child born within the selected birth year range: one mother had three children in the range, all the others had two.

6.1.2. DSM-IV-TR diagnoses of the HR and control mothers and fathers

The diagnostic procedure based on the DSM-IV-TR criteria identified 92 of the 183 mothers as having schizophrenia, 18 with schizoaffective disorder, 20 with psychotic disorder not otherwise specified (NOS), one with brief psychotic disorder, six with schizophreniform disorder, one with schizotypal personality disorder, 16 with bipolar I disorder, four with major depressive disorder with psychotic features, one with major depressive disorder without psychotic features, and two with mood disorder NOS. Axis I comorbidity was relatively common among the HR mothers. Of the HR mothers, 55% had only one, 36% had two, and 9% had at least three Axis I disorders.

Lack of adequate information meant we were unable to assign a diagnosis for 22 mothers (with 24 offspring). For 20 of them we could not obtain the case records, either because all information on the patient had been destroyed (n=4), or the case records had been destroyed (n=16). For only two of them was the information in the hospital case notes too limited to assign a diagnosis (n=2). In contrast, for HR fathers as well as for their offspring and the control group, inadequate information leading to diagnostic deferral was often caused by a scarcity of data from a short treatment period for non-psychotic symptoms. The Hospital Discharge Register data for the mothers for whom we could not assign any diagnosis revealed the following diagnoses at discharge: 12 with schizophrenia, two with schizophreniform disorder, one with psychosis due to a general condition, two with psychotic disorder NOS, and one with depressive disorder NOS. Of their 24 offspring, two had psychiatric hospitalisations. The consensus diagnosis for one of them was psychotic disorder NOS, while the case notes of the other were missing and the only relevant document found was a register diagnosis of schizophreniform disorder.

The final HR sample consisted of 161 mothers with 179 offspring. For 149 offspring, the father was identified (altogether 132 fathers), whereas for the remainder the father was unknown to the Population Register. The final control group consisted of 176 offspring, 176 mothers and 176 fathers. Three controls were missing because of problems in their identification.

The odds of having any psychiatric disorder were higher for HR than control fathers (OR 2.57; 95% CI 1.32, 5.00, χ^2_1=8.04, p=0.0046). The odds of having alcohol or other substance abuse or dependence were 3.36 times higher for HR than control fathers (95% CI 1.26, 9.00, χ^2_1=6.42, p=0.011). Other Axis I disorders were not more common among HR fathers. None of the fathers of offspring in the affective disorder HR group had psychiatric disorders. In one family, both parents had schizophrenia. The number of fathers that were not known was highest in the schizoaffective HR group, and the number of married parents at the birth of the index child was also lowest in this diagnostic group.

One control mother had developed schizophrenia, and two had psychotic disorder NOS, but their children had no psychiatric hospitalisations.

6.1.3. Cumulative incidences of psychiatric disorders among HR offspring

The cumulative incidence of any psychotic disorder for the offspring of mothers with schizophrenia was 13.5% (RR 12.6 compared with controls; 95% CI 2.87, 55.5), for the offspring of mothers with schizoaffective disorder 10.0% (RR 9.4, 95% CI 1.33, 66.9), and for the offspring of mothers with other schizophrenia spectrum disorder 10.0% (RR 9.6, 95% CI 1.60, 57.3). After combining mothers with schizophrenia or schizophrenia spectrum disorders, the cumulative incidence of any psychotic disorder was 12.3% (RR 11.61, 95% CI 2.71, 49.86). Among the offspring of mothers with affective disorder, the cumulative incidence of any psychotic disorder was 4.0% (RR 3.6, 95% CI 0.33, 39.7), and not significantly different from controls. The only psychosis observed in this group was bipolar I disorder, in a child of a mother with similar disorder (Table 7). The cumulative incidence of all psychotic disorders among control offspring was 1.14% (n=2).

The cumulative incidence of schizophrenia among offspring of mothers with schizophrenia was 5.8% (RR 10.50; 95% CI 1.27, 87.4), while the cumulative incidence of schizophrenia or other schizophrenia spectrum disorders in that group was 11.5% (RR 19.7; 95% CI 2.54, >100) (Table 7). The cumulative incidence of schizophrenia among offspring of mothers with schizoaffective disorder was 5.0% (RR 9.26, 95% CI 0.58, >100), and the cumulative incidence of offspring of mothers with other schizophrenia spectrum disorder was 6.7% (RR 12.5, 95% CI 1.14, >100). None of the offspring of mothers with affective disorder developed schizophrenia. The cumulative incidence of schizophrenia among control offspring was 0.57% (n=1) (Table 7).

Table 7. Offspring DSM-IV-TR diagnoses of Axis I disorders in different maternal diagnostic groups; cumulative incidences are reported in parentheses

Diagnoses	HRsch (n=104)	HRschaff (n=20)	HRother (n=30)	HRaff (n=25)	HRdef (n=24)	Control (n=176)
Schizophrenia	7 (6.7%)	1 (5.0%)	2 (6.7%)	0	0	1 (0.57%)
Schizoaffective disorder	1 (1.9%)	1 (5.0%)	0	0	0	0
Delusional disorder	1 (0.96%)	0	0	0	0	0
Psychotic disorder NOS	2 (1.9%)	0	1 (3.3%)	0	1 (4.2%)	0
All schizophrenia spectrum disorders	11 (10.6%)	2 (10%)	3 (10%)	0	1 (4.2%)	0
Bipolar I disorder, with psychotic features	1 (0.96%)	0	0	1 (4.0%)	0	0
Major depressive disorder, with psychotic features	2 (1.9%)	0	0	0	0	1 (0.56%)
Major depressive disorder, without psychotic features	1 (0.96%)	0	3 (10%)	0	0	1 (0.56%)
Other mood disorders	9 (8.7%)	1 (5.0%)	1 (3.3%)	1 (4.0%)	0	4 (2.27%)
Anxiety disorders	1 (0.96%)	0	0	1 (4.0%)	0	0
Alcohol abuse or dependence	11 (10.6%)	1 (5.0%)	3 (10%)	0	3 (12.5%)	4 (2.27%)
Other substance abuse or dependence	5 (4.8%)	0	0	0	2 (8.3%)	1 (0.56%)
Alcohol or substance -induced psychotic disorders	1 (0.96%)	0	2 (6.7%)	0	1 (4.2%)	0
Other alcohol or substance -induced disorders	2 (1.9%)	0	0	0	0	0
Mental retardation	1 (0.96%)	0	0	0	0	2 (1.14%)
Suicide or parasuicide	1 (0.96%)	0	0	1 (4.0%)	0	0
Other psychiatric disorders	1 (0.96%)	1 (5.0%)	0	0	0	2 (1.14%)
Diagnosis deferred due to inadequate information	4 (3.8%)	0	0	0	1 (4.2%)	5 (2.84%)

HRsch=offspring of mother with schizophrenia, HRschaff=offspring of mother with schizoaffective disorder,
HRother=offspring of mother with other schizophrenia spectrum disorder, HRaff=offspring of mother with affective disorder,
HRdef=offspring of mother with diagnosis deferred

HR offspring had surprisingly high risk of developing alcohol or substance use related problems. Because of this, we did a poct hoc analysis where we analysed, using logistic regression, whether maternal and/or paternal alcohol or substance use disorder explained these disorders among the offspring. It turned out that paternal (OR 6.31, 95% CI 1.63, 24.5) but not maternal (OR 0.86, 95% CI 0.18, 4.16) alcohol or substance abuse increased the offspring's risk of these disorders. Non-psychotic mood disorders were more common among the schizophrenia HR offspring than other groups (Table 7). The prevalence of hospital-treated Cluster B personality disorders was also higher in the offspring of mother with schizophrenia or other psychotic disorder than in other offspring groups, being 4.8% in the offspring of mothers with schizophrenia and 10.0% in the offspring of mothers with other psychosis, compared to 0.6% among controls and 0% among offspring of mothers with affective disorder or with schizoaffective disorder (χ^2_4=9.61, p=0.048). In logistic regression analysis, maternal substance abuse was not related to the offspring's risk of having substance abuse (OR 0.86; 95% CI 0.18, 4.16), but paternal substance abuse increased the offspring's risk of having hospital-treated alcohol or other substance abuse or dependence (OR 6.31; 95% CI 1.63, 24.5). There were no interactions between maternal and paternal alcohol or other substance abuse or dependence.

Two of the control group offspring had developed psychotic disorder, and none of their parents had any psychiatric diagnoses.

Among the schizophrenia HR offspring, four had case records whose information was inadequate for assessing consensus diagnoses. Their diagnoses at discharge were schizoaffective disorder plus alcohol dependence, autism, mental disorder NOS, and depressive disorder NOS. For eight HR and 12 control offspring currently living abroad our register information was incomplete.

The cumulative incidences of the Finnish Hospital Discharge Register diagnoses for schizophrenia and for all psychotic disorders was also calculated for both our sample and the whole population cohort born in Helsinki between 1960 and 1964 (n=41,749). By the end of 1998, 396 individuals of the population cohort had developed schizophrenia and 487 had developed any psychotic disorder. Thus, the register-based cumulative incidence of the population cohort was 0.95% for schizophrenia and 1.17% for any psychotic disorder, while the register-based incidences of the HR cohort were 3.91% for schizophrenia and 16.8% for any psychotic disorder.

6.2. Maternal symptomatology and its effect on offspring's morbidity from psychotic disorders (Study III)

6.2.1. The average scores of different maternal diagnostic groups

Mothers with schizophrenia consistently received the highest scores in items assessing positive, disorganization, and most negative symptoms. Mothers with schizoaffective symptoms received the next highest scores in these items, and actually scored higher on items assessing catatonic behaviour and negative thought disorder. They also scored higher than mothers with affective disorders on depressive symptoms, but mothers with affective disorders scored highest on manic symptoms. The mean maternal symptom scores did not differ significantly between the offspring who later developed schizophrenia and those who did not.

6.2.2. Factor analysis

The principal factor analysis with VARIMAX rotation produced four factors, which were termed 1) negative, 2) positive, 3) catatonic, and 4) affective. The negative symptom factor explained 25.4% of the variance and had the highest loadings on avolition-apathy (0.80), anhedonia-asociality (0.81), poor outcome (0.81), and affective deterioration (0.73). The positive symptoms factor explained 16.2% of the variance and had the highest loadings on bizarre delusions (0.75), hallucinations (0.64), delusions (0.58) and positive thought disorder (0.53). The catatonic symptoms factor explained 10.4% of the variance and had the highest loadings on catatonic behaviour (0.78) and negative thought disorder (0.79). Finally, the affective symptoms factor explained 6.3% of the variance and had the highest loadings on manic symptoms (0.67) and depressive symptoms (0.48). Actually, the maximum likelihood method suggested a five-factor solution. However, the fifth factor explained only 3.5% of the variance and was ambiguous, the highest loadings being 0.32 for positive thought disorder, and -0.48 for the presence of precipitating factors in the first episode. Since the interpretation of the other four factors did not change, we chose the four-factor solution as the final factor structure. We did not find a separate "disorganization" factor. The disorganization symptoms, bizarre behaviour and positive formal thought disorder, loaded almost equally on factors one and two. When we did the same principal factor analysis for the subsample of mothers with schizophrenia separately, we found the same factor solution with the same factors: negative, positive, catatonic and affective. The only difference was that now both disorganization symptoms loaded most strongly on factor 2 (bizarre behaviour 0.67, and positive formal thought disorder 0.57).

6.2.3. Effect of maternal symptoms to offspring's morbidity

The factor scores were standardized for the analysis. GAM analysis showed an inverse relationship between maternal positive symptoms factor 2 and offspring's probability of developing schizophrenia. The logistic regression model confirmed a significant effect of maternal positive symptoms on the offspring's probability of developing schizophrenia (χ^2_1=6.67, p=0.0098). One unit increase, corresponding to one standard deviation increase, in factor 2 score lowered the probability of schizophrenia by 64% (OR 0.34, 95% CI 0.14, 0.082). All six interactions of the factor scores were tested and no significant interactions between them was detected.

When we included only mothers with schizophrenia in the analysis, the effect was even stronger (p=0.0022). None of the other analyses showed significant effects. We tested all six interactions of the factor scores and detected no significant interactions between them. Offspring's gender had no effect on the results.

6.3. Childhood developmental predictors of psychiatric morbidity (Study IV)

6.3.1. Differences between HR and control children

Compared to controls, HR children more often had emotional symptoms during childhood (χ^2_1=7.4, p=0.006), and neurological soft signs (χ^2_1=4.8, p=0.024), and were more prone to social inhibition during school age (Fisher's exact test, p=0.044) (Table 8).

Table 8. Factors differentiating HR and control children

Factor	p-value
Emotional symptoms during childhood	<0.01
Neurological soft signs	<0.05
Social inhibition during school-age	<0.05
Thinness at birth (girls only)	<0.05
Shortness at the age of 10 (boys only)	<0.05

6.3.2. Factors predicting later development of mental disorders among HR offspring

Neither of the dependent variables (social class or sex) significantly influenced the odds of developing mental disorders.

Among HR children, after adjusting for sex and social class, problems in social adjustment at five or six years predicted later development of schizophrenia spectrum disorder (OR 9.73, 95% CI 1.83, 51.8, p=0.008). Two HR children had severe neurological symptoms and both developed schizophrenia (Fisher's exact test, p=0.006); the OR could not be calculated due to the denominator of zero (Table 9).

Problems in social adjustment at five or six years (OR 4.51, 95% CI 0.99, 20.6, p=0.052) and emotional symptoms during school age (OR 2.88, 95% CI 0.99, 8.34, p=0.051) tended to predict later development of any psychotic disorder.

Emotional symptoms (OR 15.7, 95% CI 3.32, 74.1, p=0.001), conduct problems (OR 18.0, 95% CI 4.41, 73.5, p<0.001) and social inhibition (OR 34.9, 95% CI 5.71, >100, p<0.001) during school age predicted later development of any mood disorder; attention problems were an almost significant predictor (OR 6.71, 95% CI 0.99, 45.5, p=0.051).

Delayed mental development (OR 3.98, 95% CI 1.07, 14.9, p=0.040), and emotional symptoms (OR 4.70, 95% CI 1.92, 11.5, p=0.001), conduct problems (OR 9.44, 95% CI 2.44, 36.3, p=0.001) and social inhibition (OR 13.62, 95% CI 2.30, 80.6, p=0.004) during school age predicted later development of any mental disorder. Problems in social adjustment at five or six years (OR 4.10, 95% CI 0.99, 17.0, p=0.052) tended to predict later development of any mental disorder.

Table 9. Factors predicting mental disorders among HR offspring

Factor	Schizophrenia	Schizophrenia spectrum disorder	Any psychotic disorder	Any mood disorder	Substance related disorder	Personality disorder
Severe neurological symptom	Fisher's exact test, p=0.006					
Delayed mental development (C)						OR 10.5, 95% CI 1.95, 56.4, p=0.005
Problems in social adjustment (C)		OR 9.73, 95% CI 1.83, 51.8, p=0.008	OR 4.51, 95% CI 0.99, 20.6, p=0.052			OR 6.22, 95% CI 1.0, 38.7, p=0.050
Conduct problems (S)				OR 18.0, 95% CI 4.41, 73.5, p<0.001	OR 13.24, 95% CI 3.14, 55.8, p<0.001	OR 5.88, 95% CI 1.23, 28.2, p=0.027
Attention problems (S)				OR 6.71, 95% CI 0.99, 45.5, p=0.051	OR 7.62, 95% CI 1.09, 53.4, p=0.041	
Emotional symptoms (S)			OR 2.88, 95% CI 0.99, 8.3, p=0.051	OR 15.7, 95% CI 3.32, 74.1, p=0.001	OR 7.23, 95% CI 1.82, 28.6, p=0.005	OR 9.55, 95% CI 1.91, 47.8, p=0.006
Social inhibition (S)						OR 12.27, 95% CI 2.19, 68.6, p=0.004
Catch-up growth	OR 22.8, 95% CI 2.0, >100, p=0.040					

C= childhood (before 7 years of age), S= school-age (7-17 years of age)
Note: High maternal positive symptom factor score predicted decreased morbidity from schizophrenia among offspring (p=.0098)

6.3.3. Factors predicting later development of mental disorders among schizophrenia HR offspring

Analysing offspring of mothers with schizophrenia spectrum disorder separately changed the results only slightly. Among schizophrenia spectrum HR children, neurological soft signs tended to predict later development of schizophrenia spectrum disorder (OR 4.48, 95% CI 0.98, 20.5, p=0.053), while problems in pre-school social adjustment no longer predicted later development of any psychotic disorder, personality disorder or any mental disorder. Social inhibition no longer predicted later development of any mood disorder.

6.4. Childhood growth and its effect on morbidity from psychotic disorders (Study V)

6.4.1. Differences between HR and control children

The high-risk girls were shorter and lighter at birth, the height difference between HR and control girls at birth being statistically significant (p=0.033). However, the HR girls caught up the controls in growth by seven years of age. In contrast, HR boys were only slightly shorter and lighter at birth than controls, but the height disparity increased with age, being statistically significant at 10 years (p=0.020). To analyse these effects further, we performed two-way ANOVAs using group (HR or control) and social class (higher or lower) as explanatory variables separately for boys and girls, with weight, height and BMI as outcome variables. The height differences between HR and control groups persisted. Among all girls, high social class was associated with low BMI at one year (p=0.022), 10 years (p=0.02) and 14 years of age (p=0.002), and with low weight at 14 years (p=0.032).

6.4.2. Factors predicting later development of mental disorders among HR offspring

Within the HR group, after controlling for sex and social class, none of the variables related to height, weight and BMI predicted future development of schizophrenia, schizophrenia spectrum or psychotic disorders in logistic regression models. However, the combination of being in the lowest tertile for ponderal index at birth but in the highest tertile for BMI at seven years predicted later development of schizophrenia (OR 22.8, 95% CI 2.0, >100, p=0.04) (Table 9).

7. DISCUSSION

7.1. Methods and methodological limitations

As one of the largest high-risk studies ever undertaken, the Helsinki HR Study offers excellent potentials for assessing the development of HR offspring from childhood to adulthood. Compared with HR studies begun before the 1980s, it also benefits from systematic case ascertainment, and is the only one that can be considered as epidemiologically representative.

This cohort was initially constructed on the basis of hospital diagnoses of schizophrenia, schizoaffective disorder, or schizophreniform disorder found in the archives of Helsinki City hospitals. Although the reliability of hospital diagnoses in the 60s and 70s has not been studied, more recent data show that Finnish psychiatrists tend to apply a narrow definition of schizophrenia in clinical practice and that the hospital diagnosis of schizophrenia is reasonably reliable (Suvisaari et al., 1999b). The advantage of this selection method was that all mothers, independent of the duration of hospital treatment, were included in this study.

Mothers for whom a DSM-IV-TR diagnosis could not be assigned because of inadequate information were excluded. This group were mostly cases with severe psychotic disorders who had died before 1976 and whose case notes had therefore been destroyed, plus two cases who only had short hospital treatments and thus insufficient case note information to assign diagnoses. Among the offspring of mothers with diagnoses deferred, one had psychotic disorder NOS and another had a hospital diagnosis of schizophreniform disorder, but the case notes were missing. Thus, the cumulative incidence of any psychotic disorder among the offspring of mothers with diagnoses deferred was 8.3%, and the exclusion of these cases from the HR group did not have a major effect on the cumulative incidences of psychotic disorders in the HR group. However, these offspring could have added some information to the data on childhood development.

Finnish Hospital Discharge Register was used to select offspring who had been treated for a psychiatric disorder. The accuracy of data on psychiatric diagnoses in the Finnish Hospital Discharge Register was assessed in 1986 and found to be excellent: the diagnosis in the register and in the hospital case notes was identical in 99% for schizophrenia and in 98% for all mental disorders (Keskimäki & Aro, 1991). The reliability of schizophrenia diagnosis in the Hospital Discharge Register has been assessed in several studies (e.g. (Isohanni et al., 2001a)), and found to be acceptable. In theory, it is possible that HR

offspring with psychotic symptoms may not be hospitalised as often as individuals with psychotic symptoms in the general population; in families where one family member already has a psychotic disorder, symptoms of emerging psychosis or schizophrenia spectrum personality disorder might draw less attention than in other families. However, a study that compared the ability of relatives to recognise symptoms of emerging schizophrenia in families with one vs. no previous member with schizophrenia observed that relatives in affected families were more sensitive to positive symptoms of schizophrenia, although they were less sensitive to negative symptoms than relatives in families without such history (Hambrecht, 1995).

Because case notes included data on family history, the raters could not always remain blind to whether the child belonged to the HR or control group. However, they were blind to the actual parent-child pairs, and thus the parental diagnoses did not affect the diagnostic assignment of offspring.

Although our sample size was large compared with other high-risk studies (Study I), the number of children who developed schizophrenia or other psychotic disorders was small and, as a consequence, the confidence intervals were wide. The small numbers of affected individuals prevented us from using more complex multivariate methods. Therefore, the results are rather descriptive. Nevertheless, they provide valuable information on factors that might underlie the development of schizophrenia and may thus suggest ways for larger epidemiological studies to study the aetiology and early detection of schizophrenia.

Unlike some other HR studies (Study I), it was not possible to interview the study sample, which clearly was a limitation. This may have allowed some hidden morbidity in the cohort, especially from less severe psychiatric disorders. Nevertheless, it is reasonable to assume that the prevalence of psychotic disorders is accurate: in a Finnish health survey of 8000 individuals, 99% of those with a psychotic disorder had received psychiatric treatment (Lehtinen et al., 1991). Of the 73 individuals who had developed schizophrenia by 1994 in the Northern Finland 1966 Birth cohort, only two had been treated as outpatients only (Isohanni et al., 1997). The lack of personal contact with the cohort members also makes the assessment of symptomatology less precise, and prevented us from gaining detailed information on childhood rearing environment, or specific genetics. The data available in this study reflect symptoms and conditions during hospitalisations and visits to outpatient clinics, while information from other time periods was limited. However, the average duration of treatment contact was long: over 20 years for the mothers, and half as long for the fathers and the offspring. Thus, the case-record based information usually spanned several years and was quite detailed. Further, all available information was assessed, for example the notes made by nurses and psychologists, and not just those made by the treating psychiatrists. The advantage here is that the rating of cohort members was based on life-long symptomatology, rather than symptomatology at a specific time-point as in all other HR studies. Nevertheless, although the case-record based information was quite detailed, the information on psychiatric symptomatology was less detailed than it would have been optimally.

Compared with some other high-risk studies, the information on childhood development in this study was less detailed, consisting of nurses' and doctors' ratings of regular childhood assessments coded in standard forms that were used throughout the country. The advantage of this is that the ratings were made without knowledge of the high-risk status and of the ongoing study, and so the results may be more generalizable to clinical work in primary health. However, only clinically relevant problems were recorded on the health cards, while more subtle developmental problems may have remained unrecognized, or unrecorded. The lack of information in the variables measuring the attainment of motor milestones was considerable. Information on childhood rearing environment was received from maternal, paternal and offspring's hospital records. However, it has not been analysed yet, because the quality of the information varied significantly according to how long and intensive the treatment contact had been. Therefore, these environmental factors were not considered, although they probably influenced the overall outcome or the childhood development. For example, a study has shown that maltreated children have more developmental deviations, and that maltreatment is more common among families with a psychotic parent (Bergman et al., 1997). Some of the children in this study were found to be maltreated, but since we did not have accurate information concerning maltreatment, this was not taken into account in the analyses.

Although all HR offspring have a high familial risk for schizophrenia we still do not know to what extent the familiality for schizophrenia in these families is transmitted through genes and who of the HR offspring are truly susceptible gene carriers. All HR children lived in a family environment where the mother had a psychotic disorder, or they were adopted away. This may have increased the psychological and social stress of the offspring and influenced the overall outcome. Mother's schizophrenia can have a significant effect on habits and living conditions within the family. Parental illness may also increase the instability of the rearing environment, and also cause pronounced assortative mating (Parnas et al., 1993). Thus, the problems in HR families are probably more diverse and there might have been many confounding factors that have not been taken into account.

HR children who develop schizophrenia may represent a special form of schizophrenia, since they all have an exceptionally high genetic risk. Thus, the findings on childhood development may not be generalizable to less familial forms of the disorder. However, the advantage of the HR method is that the information is collected without knowledge of the ongoing study, and can be quite detailed compared to cohort studies. Those HR children who remained unaffected formed an ideal control group. These advantages of HR research outweigh the drawbacks of the method.

7.2. Cumulative incidence of mental disorders among high-risk offspring (Study II)

7.2.1. Cumulative incidence of schizophrenia

The cumulative incidence of schizophrenia among the offspring of mothers with schizophrenia in this study is lower than in previous HR studies. The cumulative incidence was 5.8%, compared with 16.2% in the Copenhagen HR Study (Parnas et al., 1993), 13.1% in the New York HR Study (Erlenmeyer-Kimling et al., 1997), 8.0% in the Israeli HR Study (Ingraham et al., 1995), and 8.3% in the New York Infant Study (Fish, 1987). Several factors may have caused this. In this study, only hospital-treated cases were diagnosed and the individuals were not interviewed. In addition, the case-note information was incomplete for four offspring. Two additional offspring would probably have been diagnosed if their hospital records had been available. Both offspring had a mother with schizophrenia.

Moreover, there was only one family in this cohort in which both parents had schizophrenia, whereas in the New York and Copenhagen HR studies this super-high-risk group was considerably bigger (Erlenmeyer-Kimling et al., 1984; Parnas, 1985). However, it is also possible that the high prevalences observed in the New York and Copenhagen HR studies were partly due to their case selection methods. The follow-up period in the Copenhagen HR Study was also slightly longer than ours, up to 48 years of age, but because of the declining incidence of schizophrenia with increasing age, the late-onset schizophrenia cases would probably have raised the cumulative incidences in this study only slightly. In addition, the incidence of schizophrenia in Finland, as in Denmark, was higher for the cohorts in the 1950s than in the 1960s, when the offspring in our cohort were born (Munk-Jorgensen & Mortensen, 1992; Suvisaari et al., 1999b). Thus, the offspring of the Copenhagen HR Study may have born during a period (1942-52) when the incidence of schizophrenia in the general population was in fact higher than in the 1960s.

The findings of this study are similar to those from family and adoption studies. Numerous family studies have found a morbid risk of schizophrenia among first-degree relatives ranging from 1.4% to 6.5% (Kendler & Diehl, 1993). The prevalence of schizophrenia among adoptees with a biological mother with schizophrenia was 6.9% in the Finnish (Tienari et al., 2000) and 5.7% in the Danish Adoption Study (Kendler & Gruenberg, 1984). A Danish population-based study found that having a mother with schizophrenia was associated with a 7-fold risk of developing schizophrenia, which is more in accordance with our results than those from the New York and Copenhagen HR studies (Pedersen & Mortensen, 2001a). However, the Danish study, like the Helsinki HR Study, was based on a hospital discharge register which until recently included only inpatient treatments.

7.2.2. Cumulative incidence of other mental disorders

The cumulative incidence of bipolar I disorder (0.97%) and major depressive disorder with psychotic features (1.9%) among the schizophrenia HR offspring in this study is similar to the findings of the New York HR Study (bipolar I disorder 2.4%, major depressive disorder 1.2%) (Erlenmeyer-Kimling et al., 1997). In addition, the cumulative incidences of hospital-treated non-psychotic mood disorders in the present study were increased in the schizophrenia and the remaining HR groups. Apart from bipolar disorder, the cumulative incidence of hospital-treated mental disorders among the offspring of mothers with affective disorders was rather low and similar to those among controls, whereas in the New York HR Study, the cumulative incidences of schizophrenia-related psychotic disorders (6.0% vs. 0.7%), schizoaffective disorders (mainly schizophrenic 6.0% vs. 0.7%, mainly affective 1.5% vs. 0.0%), and non-psychotic and psychotic affective disorders (49.3% vs. 35.3%) were all increased among the affective disorder HR offspring as compared with controls (Erlenmeyer-Kimling et al., 1997). It is likely that the cumulative incidences in this study would have been higher if we had interviewed the probands.

Alltogether, HR mothers, fathers and offspring had increased rates of hospital-treated alcohol and other substance abuse or dependence disorders compared to controls (12.8% vs. 3.4%). In the Copenhagen HR Study, alcohol or other substance abuse was more common among the HR than control offspring (Parnas et al., 1993), whereas there was no significant difference between the HR and control groups in the New York HR Study (Erlenmeyer-Kimling et al., 1997). The rates among control offspring were different in these studies, too, being 11.9% in the former and 31.6% in the latter. In this present study, however, these cumulative incidence rates are based on hospital records only and reflect severe, hospital-treated forms of the disorders. Paternal, but not maternal, substance abuse increased the offspring's risk for substance abuse. This may have been partly caused by the fact that paternal substance use disorders were severe and had usually been the cause for their hospitalisations, whereas maternal substance use disorders were rarely sufficient to cause hospitalisation by themselves. Consistent with this study, the occurrence of alcoholism and/or antisocial personality disorder in the Copenhagen HR Study was higher among HR than control fathers (27% vs. 17%) (Parnas, 1985).

In this present study, the risk of developing schizophrenia or schizophrenia spectrum disorder was approximately equal in the HR groups of mothers with schizophrenia, schizoaffective disorder, or schizophrenia spectrum disorders. This finding agrees with the Irish Roscommon Family Study, in which the risk of schizophrenia and schizophrenia spectrum disorders was approximately equal among the relatives of probands with schizophrenia, schizotypal personality disorder, schizoaffective disorder, or other non-affective psychotic disorders (Kendler et al., 1993c).

There was also an excess of individuals with hospital-treated borderline personality disorder and non-psychotic affective disorders among HR offspring compared to controls in this study. The prevalence of any psychotic disorder among offspring of mothers with schizoaffective disorder or with other psychosis was also increased compared to controls. The risk of developing schizophrenia spectrum disorders was comparable in the HR groups of mothers with schizophrenia, schizoaffective psychoses, or other nonaffective psychoses. Our method was clearly insensitive for detecting Cluster A personality disorders. This accords with the findings of the Copenhagen HR Study (Parnas et al., 1993), where only 9.8% of persons with schizotypal personality disorders had received hospital treatment, the respective figures for paranoid and schizoid personality disorders being 20% and 0%; of the other Axis II disorders 5.6% had received inpatient treatment. We found that both borderline and antisocial personality disorders were more common among offspring of mothers with schizophrenia and schizophrenia spectrum disorders compared to controls. Many previous HR studies have found behaviour suggestive of childhood or adolescent conduct disorder among offspring of mothers with schizophrenia (Study I). The increased prevalence of Cluster B personality disorders in this cohort could suggest that adulthood personality disorders might be the continuum of behavioural problems found during childhood. In the Finnish Adoption Study, too, the risk of developing Cluster B and C personality disorders was increased among adoptees with a biological mother with schizophrenia (Tienari et al., 2000).

7.3. Maternal symptomatology and its effect on offspring's morbidity from psychotic disorders (Study III)

7.3.1. Factor solution

The factor analysis in this study was conducted in a rather unusual sample of patients with psychotic disorders: all patients were females, and all had offspring. Two studies have conducted a factor analysis based on the MSSS (Burke et al., 1996; Kendler et al., 1997a; Kendler et al., 1997b). Their study samples consisted of patients from families with at least two affected siblings, the majority of whom were males (Burke et al., 1996; Kendler et al., 1997b). Both studies found a three-factor solution. The first factor was negative symptom factor in both studies, but factors two and three were disorganization and positive symptom factors in the first study (Burke et al., 1996), and positive and affective symptom factors in the second (Kendler et al., 1997b).

In the present study, the most noteworthy difference from these findings is that we found a separate factor representing catatonic symptoms. Two symptoms, catatonic behaviour and negative thought disorder, loaded on the catatonia factor. Interestingly, the negative thought disorder, usually regarded as a negative symptom, did not have a high loading on the negative symptom factor. It may be that alogia and catatonic mutism are somehow related phenomena. Three other studies, which all included patients with all types of

psychoses, found a catatonia factor (Andreasen & Olsen, 1982; Kitamura et al., 1995; McGorry et al., 1998). However, we found the same catatonia factor even when only patients with schizophrenia were included. This was not explained by having a substantial number of mothers with catatonic schizophrenia, as none of the mothers received a consensus diagnosis of catatonic schizophrenia. One possible explanation for the lack of a separate catatonia factor in previous studies is that the scales on which the analysis were based did not assess catatonia symptoms. For example, SANS (Andreasen, 1982) and SAPS (Andreasen, 1984), which may be the most frequently used scales for the assessment of symptoms in schizophrenia, and have often been used in factor analytic studies (Peralta & Cuesta, 2001), do not rate catatonic symptoms. OCCPI (McGuffin, 1991), another instrument frequently used in factor analysis studies, has one item for catatonic symptoms but ten items for different types of delusions. Another explanation could be that catatonic symptoms occur more frequently among female patients. However, a previous study found no gender differences in the prevalence of catatonic symptoms among patients with schizophrenia (Cernovsky et al., 1998), and catatonic schizophrenia seems to be more common among males (Kendler et al., 1994c; Erlenmeyer-Kimling et al., 1997; Stober et al., 1998). The third explanation is that all mothers had been born before 1948 and had their first illness episode before 1975, at a time when catatonic symptoms and catatonic schizophrenia were more prevalent than nowadays (Stompe et al., 2002).

7.3.2. Association between maternal symptomatology and offspring's morbidity

The inverse relationship between positive symptom factor score and risk of schizophrenia among offspring calls for explanation. One possibility is that offspring of mothers with paranoid schizophrenia have a lower risk of schizophrenia compared with offspring of mothers with non-paranoid schizophrenia. Some earlier studies have found that relatives of probands with paranoid schizophrenia have a lower risk of developing schizophrenia than relatives of probands with non-paranoid schizophrenia (Kendler & Davis, 1981). The Copenhagen HR Study found that the risk of schizophrenia was considerably lower among offspring of mothers with paranoid schizophrenia (5%) than among offspring of mothers with other types of schizophrenia (29%) (Jorgensen et al., 1987). We failed to confirm this finding: the cumulative incidence of schizophrenia among offspring of mothers with paranoid schizophrenia was 3.8% (1 of 26) compared with 6.4% (5 of 78) among offspring of mothers with other types of schizophrenia (χ^2_1=0.22, p=0.64). Thus, the negative relationship between positive symptoms and offspring's risk of schizophrenia was not explained by a lower risk of schizophrenia among offspring of mothers with paranoid schizophrenia. This accords with the Roscommon and Iowa studies, which found no relationship between subtype of schizophrenia and risk of schizophrenia or other psychotic disorders among relatives (Kendler et al., 1988; Kendler et al., 1994c). Nevertheless, it

could be that with a larger sample size, the difference in the cumulative incidence of schizophrenia between offspring of mothers with paranoid and non-paranoid schizophrenia would have been statistically significant. However, a Danish adoption study found that the risk of chronic schizophrenia was predicted by the presence of pervasive negative symptoms, and by the absence of pervasive positive symptoms (Cardno et al., 2002).

Another explanation for the observation could be that positive symptoms were associated with better outcome, but this was not the case in this sample: poor outcome also loaded to the positive symptom factor, although the loading was smaller than in the negative symptom factor. We did not find any association between offspring's age when mother had her first psychotic episode and offspring's probability of developing schizophrenia, and neither did age modify the positive symptoms factor effect on schizophrenia. There was no association between offspring's age when mother had her first psychotic episode and the factor score of positive symptoms (correlation -0.05).

In this study, the DSM-IV-TR diagnoses were far better predictors of offspring morbidity than symptom factors. This accords with the Roscommon Study, which found no relationship between any measures of symptoms, course or outcome, and the risk of schizophrenia or psychosis among relatives (Kendler et al., 1994b).

It is important to note that all mothers suffered from psychotic disorder. The results of this study only suggest that maternal positive symptoms are less harmful to the child than other maternal psychotic symptoms, not that they are protective against schizophrenia.

Tsuang et al. have suggested that 'psychosis is the fever of severe mental illness - a serious but nonspecific indicator', and that other types of symptoms, particularly negative ones, are more important in the diagnosis of schizophrenia (Tsuang et al., 2000). The negative association between positive symptom factor score and risk of schizophrenia among offspring supports this view. However, this study failed to find any association between negative symptom factor score and risk of schizophrenia.

Some previous studies have found that disorganization symptoms are associated with increased risk of nonaffective psychotic disorders in first-degree relatives (Cardno et al., 1997; van Os et al., 1997b). There was no separate disorganization factor in our study. However, symptoms of disorganization loaded most strongly on the positive symptom factor. In this respect, these findings are at odds with previous studies.

Nevertheless, some maternal symptoms seemed to be less harmful to the children than others. Whether this association could be explained by different genetic loading of these symptoms, by different impact of these symptoms on rearing environment, or by some other risk factor associated with the specific symptomatology, is not known. Previous studies have shown that some factors related to rearing environment are associated with later development of schizophrenia (Walker et al., 1981; Parnas et al., 1985; Mirsky et al., 1995b; Schiffman et al., 2002). Although these findings concerning rearing environment

have received little attention lately, they complement results from the Finnish adoptive family study suggesting that an unstable or otherwise nonoptimal rearing environment interacts with genetic risk in elevating the risk of schizophrenia (Wahlberg et al., 1997; Tienari et al., 2004). Thus, it is possible that supportive measures for the family, particularly during early childhood, may help prevent schizophrenia among HR children.

7.4. Childhood developmental predictors of psychiatric morbidity (Study IV)

7.4.1. Differences between HR and control children

HR offspring more often had emotional symptoms before school age than controls. This accords with many previous HR study findings that HR children are more depressive, hyperactive, and immature (Study I). The most prevalent pre-school emotional symptoms in our cohort were regressive behaviour, withdrawal, restlessness and psychosomatic symptoms, and these symptoms were most common among offspring of mothers with schizoaffective disorder. The New York HR Study found that schizophrenia HR offspring performed worse in the Wisconting Card Sorting Test in young adulthood than affective disorder HR offspring or controls, independently of whether they later developed schizophrenia or not (Wolf et al., 2002). Consistently with previous studies (Study I; Schubert & McNeil, 2004), HR children in our study more often had neurological soft signs than controls. Neurological soft signs were most common when the mother had affective disorder, although in the Swedish HR Study, offspring of mothers with affective disorder did not have neurological signs more often than controls (Schubert & McNeil, 2004). A recent family study found that neurological soft signs were more common among parents of patients with schizophrenia who were the presumed carriers of the genetic loading based on their family history than among parents who were presumed non-carriers, supporting the hypothesis that neurological signs are associated with genetic risk of schizophrenia (Gourion et al., 2004). HR offspring, particularly of mothers with schizophrenia, also differed from controls in being socially inhibited during school age. Many previous HR studies have also found the behaviour of HR offspring to be more often disturbed during school-age compared with controls (Study I).

Attention problems were more common among school-aged HR children than among controls, and these problems tended to predict schizophrenia spectrum disorders and mood disorders, although not to a statistically significant degree. Attention deficit is seen as one of the most promising phenotypic indicators of vulnerability to schizophrenia (Michie et al., 2000). Attention deficit may lead to academic difficulties, which have been found to be more common among HR children and adolescents than controls in previous HR studies (Study I), although academic difficulties could also reflect other risk factors that are more prevalent in these families, as suggested by the Rochester Longitudinal Study (Sameroff et al., 1998).

7.4.2. Developmental factors predicting future development of schizophrenia spectrum disorders

Problems in social adjustment were equally common among HR and control offspring, but HR offspring who had problems in social adjustment at pre-school-age had an increased risk of schizophrenia spectrum disorders. Instead, social adjustment problems, conduct problems and emotional symptoms during school age predicted future non-psychotic psychiatric disorders, and emotional symptoms tended to predict psychotic disorders. Problems in pre-school social adjustment in our cohort were assessed at five and six years, when a health assessment priority is to identify children who may be unable to start education at the normal age of seven. Two of the five HR boys and one of the six HR girls with problems in pre-school social adjustment developed schizophrenia spectrum disorder. The adolescents with future schizophrenia spectrum disorders in our cohort no longer differed significantly in their social adjustment from HR children who did not develop mental disorders. Many previous studies have suggested an association between problems in social adjustment and behaviour, and schizophrenia (Jorgensen et al., 1987; Mirsky et al., 1995a; Olin et al., 1995). According to previous research, pre-schizophrenic children and adolescents also have emotional symptoms more often than others (Carter et al., 1999; Poulton et al., 2000; Bolinskey et al., 2001). In this study, social inhibition during school-age tended to be more common among HR children who later developed schizophrenia spectrum disorders. Poor social and school adjustment seem to be among the most commonly found development abnormalities in pre-schizophrenic individuals.

Conduct and attentional problems and social inhibition were more common among HR children who developed schizophrenia spectrum disorders, but not statistically significantly. It may be that these children's problems did not draw as much attention at school-age as they did at the pre-school assessments.

In cohort studies, children who later develop schizophrenia have been found to reach motor milestones later, and to learn to speak later than those who remain unaffected (Study I). The divergent finding in this study may be explained by our smaller sample size or by the less detailed information we had (only whether the child had reached the milestones by a certain age). Because of the nature of our data in the present study, cautious is needed in making any further conclusions, although it might also be that the developmental adversity necessary to develop schizophrenia is somehow different among offspring who have an especially high genetic risk than in those who have no family history of schizophrenia. This might be interesting to assess in further studies.

7.4.3. Developmental factors predicting other mental disorders

Emotional symptoms during school age tended to predict later development of any psychotic disorder. Previous studies have found that school age internalising and externalising symptoms both predict future psychotic disorders (Cannon et al., 2001).

Emotional symptoms, conduct problems, social inhibition, and attention problems during school age were strong predictors of future mood disorders among HR offspring. The Dunedin Multidisciplinary Health and Development Study found that individuals with juvenile-onset depression had an excess of behavioural and emotional problems, as well as motor development problems (Jaffee et al., 2002). The results of this study suggest that emotional and conduct problems and social inhibition increase the risk of future mood disorders among individuals with high genetic risk for psychotic disorders. The odds ratios increased when only HR offspring whose mothers had a schizophrenia spectrum disorder were analysed, suggesting that the observed associations were not caused by elevated genetic risk of affective disorders. Conduct and attention problems were also highly predictive of future mood disorders. The Dunedin Multidisciplinary Health and Development Study found that particularly juvenile-onset depression is highly comorbid with conduct disorder and attention-deficit disorder (Jaffee et al., 2002), which complements our findings. Although neurological soft signs did not predict later development of mood disorders in this study, it is interesting that the British 1946 National Birth cohort found excess twitching and grimacing among children with childhood affective disturbance (van Os et al., 1997a), and in our cohort, neurological soft signs were most common among offspring of mothers with affective disorder, suggesting a possible connection also between familial risk for affective disorder and neurological soft signs. In many studies patients with affective disorder and their relatives have neurological signs more often than controls, but fewer neurological abnormalities than patients with schizophrenia and their relatives (Schubert & McNeil, 2004).

Interestingly, besides psychotic disorders only personality disorder was predicted by behavioural problems before school age, and was the only diagnosis where developmental predictors were observed from early childhood through adolescence. Delayed mental development and problems in social adjustment during childhood, as well as emotional symptoms, conduct problems, and social inhibition during school age, predicted later personality disorders. Two HR children developed antisocial personality disorder, five borderline personality disorder, and two personality disorder NOS. That no cluster A personality disorders were found reflects our method of case selection. As the Copenhagen HR Study showed, individuals with cluster A personality disorders rarely receive hospital treatment (Parnas et al., 1993), whereas individuals with Cluster B disorders often become hospitalised for their impulsive, aggressive or self-destructive behaviour. Cluster B personality disorders being so common in our sample, our findings concerning delayed mental development in early childhood could be explained by previous research suggesting that persistent antisocial behaviour is associated with both pre-school and school-age neurocognitive deficits (Moffitt, 1993; Raine et al., 2002). Consistent with our findings, earlier studies have found that childhood aggressivity, withdrawal, lack of social skills and mental health problems are risk factors for antisocial personality disorder (Holmes et

al., 2001; Moffitt et al., 2002). Individuals who develop borderline personality disorder also have more emotional symptoms and conduct disorder throughout childhood and adolescence (Joyce et al., 2003). Conduct problems self-evidently predict future antisocial personality disorder since they are part of its diagnostic criteria.

Emotional symptoms, conduct problems, and attention problems during school age predicted future substance related disorders. Similarly, the Danish Longitudinal Study of Alcoholism found that childhood unhappiness and antisocial personality disorder predicted alcohol abuse and dependence (Knop et al., 2003).

Overall, developmental problems predicting personality, mood, and substance use disorders among individuals at high genetic risk of schizophrenia do not differ from those identified in population-based cohort studies, but the observed odds ratios are much higher. Thus, the effect of these problems is more severe in the presence of genetic vulnerability to psychotic disorders.

7.5. Childhood growth and its effect on morbidity from psychotic disorders (Study V)

7.5.1. Differences between HR and control children

Both boys and girls were shorter than controls at birth, although the difference was statistically significant only for girls. The most likely explanation could be that their gestational age was slightly shorter; delivery prior to the 38th week was more common in the HR group (Wrede et al., 1980). Social class did not explain the lower height at birth among HR girls. The fact that HR boys but not girls were shorter than controls later in childhood is more difficult to explain. The difference in centimetres was larger at each successive measurement point, although it was statistically significant only at age 10. Since there was no difference in the ponderal index or BMI, inadequate caloric intake is an unlikely explanation, because it causes the weight percentile to fall first, and height only thereafter (Foye & Sulkes, 1990). One possible explanation could be delayed puberty, but unfortunately we were unable to estimate the onset of puberty from the health cards. Numerous factors related to childhood rearing environment, such as father's or own social class (Walker et al., 1988; Peck & Lundberg, 1995), education (Silventoinen et al., 1999), maternal care (Kuh & Wadsworth, 1989), economic difficulties (Peck & Lundberg, 1995; Silventoinen et al., 2001), large family (Peck & Lundberg, 1995) and family discord and divorce (Peck & Lundberg, 1995), have been found to have an effect on adult height. A Finnish study found that the effect of childhood economic difficulties, education and social class on adult body height is more marked among males than females (Silventoinen et al., 2001). Since economic difficulties, family discord and divorce, and poor parenting may all be more common in HR families, these factors could explain the lower childhood and adolescence height among HR boys. We investigated whether social class could explain the

differences in height and weight among offspring, but found no significant association between social class and growth variables among male offspring. Instead, among female offspring (both HR and controls), lower BMI at the age of 1, 10, and 14 years was significantly associated with higher social class, as well as lower weight at the age of 14 years.

7.5.2. Factors related to growth predicting future development of schizophrenia

In this study, the transition from being thin at birth to having BMI in the highest tertile at age seven predicted later development of schizophrenia, while an earlier Finnish study found an association between low BMI during childhood and later development of schizophrenia (Eriksson et al., 1999). One possible explanation for this controversial finding could be the different time period when the members of these cohorts were born. The earlier cohort was born between 1924 and 1933, while ours was born between 1960 and 1964. Low BMI during the 1920s and 1930s was often related to poverty and poor nutrition, while nowadays in the developed world, low social class is more commonly associated with high BMI (Sobal & Stunkard, 1989). In fact, low BMI during childhood and adolescence was associated with higher social class among females in our cohort.

Childhood BMI is influenced by both genetic and environmental factors (Borjeson, 1976; Stunkard et al., 1986). Mother's nutritional state already during pregnancy seems to influence child's later metabolism (Barker, 1998; Parizkova, 1998). Both nutritional deprivation and overnutrition during pregnancy have been found to be associated with later obesity (Ravelli et al., 1976; Pettit et al., 1983). Offspring who were exposed to undernutrition during the first and second trimester of pregnancy due a famine in the Netherlands during the Second World War were more often obese in adolescence than controls, while those who were exposed to undernutrition during the last trimester of pregnancy were less often obese (Ravelli et al., 1976). Interestingly, there is also an association between increased incidence of schizophrenia among those individuals who were exposed to severe famile during the first trimester in utero during this famine (Susser et al., 1996). According to this, our results concerning the BMI change could be related to prenatal nutrition.

Many studies have suggested that catch-up growth in previously growth-restricted children, especially among males, is a risk factor for later development of chronic diseases, such as cardiovascular diseases and high blood pressure (Law et al., 2002; Adair & Cole, 2003). This has been interpreted as evidence of foetal programming of cardiovascular diseases (Adair & Cole, 2003). Interestingly, the risk growth profile for schizophrenia in our study is similar to that found for cardiovascular diseases (Eriksson et al., 1999). All HR offspring with catch-up growth who later developed schizophrenia were males. Our finding was also specific to schizophrenia: there were no cases with catch-up growth among offspring with other psychotic disorders. The geographical variation in the incidence and prevalence of cardiovascular diseases (Tunstall-Pedoe et al., 1994, Jousilahti et al 1998)

and schizophrenia (Salokangas et al., 1987; Lehtinen et al., 1990; Hovatta et al., 1997) in Finland is similar. Further, the overall morbidity and mortality from cardiovascular diseases is higher among schizophrenia patients than in the general population (Brown, 1997; Joukamaa et al., 2001). This may suggest that cardiovascular diseases and schizophrenia may share some environmental or genetic risk factors.

7.6. General discussion

The findings of Studies II to V confirm the conclusion of Study I that children of mothers with psychotic disorder are more likely to have behavioural and developmental problems than control children, and that some of these problems are associated with later development of mental disorders.

Whether the developmental and behavioural differences between children and adolescents with or without a mother with psychotic disorder are caused by a genetic variation, stressful environment or some other environmental factor, is not known. The neurodevelopmental aspect of schizophrenia suggests that these abnormalities are due to an underlying abnormality of neural networks. These findings, however, are not specific to schizophrenia. Offspring at high risk for other disorders also tend to show similar developmental problems, although usually milder than those experienced by schizophrenia HR children, while severe neurological abnormalities seem to be specific to schizophrenia (Cannon et al., 2002a). Nevertheless, it has been shown that maternal social class, severity and chronicity of maternal illness despite the specific diagnosis, and maltreatment are often stronger predictors of poor functioning among children than parental schizophrenia (Sameroff et al., 1984; Bergman et al., 1997). At least part of these developmental problems, maybe the mildest ones, may thus have been caused by living in a nonoptimal family environment, rather than by having a high risk for developing schizophrenia due to parental psychotic disorder.

Some of these developmental or behavioural abnormalities are predictive of psychotic disorders. Still, none of the developmental precursors identified thus far is specific for schizophrenia, and none provides a necessary and sufficient relationship with it (Jones & Tarrant, 1999). Most individuals who have problems in childhood development, even within the high-risk group, do not develop schizophrenia. Conversely, even if the average performance on most measures is poorer among schizophrenia high-risk subjects, the performance of individual high-risk subjects is usually within the normal range. Most of these developmental problems found are relatively common, and most of the children with these symptoms remain unaffected. It is also not known if these factors associated with later development of psychotic disorders are independent risk factors, indicators of an ongoing disorder-related process, or reflections of other risk factors (Ellison et al., 1998). The concept of schizophrenia as a neurodevelopmental disorder may carry with it an unwarranted determinism, which may lead to therapeutic nihilism (Lieberman, 1999). There are several facts about developmental psychopathology worth remembering here. Firstly, genetic influences are probabilistic, not deterministic (Rutter & Sroufe, 2000). Secondly, for many developmental outcomes, it is the quantity rather than quality of risk factors

that is most predictive (Sameroff, 2000). Thirdly, positive experiences in adolescence and adulthood can have a crucial influence in protecting from some adulthood psychiatric disorders, provided that they bring about a substantial change in life opportunities or in self-concept (Rutter & Sroufe, 2000). Whether they can also have an impact on the diminishing risk for developing schizophrenia is unknown. Fourthly, a child's development includes factors that protect from developmental problems, and these are usually simply the positive pole of the risk factors (Sameroff, 2000).

Although the HR study method offers the possibility of assessing childhood developmental factors associated with schizophrenia, one problem is that only approximately 10% of HR children develop schizophrenia, making the predictions concerning vulnerability indicators unprecise. In our study, 75% of the HR offspring had never been hospitalized because of a psychiatric disorder. More than half of the children who had problems in social adjustment at pre-school-age did not develop a schizophrenia spectrum disorder, and a large majority of children who had psychiatric symptoms in school did not develop a psychotic disorder. The only marker with high specificity was severe neurological symptoms, in which case both of the children developed schizophrenia. On the other hand, most of the children who later developed schizophrenia spectrum disorder had some problem during childhood or adolescence noted in primary care. Most of these children had multiple problems, for example emotional symptoms during childhood, academic impairment and problems in social adjustment at pre-school-age, supporting the view that the quantity of risk factors is more predictive than the quality. Carter et al created a multivariate prediction model of schizophrenia based on the results of the Copenhagen HR Study (Carter et al., 2002). Using the estimations for genetic risk, birth factors, autonomic responsiveness, cognitive functioning, rearing environment, personality and school behaviour, they found that schizophrenia was predicted by the interaction of genetic risk with rearing environment and disruptive school behaviour (Carter et al., 2002). 75% of adolescents with future schizophrenia were correctly predicted using this estimation (Carter et al., 2002).

Although HR research has generated valuable information on the identification of early developmental factors and early antecedents of schizophrenia, one problem is that about 90% of all individuals with schizophrenia do not have a parent with the disorder, and about over half of all individuals with schizophrenia have neither a first nor second degree relative with schizophrenia (Gottesman & Erlenmeyer-Kimling, 2001). Thus, case selection methods for research other than the traditional HR case selection method have been suggested. These include the longitudinal assessment of individuals at considerably high risk for schizophrenia and other psychotic disorders because of a genetic abnormality, such as chromosome 22q11 deletion (Murphy & Owen, 2001) or t(1:11)(q43,q21) translocation (Clair et al., 1990), or because of an extreme exposure to environmental risk factors possibly associated with schizophrenia, such as very preterm birth, prenatal viral infection or instability of early rearing environment. Another possibility for detecting the most vulnerable children is to use liability indicators detected by HR studies, such as attention deficits or MMPI-derived scales, or to use other scales developed to identify psychosis-prone individuals (Chapman & Chapman, 1987). However, it may be difficult to find a sufficient number of such individuals, and findings from these special groups may not be generalizable to other patients with schizophrenia.

The prediction of psychotic disorders might help us to understand the process of onset and might enable us to intervene prior to psychosis onset during the prodromal phase, and at best to prevent schizophrenia. Indeed, there is evidence to suggest that the prevention of, or at least the ability to delay the onset of a psychotic disorder could be possible (Yung, 2003). However, there are some ethical problems concerning prevention and prodromal research. Many individuals who experience attenuated psychotic symptoms do not develop psychotic disorders. Calling such symptoms prodromal implies inevitable progression to psychosis, although psychosis is not an invariable outcome of such symptoms. Therefore, the trials where undiagnosed children or prodromal adolescents receive antipsychotic medication have been criticized (Gottesman & Erlenmeyer-Kimling, 2001).

Although antipsychotic drugs are the most obvious choice due to their efficacy in treating the fully psychotic disorder, it has also been suggested that other interventions may be more appropriate for the early stages of illness (Gottesman & Erlenmeyer-Kimling, 2001; Yung, 2003). Treating a person with prodromal symptoms may just make the patient feel better without perhaps treating the underlying disorder, and it may progress, leaving the individual at risk of relapse (Yung, 2003). Neuroprotective agents, antidepressants, and nonpharmacologic therapies may be of more benefit in the high-risk groups (Yung, 2003). Psychotherapies and other strategies that present little danger of deleterious effects can obviously tolerate higher false positive and lower sensitivity rates (Gottesman & Erlenmeyer-Kimling, 2001). Possible psychological costs should also be taken into account, such as stigmatization among peers versus the benefits afforded by psychological therapies, even for subjects who prove to be false positive (Gottesman & Erlenmeyer-Kimling, 2001). Factors that predict psychotic and non-psychotic disorders are partly similar, which also suggests not treating adolescents with such symptoms with antipsychotic medication. Another problem is that most prevention projects have included only subjects who were seeking help, whereas at the population level most individuals with attenuated psychotic symptoms do not seek help (Yung, 2003).

The HR study method also poses ethical questions. Mental disorders have long been among the most stigmatising disorders (Mueser & McGurk, 2004). Widely held myths about individuals with schizophrenia are that they are violent, childlike and irresponsible (Mueser & McGurk, 2004). They are also likely to be held more responsible for their disorders than people with other disorders, which leads to discrimination (Mueser & McGurk, 2004). Stigma can also contribute to denial of the illness by patients, which may lead them to delay seeking help. Being this kind of a high-risk, i.e. a "special family" in health care services, could also lead to concern in the child, maybe even to a feeling of stigma, and thereby increasing the inner distress in the family.

Although HR offspring who develop schizophrenia are not representative of all persons with schizophrenia, because only a minority of the latter have an affected parent(s), findings from cohort studies support the validity of these developmental and behavioural markers as vulnerability indicators of schizophrenia. Their sensitivity and specificity on the population level are unacceptably low, but they might be useful in genetic studies of psychotic disorders, and in identifying the most vulnerable high-risk children for preventive programs.

8. IMPLICATIONS FOR FURTHER RESEARCH

The cumulative incidences of schizophrenia and schizophrenia spectrum disorders among HR offspring were in the same range as among first-degree relatives of probands with schizophrenia and among adoptees having a biological mother with schizophrenia, but lower than those found in most previous HR studies. The prognosis of HR children may thus not be as poor as suggested by previous HR studies. When planning new HR studies, the case selection method and awareness of paternal status should be carefully considered.

Having a mother with schizophrenia increases the risk of a wide range of mental disorders among offspring, not just nonaffective psychotic disorders. The risks for schizoaffective disorder, schizophrenia and other nonaffective psychoses were in the same range among HR offspring, supporting the view of a shared genetic (or other) background of schizophrenia spectrum disorders. Paternal but not maternal substance abuse was associated with offspring's morbidity from substance abuse disorders. All these should be noted in genetic studies of schizophrenia.

Factor analytic studies offer an opportunity for genetic studies searching for specific phenotypes for schizophrenia. Interestingly, we found a separate catatonia factor. Further research might thus study catatonic symptoms more carefully. Although DSM-diagnoses were better predictors of schizophrenia, it might be useful to divide patients into different subgroups according to symptomatology, for example for pharmacogenetic purposes, because in clinical work it is often noted that patients with different symptoms respond differently to specific pharmaceuticals.

The HR method may be helpful in searching for the endophenotype underlying schizophrenia by assessing factors that differentiate HR and control children more precisely, although at least some of them are probably due to other than genetic factors. Findings of HR studies may be replicated in larger cohort studies. If specific genetic methods were included in HR study methodology, it might offer a unique possibility to separate the effects of genes and environment.

The finding that HR children were shorter than controls in this study needs to be replicated in larger cohorts. However, it is important to note that maternal status affects offspring's birth status. This should be considered when interpreting findings of associations between, for example, low birth weight or shortness at birth and later schizophrenia. In general, cohort studies should, if possible, take parental status into account as an explanatory variable. Theoretically, it is possible that some of the

childhood predictive factors found in cohort studies are caused by children with a high familial risk, and some others by more sporadic cases. The developmental problems that underlie familial and sporadic schizophrenia might not be the same.

Severe neurological symptoms are perhaps a strong marker for genetic vulnerability for schizophrenia, and this might be useful to take into account when planning new strategies to detect most vulnerable children. However, it is also possible that there is a specific subtype of schizophrenia which is more likely to be associated with severe neurological symptoms. The association of catch-up growth and later schizophrenia needs to be replicated with larger study samples, and possible confounding factors should be taken into account. It would also be interesting to assess if this association is also present among individuals who develop schizophrenia but do not have a genetic predisposition.

It might also be useful to study in more detail individuals who have a developmental abnormality, but who do not develop the disorder. It would be interesting to assess whether there is a combination of risk factors, or one specific risk factor, among those who develop the disorder, or if there are some protective factors among those who have the abnormalities but do not develop the disorder.

9. CONCLUSIONS AND CLINICAL IMPLICATIONS

These results confirm that offspring of mothers with psychotic disorder have an increased risk for various mental disorders and more emotional and developmental problems from early childhood onwards, and that some of these factors are predictive of later psychiatric morbidity.

These children have an increased risk especially for psychotic and substance related disorders. Whether this is caused by shared genetic or environmental risk factors is not known. However, almost two-thirds of the HR individuals in this study had never been hospitalized for psychiatric reasons, indicating that the prognosis of HR offspring is not as poor as suggested.

Psychiatric disorders, especially alcohol and substance abuse disorders, were more common among HR than control fathers, which further increased the risk of mental disorders among the offspring. HR fathers seemed quite often to have pathological personality traits, although usually so mild that they were not hospitalized because of them. Problems appear to accumulate in certain families: the spouses of women with psychotic disorder have often also had (psychiatric) problems, maybe due to assortative mating, and the child may himself have personality traits that lead him to problems with behaviour and social adjustment. All this renders such families more and more susceptible to, for example, adversity or social problems, such as withdrawal from social contacts. This suggests that mental health services should perhaps devote special attention to the whole family if it includes a member with a psychotic disorder, whether noted in adult psychiatric units, social services, or in childhood health care. Relieving the stigma of receiving psychiatric support could make it easier for such families to seek psychiatric help. Although positive symptoms are presumably not protective against schizophrenia, it should also be noted in clinical settings that the most visible symptoms (i.e. positive symptoms) are not necessarily the most harmful to a child. It should also be recognized that having a mother with schizophrenia increases the risk of various other mental disorders among offspring. They are also at an increased risk of developing non-psychotic disorders, particularly affective and substance abuse disorders, which should be noted when planning supportive measures for HR offspring.

The HR offspring have more emotional and developmental problems than controls. This may be caused by a specific genetic vulnerability, environmental factors, or both. Several studies have shown that instability of early rearing environment and other family related

factors are predictive of developmental and behavioural problems in the child. This may suggest that at least in some cases, childhood emotional and developmental problems might be a sign of familial instability. Thus, families having a child with these problems should perhaps be offered more intensive social support, if needed. It may even be worthwhile assessing if these mothers need some support in the overall management of their children, especially if they have a psychotic disorder.

Developmental epidemiological research poses the question of whether prevention of schizophrenia and other psychotic disorders is possible, at least in some cases. Findings of childhood factors associated with psychotic disorders may offer some strategies for the prevention of schizophrenia. The prevention model for high-risk individuals contrasts with universal and selective prevention strategies, although there might be some shared risk factors in both. As pregnancy and birth complications seem to increase the risk for schizophrenia, especially among HR offspring, intensive care already during pregnancy might be offered to women with a history of psychotic disorder. Prevention of schizophrenia may also include, for example, more careful health and social care of families with children (especially families with a parent with psychotic disorder), and political strategies against drug (especially cannabis) abuse.

In this study, predictive developmental symptoms have been identified in primary care. The problems predictive of schizophrenia spectrum disorders and personality disorders were seen already prior to school-age. Thus, it might be suggested that special attention should focus on problems in social adjustment and neurological development at the five-year health check, especially if the child has a mother with a psychotic disorder. On the contrary, some adolescents prone to non-psychotic disorders, and perhaps those prone to psychotic disorders, might be identified during school-age by displaying behavioural problems, for example disruptive or withdrawn behaviour. Children and adolescents with behavioural, especially psychotic-like, symptoms in clinical settings should perhaps be followed up through childhood and adolescence even after their presenting problems have resolved, particularly if they have a family history of schizophrenia.

Although treatment may be indicated on clinical grounds at an individual patient level, the setting of specific programs, especially if they are to include pharmacotherapy, is not justified with our present state of knowledge. Nevertheless, children or adolescents at high risk for psychosis should perhaps be offered intensive monitoring of their mental state, discrete counselling for risk factors and emerging signs of psychotic disorder, and, depending on the clinical condition, age, and other (e.g. ethical) factors, they could perhaps be offered either low-dose medication or other biological or psychological treatments, particularly if they have a family history of schizophrenia. In this way it might be possible to relieve the human suffering of these families, delay the onset, or at best even prevent an individual from developing a psychotic disorder.

10. SUMMARY

This thesis comprises a set of studies of the Helsinki High-Risk cohort, a programme designed to investigate offspring born in Helsinki to mothers with an original diagnosis of schizophrenia, schizoaffective disorder or schizophreniform psychoses. The aim of these studies was to evaluate whether the development of HR offspring differs from that of other children, which mental disorders these offspring have a heightened risk for, and which maternal or childhood developmental factors are associated with the increased risk for mental disorders.

Psychiatric morbidity was investigated using information on hospital treatments from the Finnish Hospital Discharge Register. Based on this information, all case notes for mothers, fathers and offspring were collected. All cohort members were thereby re-diagnosed according to DSM-IV-TR criteria. Mothers were divided into four diagnostic groups: schizophrenia, schizoaffective disorder, other nonaffective psychoses, and affective disorders. Offspring's morbidity from mental disorders was calculated in all these maternal diagnostic groups. The HR offspring had a heightened risk of developing a wide range of severe mental disorders.

The cumulative incidences of any psychotic disorder, and of schizophrenia were approximately equal among offspring of mothers with schizophrenia, schizoaffective disorder, and other spectrum disorders, and they were in the same range as found for first degree relatives of patients in previous cohort studies, but slightly lower than in previous HR studies. The cumulative incidences for psychotic disorders among offspring of mothers with affective disorder were only slightly increased compared to controls, and there was no offspring with schizophrenia in the affective disorder HR group. The offspring of mothers with schizophrenia spectrum psychosis also had an increased risk for non-psychotic disorders, particularly affective and substance use disorders. The HR fathers also had psychiatric disorders more often, particularly alcohol and substance use disorders, which further increased the risk of mental disorders among the offspring. Paternal, but not maternal, alcohol and substance use disorders increased the risk of alcohol and substance use disorders among the HR offspring.

Maternal psychotic and affective symptomatology was assessed using a principal factor analysis of maternal symptoms of some items of various structured rating scales. The result was a four-factor solution (negative, positive, catatonic, and affective symptom factors). High maternal positive symptom factor score predicted decreased morbidity to schizophrenia among offspring. This result suggests that maternal positive symptoms are

less harmful to the child than other maternal psychotic symptoms, and supports the view that positive symptoms are nonspecific symptoms of psychosis rather than core features of schizophrenia.

The association of childhood developmental factors and later development of psychotic disorder was assessed using information in childhood and school health cards. Children at increased familiar risk for psychotic disorder had more emotional and neurological symptoms, and more problems in social adjustment than controls. Most of these problems predicted future psychiatric morbidity. Problems elevating the risk of schizophrenia spectrum disorders manifested before school age, and were related to neurological development and social adjustment, while problems elevating the risk for nonpsychotic disorders manifested at school-age and were related to emotional and social problems. All these problems were noted in primary care.

Information from the childhood health cards was used also to assess whether the growth of HR children differs from that of control children, and whether factors related to growth in the HR group predict later development of psychotic disorder. The high-risk girls were shorter than controls at birth, while HR boys were only slightly shorter at birth compared with controls, but the difference in height increased with age, being statistically significant at age 10. Among HR children, catch up growth (the combination of being thin at birth but having a high BMI at seven years) predicted later development of schizophrenia.

Offspring of a mother with psychotic disorder have an increased risk for various mental disorders, and more often have emotional and developmental problems during childhood and adolescence compared to controls. Some of these factors are predictive of future development of mental disorders. Whether these factors are independent risk factors, associated with other risk factors or indicators of an ongoing process, needs further study.

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13. APPENDIX

Definitions:

AFFECTIVE PSYCHOSIS= any psychosis with prominent pathological mood symptoms (such as euphoria or depression)

CATATONIA= pathological condition with motoric immobility or stupor, or with excessive motor activity not influenced by external stimuli, extreme negativism, stereotyped movements, prominent mannerisms, or grimacing, echolalia or echopraxia

COHORT STUDY= a study of the same group (cohort) over time, but not necessarily of the same individual members of that group

CONCORDANCE= proportion of twin pairs who are similarly affected

DELUSION= false beliefs held despite evidence to the contrary

FOLLOW-UP STUDY= a study of the same group (cohort) over time, with the same individual members of that group

GENE-ENVIRONMENT INTERACTION= different effects of a environmental exposure on disorder risk in persons with different genotype or vice versa (different effects of a genotype on disease risk in persons with different environmental exposures)

GENOTYPE= genetic constitution

HALLUCINATIONS= sensory perceptions occurring without the appropriate stimulation of the corresponding sensory organ

HERITABILITY= measures the degree to which genetic factors influence the variability in the phenotype: if phenotypic variability (V_p) is divided into statistically independent genetic (V_g) and environmental variability (V_e), heritability (h^2) can be calculated as the ratio of genetic and phenotype variances ($h^2 = V_g / V_p$). Specific to the population and time period studied

HIGH-RISK METHOD= a method of studying the early antecedents of a disorder by investigating individuals who are at increased risk of developing it, typically those with a family history of the disorder

INCIDENCE= number of new cases of a disorder or illness that appear in a population during a specified period. Can be divided into incidence density (number of events occurring per unit of population per unit of time) and cumulative incidence (estimate of the probability of the occurrence of an outcome event over a specified period of time)

NEGATIVE SYMPTOMS= condition with affective flattening, alogia (reduced quantity or context of speech), avolition-apathy (diminished ability to initiate and follow through on plans), anhedonia (lack of pleasure)-asociality, or inattentiveness

NONAFFECTIVE PSYCHOSIS= any psychosis without prominent pathological mood symptoms

ODDS RATIO= a ratio of one odds to another. The odds ratio is a measure of association, but unlike other measures of association, '1.0' means that there is *no* relationship between the variables. The size of any relationship is measured by the difference (in either direction) from 1.0. An odds ratio less than 1.0 indicates an inverse or negative relation; an odds ratio greater than 1.0 indicated a direct or positive relation

PHENOTYPE= the observable characteristics of an individual, determined by genetic and environmental factors

POSITIVE SYMPTOMS= condition with hallucinations, delusions, suspiciousness, persecutory ideas, or grandiosity

PREVALENCE= number of cases of a disorder present either at a particular point in time (point prevalence) or during a particular period of time (period prevalence)

PROBAND= the individual who first comes to the attention of investigators and, because of his disorder, leads to a detailed study of the genetic transmission pattern within the family to determine if there is pattern within the family that might be genotypic in nature

PSYCHIATRIC EPIDEMIOLOGY= the branch of psychiatric research that investigates how mental illness is distributed in the population, and the factors that influence the distribution

PSYCHOTIC SYMPTOMS= abnormal (pathologic) experiences that are mistakenly taken as real (including delusions, hallucinations, or bizarre behaviours); conditions where there have been some loss of contact with reality

RISK FACTOR= an attribute or exposure that is associated with an increased probability of a specified outcome (not necessarily causal)

RISK RATIO= relative risk= a ratio of two rates of categorical variables; the ratio of the risk of a disorder among the exposed compared with the risk among the unexposed (for rare diseases, such as schizophrenia, the odds ratio approximates the relative risk)

SCHIZOPHRENIA= a disorder that manifests with multiple signs and symptoms involving thought, perception, emotion, movement and behaviour. Those manifestations combine in various ways, creating considerable diversity among patients, but the cumulative effect of the illness is always severe and usually long-lasting

(Reber, 1985; Zahner et al., 1995; Vogt, 1999; Mueser & McGurk, 2004)